Discriminative Accuracy of the CAPTURE Tool for Identifying Chronic Obstructive Pulmonary Disease in US Primary Care Settings

The CAPTURE Study: Validating a unique COPD case finding tool in primary care

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STATEMENT OF COMPLIANCE

This study will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CAO	Chronic Airflow Obstruction
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
ECOPD	Exacerbation of Chronic Obstructive Pulmonary Disease
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FEV1	Forced Expiratory Volume in 1 second
FFR	Federal Financial Report
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practice
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act

IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PBRN	Practice-Based Research Network
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
RE-AIM	Reach, Effectiveness, Adoption, Implementation, Maintenance
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States
USPSTF	United States Preventive Services Task Force

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	The CAPTURE Study: Validating a unique Chronic Obstructive Pulmonary Disease (COPD) case finding tool in primary care
Study Description:	**Aims 1 and 3**. A prospective, multicenter study including a cross-sectional validation to define sensitivity and specificity of CAPTURE and its impact on clinical care across a broad range of primary care settings in a cluster randomized controlled clinical trial. The CAPTURE tool consists of a 5-item self-administered questionnaire and peak expiratory flow (PEF) measurement, designed to identify undiagnosed patients with Chronic Obstructive Pulmonary Disease (COPD). **Aim 2.** This study delivers a qualitative assessment of clinical practice acceptance of and implementation strategy for CAPTURE case finding within 10 varied primary care practices across 5 US PBRN regions. We evaluate primary care practice attitudes, beliefs and recommendations about CAPTURE's potential to feasibly integrate into clinical practice patterns, workflow and quality improvement paradigm planning in a variety of primary care clinical settings.
Definitions:	**CAPTURE+ =** Participants with • CAPTURE score $\geq$ 5, or • CAPTURE score of 2, 3, or 4 with a low PEF, defined as <350 L/min for males and <250 L/min for females **CAPTURE-** = Participants with CAPTURE score < 2 or scores 2-4 with normal PEF, defined as >350 L/min for males and > 250 L/min for females **Spirometrically defined COPD =** Participants with abnormal spirometry, defined as post-bronchodilator FEV_1/FVC <0.7. **Clinically significant COPD =** Participants with abnormal spirometry, defined as post-bronchodilator FEV_1/FVC <0.7, plus one of the following: • FEV_1 < 60% predicted, or • > 1 exacerbation-like event within the past 12 months. **Mild COPD =** Participants with abnormal spirometry, defined as post-bronchodilator FEV_1/FVC<0.7 plus both of the following: • $FEV_1 \geq$ 60% and • No prior history of ECOPD
Objectives:	**Aims 1 and 3 Primary Objectives:** • **Aim 1 -** Define the sensitivity and specificity of CAPTURE for identifying previously undiagnosed patients with clinically significant COPD in a broad range of primary care settings. • **Aim 3 –** Define the impact of CAPTURE information provided to clinicians in identifying and managing patients with respiratory symptoms (CAPTURE+) across a broad range of primary care settings.

	Aim 2 Primary Objective:
	Explore clinical practice implementation approaches to and acceptance of CAPTURE case finding for clinically significant COPD in a range of primary care practices.
	
	Aims 1 and 3 Secondary Objectives:
	• **Aim 1 –**
	  • Define the sensitivity and specificity of CAPTURE for patients with COPD across a broad range of racial and ethnic groups in a range of primary care settings.
	  • Determine positive and negative predictive values (PPV and NPV) in different practice settings.
	  • Verify the optimal use (cutoff threshold) of the CAPTURE tool in combination with PEF measurements for identifying undiagnosed COPD.
	  • Determine patient and site characteristics that, with the CAPTURE assessment, will best identify persons with undiagnosed COPD.
	  • Determine whether CAPTURE is useful in identifying other definitions of undiagnosed COPD including:
	  1) spirometry-defined COPD, and
	  2) mild COPD
	
	• **Aim 3 -**
	  • Define the impact of CAPTURE clinician education, and patient-level CAPTURE information to clinicians ("CAPTURE education") on selected additional therapeutic interventions in previously undiagnosed patients with clinically significant COPD.
	  • Assess impact of CAPTURE education on clinician interventions specific to smokers.
	  • Determine the impact of CAPTURE education on patient symptoms, exacerbations, hospitalizations, and mortality.
	  • Determine the impact of CAPTURE education when COPD is defined spirometrically.
	
	Aim 2 Secondary Objectives:
	• Qualitatively assess primary care clinical staff COPD practice behavior – including COPD screening and diagnostic perceptions, beliefs and knowledge – that will inform strategies to improve CAPTURE RE-AIM (reach, impact, adoption, implementation and maintenance of use) characteristics.
	• Qualitatively assess primary care patient opinion of CAPTURE COPD case finding that will inform strategies to improve CAPTURE RE-AIM (reach, impact, adoption, implementation and maintenance of use) characteristics.

Endpoints:	**Aims 1 and 3 Primary Endpoints:** • Aim 1 –

	○ Sensitivity and specificity of CAPTURE to identify previously undiagnosed patients with clinically significant COPD at baseline. • Aim 3 – ○ Proportion of CAPTURE+ participants who meet at least one of the following within 12 months of study baseline (composite endpoint): 1) referral for or completion of clinical spirometry testing, 2) new diagnosis of COPD, 3) newly prescribed respiratory medication (long acting bronchodilator or anti-inflammatory for respiratory condition), or 4) referral to a specialist for respiratory evaluation/treatment **Aim 2 Primary Endpoints:** • Primary care clinician recommendations that inform CAPTURE RE-AIM strategies at both provider and clinical support levels of primary care practice. • Primary clinician recommendations that inform CAPTURE-associated COPD education models for primary care clinicians. • Primary care clinician recommendations that inform CAPTURE-associated COPD clinical quality improvement designs across a variety of primary care practice types. **Aims 1 and 3 Secondary Endpoints:** • Aim 1 – ○ Sensitivity and specificity of CAPTURE to identify previously undiagnosed patients with COPD across sex, ethnic groups, urban vs rural location, and educational level. ○ Positive and negative predictive values (PPV and NPV) in different practice settings. ○ Areas under the receiving operator characteristic curve (AUC) for various cutpoints of CAPTURE and PEF_1 measurements to determine the best cutpoint for COPD+ screen. ○ AUC to identify the combination of patient/site characteristics which best discriminates those with clinically significant COPD. ○ All primary and secondary endpoints as applied to 1) spirometry-defined COPD and 2) mild COPD • Aim 3 – ○ Proportion of CAPTURE+ patients who meet the components of the composite endpoint. ○ Proportion of patients with clinically significant COPD who meet the composite endpoint. ○ In participants with clinically significant COPD who are current smokers, the incidence of physician referral to a formal smoking cessation program, prescribed smoking cessation medication, and referral to pulmonary rehabilitation program. ○ In participants with clinically significant COPD, change in CAT score, and proportion of patients who experience exacerbations, hospitalizations, or mortality.

	○ All of the above endpoints for Aim 3, with the patient population defined as those who have COPD defined spirometrically. **Aim 2 Secondary Endpoints:** • Existing COPD screening and diagnostic and case finding processes within a variety of primary care practices. • Primary care practice belief about capacity to change from existing COPD screening and diagnostic assessment strategies. • Practice-specific COPD screening and diagnostic continuing education preference.
Study Population:	**Aims 1 and 3.** Adults 45-80 years old without a prior diagnosis of COPD (total N = 5000; approximately 1000 participants per PBRN) **Aim 2.** - 10 primary care practices: 2 practices per PBRN with up to 15 clinical staff participants per practice; clinician N = up to 150 (up to 30 clinician participants per PBRN). - Aim 1 patient opinion survey population; patient N = 200 (40 patients from each PBRN; adults 45-80 years old, without a prior diagnosis of COPD). - Total N = up to 350
Phase:	N/A
Description of Sites/Facilities Enrolling Participants:	**Aims 1 and 3.** Enrollment will occur in approximately 100 primary care practices affiliated with 5 primary care based practice networks (PBRN) across the United States who exhibit a broad range of gender, ethnic, racial, socioeconomic, and regional diversity. **Aim 2.** • Two primary care practices chosen by each of the same 5 PBRN co-investigator teams make up the 10 aim 2 practices from which clinician participants are enrolled. These 10 practices are separate from the 100 chosen practices in aims 1 and 3. • Patient participants are a sub-sample of those participants enrolled in aims 1 and 3.
Description of Study Intervention:	**Aims 1 and 3.** Primary care practices will be randomized to either receive basic COPD education and patient-level CAPTURE information with CAPTURE education (initially basic then later enhanced based on data collected in Aim 2) versus COPD education only. **Aim 2.** Participating primary care clinicians from 10 varied practices are surveyed at three different time points and participate in two focus groups qualitatively assessing CAPTURE implementation strategy and COPD case finding approaches in primary care. Participating patients complete one 10-minute written opinion survey about CAPTURE.
Study Duration:	**Aim 1 and 3.** 4 years **Aim 2.** 2 years
Participant Duration:	**Aims 1 and 3.** Up to 12 months **Aim 2.**

	• Primary care practice clinicians: questionnaires and focus groups (total 3 hours/participant) over 16 months. • Primary care patients: one 10-minute questionnaire/participant over 14 months.

1.2 SCHEMA

FIGURE 1. OVERALL STRUCTURE OF AIMS

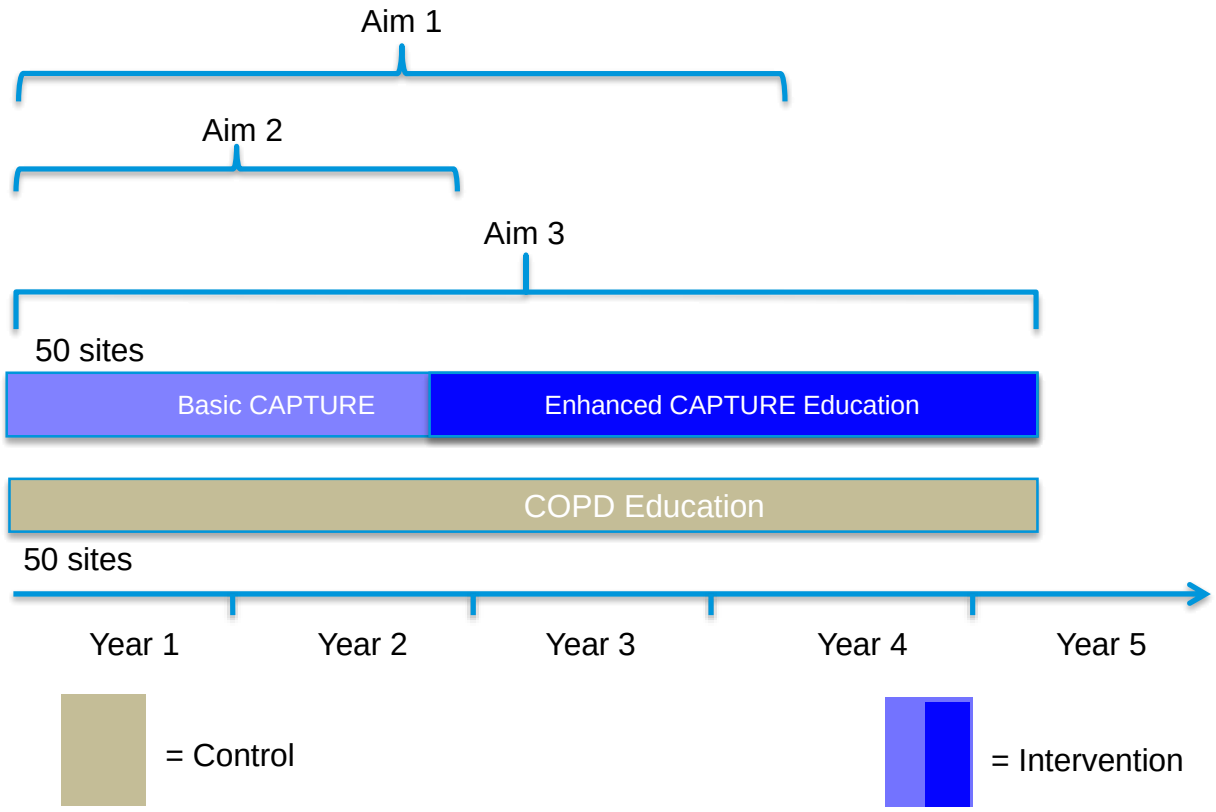

FIGURE 2. STRUCTURE OF AIM 2


CAPTURE COPD Study
Time Commitment
Introductory Phone Call
Brief phone call with CAPTURE research team to review the CAPTURE COPD: The Primary Care Practice Expert Panel aim. Discussion includes: review of the research content, timeline and scheduling of the half-day site visit for February/March 2018
Month 1
In Person Baseline Assessment/ Site Visit:
SITE VISIT INCLUDES:
• Walk through of practice and staff introduction: 2 clinical staff with CAPTURE team [60 minutes]
• Clinic flow observation and mapping [1/2 day]
• Post clinic flow observation Q&A: 2 clinical staff and CAPTURE research team [30 minutes]
• CAPTURE COPD information distribution and consent process
Online Questionnaire: 1st of three
Online/written questionnaire at baseline [20 minutes]
Month 2-3
State-of-the-Art COPD Web-based Continuing Education
Three modules encouraged; All modules optional 20 minutes/module; per Aim 3 description
Month 3-7
Practice Expert Panel Focus Group #1
Prescribers and Non-Prescribers (2 different days) 60 minute focus group
Online Questionnaire: 2nd of three
Online/written questionnaire at 6 months [20 minutes]
Month 6-10
Online Questionnaire: 3rd of three
Online/written questionnaire at 12 months [20 minutes]
Month 11-14
Practice Expert Panel Focus Group #2
Pooled prescribers and Non-Prescriber Clinical Staff [60 minutes]
Month 14-16
CAPTURE COPD: The Primary Care Practice Expert Panel Study will take place in 10 practices in 5 regions in the US. Central to the success of CAPTURE COPD is the role of clinical staff expertise in providing feedback, information and suggestions about clinical workflow for COPD diagnosis.
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1.3 SCHEDULE OF ACTIVITIES (SOA)

Table 1: Schedule of Activities (Aims 1 and 3)

	Pre-Visit Contact[1]	**Baseline**	**12 Months[4]**
Visit or Call	**C1**	**V1**	**C2/V2[6]**
Time point, days (Visit window)	**Prior to outpatient visit (≤-1)**	**Within 30 days of pre-visit contact**	**365 ±30**
Contact patient re: interest in study visit[1]	X		
Informed consent		X	
Demographics		X	
Medical history (Co-morbidities)[2]		X	
Vaccination status		X	X
CAPTURE 5-item questionnaire		X	X
CAPTURE 12-item additional questionnaire		X	
Peak Expiratory Flow (PEF)		X	
Height and weight		X	
Concomitant medications review[3]		X	X
Spirometry[5]		X	X
Respiratory symptoms, exacerbation assessment		X	X
Smoking exposure history		X	
Smoking cessation review[7]			X
COPD Assessment Test (CAT)		X	X
Adverse Events		X	X
Medical record chart review			X

1. Optional per site recruitment preferences
2. Comorbidities including cardiovascular, respiratory and malignant disorders
3. Respiratory medications
4. Recorded for a subset of participants who meet any of the following criteria: 1) CAPTURE Score ≥ 2; 2) abnormal spirometry defined as $FEV_1/FVC < 0.70$ or FEV_1 < 80% predicted at baseline; 3) CAT score ≥ 10; and, 4) a random sample of approximately 5% of those who do not meet criteria 1-3. For participants meeting criteria 1-3 who cannot or choose not to complete the 12-month assessment, medical chart review will still be completed. For participants meeting criteria 1-3 who change medical practices and chart review cannot be completed, attempts will be made to collect other data from participants where possible. For participants meeting criterion 4 where all of

the protocol-specified 12-month assessments cannot be made, another participant will be selected at random to replace this participant.

5. Pre-bronchodilator spirometry will be done for all participants. Post-bronchodilator spirometry will be performed for participants with abnormal spirometry ($FEV_1/FVC < 0.70$ or $FEV_1 < 80\%$ predicted)
6. The 12-month assessment may be a visit, mailing or telephone call, based on practice feasibility to capture patient-reported outcomes. The remainder of the data will be captured through medical record review.
7. This will be completed in those that are smoking at V1.

2 INTRODUCTION

2.1 STUDY RATIONALE

Undiagnosed COPD is a leading cause of morbidity and mortality. Spirometry, the 'gold standard' for diagnosis, is not recommended for screening in asymptomatic individuals or untargeted case finding and remains widely underutilized in primary care settings. Targeted case finding approaches have been strongly advocated but currently available approaches generally identify patients across the spectrum of mild to severe disease without reference to potential therapeutic benefit or exacerbation risk, thereby limiting clinical impact and acceptance in primary care. There is an urgent need to develop and implement simple case finding approaches that can identify patients with clinically significant COPD in primary care settings.

Through a multi-stage, iterative process we developed a simple case finding tool using five questions combined with selective peak expiratory flow **(PEF)** measurement that identifies individuals with 1) an $FEV_1 < 60\%$ predicted and/or 2) at risk for ECOPD. We call this tool CAPTURE (**C**OPD **A**ssessment in **P**rimary Care **T**o Identify **U**ndiagnosed **R**espiratory Disease and **E**xacerbation Risk)(1). As clinical trials have demonstrated benefit and therapeutic guidelines recommend therapy for these individuals we have labeled these patients as suffering from 'clinically significant' COPD. The long-term goal of this project is to identify these patients so that they can be treated and result in improved health status, reduced exacerbations, and decreased morbidity.

The *overall objectives* of Aims 1 and 3 of this project are to 1) validate the sensitivity, specificity, and predictive value of CAPTURE to identify undiagnosed, clinically significant COPD patients in a diverse primary care population; and explore whether identifying these patients results in improved COPD specific care and health status. Our *principal hypothesis* is that CAPTURE can effectively and efficiently identify primary care patients with undiagnosed, clinically significant COPD. We objectively test our principal hypothesis by completing to two separate and linked aims:

Aim 1 – Determine the sensitivity and specificity of CAPTURE in identifying clinically significant COPD patients in a broad range of primary care outpatient practices.

Working hypothesis - A simple case finding methodology using a five-item questionnaire with selective PEF measurement will identify undiagnosed patients with clinically significant COPD.

We will conduct a 5,000 participant cohort study in 100 primary care practices affiliated with five primary care based research networks **(PBRN)** that provide access to previously undiagnosed patients with clinically significant COPD who exhibit gender, ethnic, racial, socioeconomic and regional diversity.

Aim 3 – Define the impact of CAPTURE screening in a broad range of primary care outpatient practices and evaluate practice and patient characteristics that are associated with care implementation and clinical outcomes for patients with respiratory symptoms (CAPTURE+).

Working hypothesis – Provision of patient specific CAPTURE data to practicing clinicians will result in improved management of patients with respiratory symptoms (CAPTURE+).

We will provide basic COPD education and patient level CAPTURE information and education to site clinicians at 50 of the sites and prospectively follow selective, pre-defined subgroups of patients to define relevant outcomes. Care at the other 50 clinical sites will follow standard of care with basic COPD education to clinicians.

Assessing the potential clinical impact of a novel COPD case finding strategy includes confirmation of validity in a diverse primary care patient population and a quantitative research evaluation of its impact on clinical decision-making and COPD patient outcomes, as found in aims 1 and 3 above. Equally important is exploration through validated implementation methods that the newly designed CAPTURE tool, even if valid and impactful, can provide real-world utility within a variety of primary care practice settings. While we find no evidence in previous COPD screening studies of such detailed appraisal, ascertaining the feasibility of clinical testing is a vital component of assuring that new approaches address potential clinical practice need, capacity, knowledge and diagnostic gaps. As much as possible, clinical respiratory innovations should align with busy workflow at all practice staff levels to more effectively identify primary care patients with undiagnosed, clinically significant COPD.

To maximize success of the CAPTURE adoption, education and implementation in this study and in future work, Aim 2 is introduced to assess practice experience, need and preference that can inform clinical COPD case finding and education in primary care settings:

Aim 2 – Explore clinical practice implementation approaches to and acceptance of CAPTURE case finding for clinically significant COPD in a range of primary care practices.

The *overall objective* of this aim is to qualitatively explore primary care clinical practice acceptance of COPD case finding implementation and define education and feasibility strategies to enhance adoption in primary care practice. This assessment includes understanding clinician and clinical staff COPD practice and perceptions in addition to the feasibility of case finding integration into existent clinical work patterns. To attain this objective, we address one *working hypothesis* – a COPD case finding methodology using a validated one-page, five-item questionnaire with selective PEF measurement (CAPTURE) can be incorporated into the clinical practice patterns, clinical workflow, communication and practice-based quality improvement paradigms in a variety of primary care clinical settings. The *rationale* for this objective reflects the importance of establishing if an innovative approach to COPD case finding (CAPTURE) is considered a pragmatic tool with potential utility for primary care clinicians within real-world clinical practice settings. With the completion of this aim we anticipate confirming that future validated approaches to COPD case finding can be adopted in a broad variety of clinical care settings thereby providing further impetus for the rigorous evaluation of a) case finding guided patient outcomes as part of routine primary care clinical practice; b) case finding use in a range of primary care health professional COPD-related education approaches, clinical quality improvement models and diagnostic guidelines; and c) the capacity of clinical case finding with informed follow-up to enhance future COPD clinical care therapeutic paradigms used in primary care practice.

2.2 BACKGROUND

Aims 1 and 3.

COPD remains a major cause of morbidity and mortality. COPD results in substantial morbidity and mortality worldwide.(2-4) Globally, the prevalence of COPD and years lived with disability increased from 1990 to 2013.(5) This is particularly evident in older individuals.(6) These well-designed population based studies confirm the growing impact of COPD.

COPD is frequently undiagnosed. We recently documented that only 28% of participants with chronic airway obstruction **(CAO)** had physician diagnosed disease.(7) Importantly, an FEV_1 <50% predicted was noted in 10% of those with undiagnosed CAO; this is similar to other cohorts or population based surveys.(8-11) There is consistency in these well-conducted studies that confirm most COPD patients are undiagnosed.

Spirometry is underutilized. The U.S. Preventive Services Task Force **(USPSTF)** recently recommended against the use of spirometry for routine, general population or practice-based screening in asymptomatic individuals.(12) An editorial by the PI of this application highlighted the limitations of this conclusion.(13) Within primary care spirometry is often viewed as time consuming and difficult to implement and interpret.(14) As such, it is not routinely used.(15-19) Even the availability of less expensive and easily used spirometers(20) has not resulted in increased utilization.(21, 22)

Undiagnosed COPD is associated with a negative clinical impact. In a robust, population based study we confirmed that undiagnosed patients experienced impaired health status and a higher risk for all-cause mortality compared to those without CAO; this was particularly evident with more severe CAO.(7) Others have confirmed increased mortality,(23) health status impairment,(24) exacerbation-like respiratory events,(11) and increased health care costs.(25, 26) As such, there are consistent data suggesting that undiagnosed COPD patients experience negative clinical events and impaired health status.

Therapeutic interventions improve COPD clinical outcomes. Well designed, randomized controlled trials confirm that COPD therapy is effective, particularly in patients with an FEV_1 < 60% predicted who are symptomatic or at risk for ECOPD.(27, 28) Despite limited data, some have suggested that earlier detection of patients with previously undiagnosed, yet clinically significant COPD, in primary care settings could improve short- and long-term patient outcomes and may be cost-effective. (29, 30)

COPD case finding approaches to date have generally been methodologically limited. Several COPD case finding tools have been created based on existing epidemiologic literature or expert opinion.(31, 32) This includes tools created by investigators in this study.(33, 34) In general, current approaches were designed to identify COPD patients without reference to disease severity or ECOPD risk, resulting in the identification of a high proportion of patients with mild or minimally symptomatic disease.(21, 33-39) Several studies have tested the accuracy of handheld flow meters for case identification with varying sensitivity and specificity.(40) Although informative in terms of CAO, PEF meters have been unable to systematically identify patients at risk of ECOPD. We tested a three-staged approach (risk-factor questionnaire, PEF, and spirometry) for identifying moderate to severe COPD (FEV_1<60% predicted) in a convenience sample of the general population.(41) This study was limited by the nature of the population screened and the screening questionnaire used but supported the concept that PEF can facilitate COPD case finding.

A systematic analysis of existing databases provides insight into the best variables for COPD Case Identification. To identify potential items that could be useful in the identification of undiagnosed COPD we interrogated three robust datasets of populations in which the investigators on this application had major roles [COPD Foundation Peak Flow Study Cohort (n=5761); Burden of Obstructive Lung Disease Kentucky site (n=508); and COPDGene® (n=10,214)].(42) We utilized the machine learning statistical

method of random forests to identify and validate variables most important in identifying patients with clinically significant COPD. COPD case finding candidate content included items reflecting exposure, personal and family history, respiratory symptoms, recent health history, activity limitation and demographics.

A comprehensive, qualitative study identified key constructs for identifying recently diagnosed patients with clinically significant COPD. We completed a two phase study that included focus groups followed by cognitive interviews to refine the key constructs for identifying patients with clinically significant COPD.(43) Fifty participants were recruited including those with mild airflow obstruction, diagnosed within the previous six months and without previous ECOPD; those diagnosed within the previous six months and with a history of at least one ECOPD within the prior year; those with 2-3 risk factors for COPD but without CAO; and those with $\geq$ 4 risk factors for COPD but without CAO. Using a content analysis approach, key themes and constructs were identified and integrated with the content of the previous literature review and data mining. We identified 44 candidate items that resonated with patients and provided important insights into a case finding instrument.

A five-item questionnaire exhibits excellent operating characteristics to identify clinically significant COPD patients. We completed a prospective, multi-site, case-control study of four groups: cases with clinically significant COPD – COPD with > 1 ECOPD in the previous year (n=97) and COPD with no ECOPD but an FEV_1 < 60% predicted (n=89); controls – no known COPD (n=87) and COPD with an FEV_1 > 60% predicted and no ECOPD in the previous year (n=74). Using random forest analyses the 44 candidate items were reduced to 34-item, 21-item, 8-item and two different five-item sets. Through-out the item reduction process, the item sets maintained good performance, consistently misclassifying fewer than 27% of cases and controls, and with sensitivity greater than 80% and specificity greater than 70%. A five-item questionnaire exhibited good operating characteristics for separating COPD cases from controls. These characteristics were even better when separating COPD from controls without COPD.

Selective PEF measurement enhances the operating characteristics of a COPD case finding strategy. In the above case control study PEF was measured using a mechanical PEF meter with disposable mouthpieces. To optimize sensitivity and specificity, the following cut-off scores were selected, based on our data, for identifying cases of clinically significant COPD using PEF alone: males: <350 L/min; females: <250 L/min. The best method for predicting cases was a combination of the questionnaire and PEF **(CAPTURE)**, where PEF is used only for mid-range scores. Under this scoring scenario, patients with scores of 0 or 1 are not considered at risk of clinically significant COPD; they would not require further evaluation. Those with a score of 5 or 6 are considered to be at high risk of clinically significant COPD and should be referred directly for further evaluation, including clinical spirometry. Patients scoring in the middle range (2 to 4) would undergo PEF testing, applying the 350/250 interpretation thresholds. In our sample, 52% of the participants required PEF to determine if spirometry was indicated. The other 48% needed only the five-item questionnaire. This approach provided 90% sensitivity, 93% specificity and an overall error rate of 9%.

CAPTURE exhibits similar operating characteristics in a Spanish speaking population. To broaden our target population, the five-item questionnaire was methodically translated to Spanish using previously validated, rigorous methods(44) to yield an instrument that is equivalent to the English questionnaire and linguistically and culturally applicable to persons of diverse Spanish-speaking backgrounds residing in the US. In a subset of Spanish speaking participants CAPTURE exhibited excellent sensitivity (88%), specificity (92%) and overall error rate (10%) for identifying patients with clinically significant COPD.

Aim 2.

Consistent with national criteria for preventive and chronic disease care quality, feasibility science is designed to assist clinical and health education evaluators plan for assessing and evaluating specific implementation factors essential to the success of new diagnostic, therapeutic and programmatic options in real-world clinical practice. This aim's analysis of primary care clinical practice COPD case finding feasibility includes an initial evaluation of existing COPD diagnostic and case finding processes within the practices, assessment of practices' capacity to change from existing respiratory symptom assessment strategies and an understanding of practice-specific learning preferences associated with new diagnostics in chronic disease diagnosis and management. The aim addresses through the RE-AIM feasibility approach how a new tool might a) identify target populations (Reach); b) appraise optimal targeted respiratory history and symptoms consistent with clinically significant COPD (Effectiveness or Impact); c) integrate into practice workflow (Adoption); d) deliver changes and improvements to COPD care within the scope of real-world clinical practice (Implementation); and e) persist in use and quality over time (Maintenance) (45-53).

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Potential risks associated with Aims 1 and 3 of this study are outlined below.

Spirometry: Participants may become short of breath. Syncope, light-headedness and fainting may develop during this test. These are uncommon.

Albuterol: Tremulousness, feeling of a strong, rapid heartbeat, and palpitations can occur with inhaled albuterol. A targeted safety questionnaire will be administered to all participants prior to albuterol to exclude those with a previous adverse event with the medication and others at high risk due to cardiac abnormalities. Note that albuterol is only administered to those with abnormal spirometry on the baseline spirometry assessment (defined as $FEV_1/FVC < 0.70$ or $FEV_1 < 80\%$ predicted).

Peak Expiratory Flow: Participants may become short of breath. Syncope, light-headedness and fainting may develop during this test. These are uncommon.

Other non-physical risks of the study include those from economic loss from participation in the study; this will be minimized by scheduling tests and evaluations in a timely manner in the fewest number of visits possible. Patient and physician participants will be provided a modest fee to cover their time to participate in the study.

We anticipate few adverse events due to the non-invasive nature of the study procedures and the rarity of such events encountered during the initial visits and longitudinal follow-up. Medical care will be available at each Clinical Center to treat participants who develop adverse events during in-person study visits.

Potential risks associated with Aim 2 of this study include:

No more than minimal risk exists for participants within aim 2.

Confidentiality of information and identification are the risks associated with this project. Based on previous research and the protocols that have been developed, we believe that the likelihood of these risks to the participants would be minimal, i.e. "rare".

Potential risks associated with the study (all Aims) include:

Loss of confidentiality of study data: This is unlikely since data collected will be stored in locked file cabinets in locked rooms at the Clinical Centers. In addition, only participant IDs are used to identify participants in the secure server at the Data Coordinating Center.

Poor quality data: If the data collected are of poor quality such that it is not useable to achieve study aims, participants will have unnecessarily been exposed to other risks in the study.

2.3.2 KNOWN POTENTIAL BENEFITS

For Aims 1 and 3 of this study, participants could receive direct benefit as a result of their participation in this research. Current state-of-the-art COPD education is offered to all clinicians at participating PBRN sites (see aim 3 protocol) that could result in improved care for their COPD patients. At the conclusion of the study, both patients and their care providers will have received the results of the CAPTURE screening tool and research spirometry that could result in further diagnostic testing leading to a diagnosis of COPD or other respiratory disorder. Some participants, however, will not have respiratory disease and therefore may not benefit. For Aims 1, 2 and 3, physician participants may benefit in learning how better to identify COPD participants in clinic.

Known potential benefits for each participating clinical staff include critical review their clinical respiratory practice. In general, aim 2 offers the ability to assess and address CAPTURE-specific primary care practice feasibility issues which could augment or hamper clinical communication or implementation of COPD case-finding in real-world primary care clinical practice.

Potential benefits to society include improved understanding of how best to identify individuals with COPD in the primary care setting. This could ultimately lead to better treatments and lower morbidity and mortality for patients with COPD.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The demonstrated and potential future benefits to improved understanding of COPD case finding outweigh the minimal risks of the procedures performed.

Increased understanding of how best to diagnose individuals at risk for COPD in the primary care population has the potential to benefit both patients with COPD and society at large. The risk to individuals associated with this study protocol is small and the knowledge to be gained is substantial.

3 OBJECTIVES AND ENDPOINTS

Aims 1 and 3.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Aim 1: Define the sensitivity and specificity of CAPTURE for identifying previously undiagnosed patients with *clinically significant COPD* in a broad range of primary care settings	Sensitivity and specificity of CAPTURE to identify previously undiagnosed patients with clinically significant COPD at baseline.	Standard methodology for COPD diagnosis will be used (1).

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Aim 3: Define the impact of CAPTURE information provided to clinicians in identifying and managing patients with respiratory symptoms (*CAPTURE+*) across a broad range of primary care settings.	Proportion of CAPTURE+ participants who meet at least one of the following within 12 months of study baseline (composite endpoint): 1) referral for or completion of clinical spirometry testing, 2) new diagnosis of COPD, 3) newly prescribed respiratory medication (long acting bronchodilator or anti-inflammatory for respiratory condition), or 4) referral to a specialist for respiratory evaluation/treatment.	The composite endpoint is clinically relevant and consistent with published data (45). This will test the impact of CAPTURE on clinician behavior.
Secondary		
Aim 1: Define the sensitivity and specificity of CAPTURE for patients with COPD across a broad range of racial and ethnic subgroups in a range of primary care settings	Sensitivity and specificity of CAPTURE to identify previously undiagnosed patients with COPD across sex, ethnic groups, urban vs rural location, and educational status.	Patient characteristics will be used to assess the robustness of CAPTURE.
Aim 1: Determine positive and negative predictive values (PPV and NPV) in different practice settings.	Positive and negative predictive values (PPV and NPV) in different practice settings.	PPV and NPV will be used to assess the robustness and usefulness of CAPTURE in various settings.
Aim 1: Verify the optimal use (cutoff threshold) of the CAPTURE tool in combination with FEV_1 measurements for identifying undiagnosed COPD.	AUC for various cutpoints of CAPTURE and PEF measurements to determine the best cutpoint for clinically significant COPD screen.	The best discrimination for CAPTURE combined with FEV_1 will indicate the optimal usage of the tool.
Aim 1: Determine patient and site characteristics that, with the CAPTURE assessment, will best identify persons with undiagnosed COPD.	AUC to identify the combination of patient/site characteristics which best discriminates those with clinically significant COPD.	The best discrimination will determine which site and patient characteristics best predicted undiagnosed COPD in combination with the CAPTURE tool.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Aim 1: Determine whether CAPTURE is useful in identifying other definitions of undiagnosed COPD: 1) spirometry-defined COPD, and 2) mild COPD	All primary and secondary endpoints as applied to 1) spirometry-defined COPD and 2) mild COPD	This will determine the robustness of the CAPTURE tool.
Aim 3: Define the impact of CAPTURE clinician education, and patient-level CAPTURE information to clinicians ("CAPTURE education") on selected additional therapeutic interventions in previously undiagnosed patients with *clinically significant COPD.*	Proportion of CAPTURE+ participants who meet the components of the composite endpoint.	Each endpoint is clinically relevant and consistent with published data. (45) This will test the impact of CAPTURE on clinician behavior.
Aim 3: Assess impact of CAPTURE education on clinician interventions specific to smokers.	In participants with clinically significant COPD who are current smokers, the incidence of physician referral to a formal smoking cessation program, prescribed smoking cessation medication, and referral to pulmonary rehabilitation program.	Certain outcomes are specific to only smokers and should be assessed.
Aim 3: Determine the impact of CAPTURE education on patient symptoms, exacerbations, hospitalizations, and mortality.	In participants with clinically significant COPD, change in CAT score, and proportion of patients who experience exacerbations, hospitalizations, or mortality.	This endpoint is important for quality of life, and long-term patient outlook.
Aim 3: Determine the impact of CAPTURE education when COPD is defined spirometrically.	All of the above endpoints for Aim 3, with the patient population defined as those who have COPD defined spirometrically.	This will determine the robustness of the CAPTURE tool

Aim 2.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Explore clinical practice implementation approaches to and acceptance of CAPTURE case finding for clinically significant COPD in a range of primary care practices.	Primary care clinician recommendations that inform CAPTURE RE-AIM strategies at both provider and clinical support levels of primary care practice.	Clinical improvement models that introduce new testing must investigate practice opinion and behavior and

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	Primary clinician recommendations that inform CAPTURE-associated COPD education models for primary care clinicians. Primary care clinician recommendations that inform CAPTURE-associated COPD clinical quality improvement designs across a variety of primary care practice types.	incorporate clinician recommendation.
Secondary		
Qualitatively assess primary care clinical staff COPD practice behavior – including COPD screening and diagnostic perceptions, beliefs and knowledge – that will inform strategies to improve CAPTURE RE-AIM (reach, impact, adoption, implementation and maintenance of use) characteristics.	Existing COPD screening and diagnostic and case-finding processes within a variety of primary care practices. Primary care practice beliefs about capacity to change from existing COPD screening and diagnostic assessment strategies. Practice-specific COPD screening and diagnostic continuing education preference.	Awareness of existing clinician knowledge and behavior can influence workflow implementation and overall effectiveness of new clinical tools.
Qualitatively assess primary care patient opinion of CAPTURE COPD case finding that will inform strategies to improve CAPTURE RE-AIM (reach, impact, adoption, implementation and maintenance of use) characteristics.	CAPTURE opinion survey ascertaining participant comprehension of CAPTURE instructions and testing and ease of completion.	Patient satisfaction, understanding and ease of test completion affects staff implementation and workflow decision. Participant opinion survey results will seed CAPTURE implementation planning practice staff focus groups.

4 STUDY DESIGN

4.1 OVERALL DESIGN

A prospective, multicenter study that includes three key aims: 1) cross-sectional validation to define sensitivity and specificity of CAPTURE; 2) *qualitative* research exploration engaging clinical staff at all levels from primary care practices serving US patient populations of differing gender, racial, ethnic, urban/rural and socio-economic blends, and 3) explore the impact of CAPTURE on clinical care and patient outcomes across a broad range of primary care settings in a cluster randomized controlled clinical trial. The CAPTURE tool consists of a 5-item self-administered questionnaire and selected use of peak expiratory flow (PEF) measurement, designed to identify clinically significant Chronic Obstructive Pulmonary Disease (COPD).

For Aim 1, approximately 5,000 patients will be recruited at the time of their regularly-scheduled appointment across 100 participating primary care clinics associated with practice-based research networks (PBRNs). Eligible participants will undergo a baseline visit during which the CAPTURE tool and spirometry will be obtained, as well as PEF and other participant characteristics.

For Aim 2, approximately 150 clinicians from 10 participating primary care practices across 5 US PBRNs will undergo detailed implementation investigation of the CAPTURE case finding model for clinically significant COPD. In addition, 200 primary care patients recruited as part of Aim 1 will complete a 10-minute written CAPTURE opinion survey.

To address Aim 3, participating primary care practices will be randomized in a 1:1 fashion to one of the following interventions:

- Arm 1: Practice clinicians will receive basic COPD education, and patient-level CAPTURE information with CAPTURE interpretation education (CAPTURE+ COPD education). As the second aim addresses the optimal format for delivering practice CAPTURE education this will be incorporated at the sites randomized to this arm (see Enhanced CAPTURE education in Figure 1).
- Arm 2: Practice clinicians will receive basic COPD education only (COPD education).

Basic COPD and CAPTURE specific education will use an interactive, web-based education program which will be provided to all practice personnel, including physicians, nurse practitioners, physician assistants, nurses, medical assistants, clerical staff and administrative staff. Practitioners at sites randomized to the CAPTURE+COPD education intervention will receive the CAPTURE score from the central study coordinators soon after the baseline assessments have been completed.

Addressing Aims 1 and 3 will include a baseline visit for all participants and for Aim 3 longitudinal follow-up over 12 months for a predefined cohort of participants. Determination of the participants included in the longitudinal follow-up cohorts will be made after the baseline visit.

Baseline Data
Practices and/or study staff will pre-screen patients according to local guidelines to identify potential participants based on the following criteria: no prior COPD diagnoses, between 45 and 80 years old, and speak and read either English or Spanish. The timing of the pre-screening and the method to approach these patients for participation in the study (e.g., at the next outpatient visit, via telephone) will be flexible, depending upon site recruitment preferences. Patients who are eligible based on the pre-screening questions and agree to participate in the study will sign informed consent. After signing the consent, they will complete the CAPTURE questionnaire, PEF testing, spirometry testing, other respiratory questionnaires, and provide past medical history and demographic information. Local/PBRN study coordinators for each of the 5 PBRNs will perform the study procedures and record baseline information into the electronic data capture (EDC) system.

The EDC system will calculate a CAPTURE score for each participant, based on his/her CAPTURE questionnaire answers and PEF measurement. A binary score (positive or negative CAPTURE) will be emailed to the central study coordinator only for participants randomized to CAPTURE+COPD education intervention practices. The coordinator will communicate this information to these practitioners. Practitioners at sites randomized to the COPD education only intervention will be blinded to CAPTURE scores. Practitioners in both intervention arms will be blinded to research spirometry results.

Analyses will include a comparison of CAPTURE scores with data from spirometry testing and participant reported data to determine sensitivity and specificity of the CAPTURE tool. *The hypothesis is that a simple case finding methodology using a five-item questionnaire with selective PEF measurement will identify undiagnosed patients with clinically significant COPD.*

Based on the data collected at baseline, participants will be classified into the following groups for analyses:

Cohort	Definition
CAPTURE+	Participants with • CAPTURE score $\geq$ 5, or • CAPTURE score of 2, 3, or 4 with a low PEF, defined as <350 L/min for males and <250 L/min for females
CAPTURE-	Participants with • CAPTURE score < 2 or scores 2-4 with normal PEF (defined as $\geq$350 L/min for males and $\geq$250 L/min for females)
Spirometrically defined COPD	Participants with abnormal spirometry, defined as post-bronchodilator FEV_1/FVC <0.7.
Clinically significant COPD	Participants with abnormal spirometry, defined as post-bronchodilator FEV_1/FVC <0.7, plus one of the following: 1) FEV_1 < 60% predicted or > 1 exacerbation like event within the past 12 months.
Mild COPD	Participants with abnormal spirometry, defined as post-bronchodilator $FEV_1/FVC<0.7$ plus both of the following: • $FEV_1 \geq 60\%$ and • No prior history of ECOPD

Longitudinal Follow-up
A pre-defined subgroup of enrolled participants, who meet any of the below criteria will undergo longitudinal follow-up at 12 months,

1. Participants with a CAPTURE Score $\geq$ 2
2. Participants who have abnormal spirometry results, defined as post-bronchodilator $FEV_1/FVC < 0.7$ or $FEV_1 < 80\%$ predicted at baseline
3. CAT score $\geq$ 10
4. A random sample of approximately 5% who do not meet criteria 1 - 3

Participants who meet the criteria for follow-up will be sent notification/reminder letters within the first 3 weeks of enrollment and at 3, 6, and 9 months. Patient-reported data will be collected by telephone, secure web-based server, and mail-based methodologies, as well as medical record abstraction, depending upon practice site preferences and feasibility. Clinic site data will also be collected from the medical record to assess for changes in practice-level care.

The hypothesis for Aim 3 is that sites where COPD and CAPTURE education and patient-level CAPTURE data are provided to clinicians will exhibit improved COPD diagnosis and COPD-related care compared to sites where COPD education is provided to clinicians.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Aims 1 and 3

The totality of the published data confirms the clinical and economic impact of undiagnosed COPD, continuing under-diagnosis, and incomplete application of spirometric testing in the primary care community. It suggests that there is value in COPD case-finding that targets COPD patients most likely to benefit from available therapies. These points identify a pressing health care problem that requires an innovative approach to facilitate identifying these individuals. Our preliminary studies enumerated in section 2.2 extend these concepts by demonstrating that:

- Six key domains identify patients with clinically significant COPD.
- Forty-four distinct items resonate with patients and provide important insights for COPD case-finding.
- Five items exhibit excellent sensitivity and specificity in identifying patients with clinically significant COPD.
- PEF provides incremental value in a case-finding strategy.
- The combination of a five-item questionnaire and PEF optimizes a COPD case-finding strategy in English and Spanish speaking patients.

Our proposed study will provide crucial data to address the operating characteristics and clinical translation to our COPD case-finding strategy into the primary care setting. It will also provide an important initial evaluation of the potential clinical impact of the systematic identification of previously undiagnosed COPD patients.

Aim 2

The rationale for this aim reflects the importance of establishing if an innovative approach to COPD case finding is considered a pragmatic tool with potential utility for primary care clinicians within real-world clinical practice settings. With the completion of this aim we anticipate confirming that future validated approaches to COPD case finding can be adopted in a broad variety of clinical care settings thereby providing further impetus for the rigorous evaluation of a) case finding guided patient outcomes as part of routine primary care clinical practice; b) case finding use in a range of primary care health professional COPD-related education approaches, clinical quality improvement models and diagnostic guidelines; and c) the capacity of clinical case finding and informed follow-up to enhance future COPD clinical care therapeutic paradigms used in primary care practice.

Consistent with Institute of Medicine criteria and US health quality standards for preventive and chronic disease care, the feasibility science qualitative research framework is designed to assist clinical and health education evaluators prepare, assess and evaluate specific implementation factors essential to the success of new diagnostic, therapeutic, educational and programmatic options in real-world clinical practice. This aim's analysis of primary care clinical practice COPD case finding feasibility considerations for CAPTURE includes an initial evaluation of existing COPD diagnostic and case finding processes within the practices, assessment of practices' capacity to change from existing respiratory symptom

assessment strategies and an understanding of practice-specific learning preferences associated with new diagnostics and chronic disease diagnosis and management. Patient perceptions of the CAPTURE case-finding process are also obtained to provide a holistic perspective of the clinical feasibility of CAPTURE implementation in primary care practice. Borrowing from the RE-AIM implementation science approach, this aim explores how real-word primary care practices might potentially use CAPTURE to: a) identify target populations (Reach); b) refine current practice appraisal of patient respiratory history, symptoms and diagnostics used to identify clinically significant COPD (Effectiveness/Impact); c) change or integrate COPD case finding into practice workflow (Adoption); d) alter practice communication, education and/or care quality improvement planning for COPD diagnosis and management (Implementation); and e) use COPD case finding consistently over time (Maintenance).

Ten primary care practices will undergo detailed implementation investigation of the CAPTURE case finding model designed to identify patients with COPD most likely to benefit from available therapeutic options. CAPTURE, a one-page questionnaire with selective PEF measurement, is presented to the clinicians of ten practices not participating in aims 1 and 3 as a prospective COPD case finding option awaiting validation. By representing CAPTURE as a model—and not introducing it into actual practice—aim 2 gains recommendation from primary care clinical practice experience with sufficient feasibility generality to circumvent interdependence between the operating characteristic exploration (aim 1) and qualitative feasibility understanding (aim 2) components of our study. The aim 2 results, that include the pooled CAPTURE clinical communication, education and implementation recommendations from real-world primary care practice, are analyzed and applied in concert with local and national research team expertise to enhance the potential impact of CAPTURE's introduction into clinical care in aim 3. Aim 2 results also provide previously unexplored qualitative information necessary for future long-term patient outcome studies of COPD case finding approaches in primary care.

4.3 END OF STUDY DEFINITION

Participants that do not meet the criteria for, or are not selected for, longitudinal follow-up will be considered to have completed the study after completion of the baseline visit.

Participants included in the longitudinal follow-up phase will be considered to have completed the study after completion of the Month 12 Assessment as shown in the Schedule of Activities (SoA), Section 1.3.

Clinician participants in aim 2 will have completed the study after participation on their second focus group between months 14 and 16 as shown in the Figure 2, Structure of Aim 2.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Inclusion criteria for Aims 1 and 3
In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Male or female, aged 45 – 80 years

Inclusion criteria for Aim 2

Two Aim 2 practices are selected by each of their 5 affiliated PBRNs based upon willingness to participate and variability of primary care practice type within the PBRN. Differences in practice size, staffing, ownership, prior quality improvement engagement, geography, patient population socioeconomic status (SES) or languages spoken are among the among the selection criteria the PBRNs will utilize to choose.

Clinician participants (10 practices with up to 15 clinicians per practice):
1. Provision of signed and dated informed consent form.
2. Stated willingness to comply with availability and all study procedures for the duration of aim 2 by the 10 practices (through PBRN recruitment) and their up to 15 clinicians within (through informed consent).

Patient participants [200 patients (approximately 40 from each PBRN)] for CAPTURE survey:
1. Provision of signed and dated informed consent form.
2. Stated willingness to comply with all study procedures and availability for the duration of the study.
3. Male or female, aged 45 – 80 years.

5.2 EXCLUSION CRITERIA

Exclusion criteria for Aims 1 and 3
An individual who meets any of the following criteria will be excluded from participation in this study:

1. Previous clinician provided diagnosis of COPD
2. Treated respiratory infection (with antibiotics and/or systemic steroids) in the past 30 days of baseline
3. Participants unable to perform spirometry due to any of the following conditions within the past 30 days of baseline
    a) Chest surgery
    b) Abdominal surgery
    c) Eye surgery
    d) Heart attack
    e) Stroke

Exclusion criteria for Aim 2

1. Clinician participants: current employment at practices participating in aims 1 and/or 3
2. Clinician participants: from practices providing fewer than 2 clinician participants
3. Patient participants: meeting the exclusion criteria for aims 1 and 3 (above)

5.3 SCREEN FAILURES

PBRN coordinators, in conjunction with clinical study site personnel, will pre-screen individuals who are unlikely to be able to complete research spirometry. These individuals will be considered *pre-screen failures*.

Participants who are consented to participate but have a prior clinician diagnosis of COPD will be considered *screen failures*.

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment and retention strategies for Aims 1 and 3

Approximately 5,000 participants will be recruited from 100 primary care clinics affiliated with five PBRNs. Each PBRN has centrally-based research coordinators with a history of success working in PBRN practices, documented expertise in previous large diagnostic or therapeutic trials, and personnel experienced in recruitment and data collection.

IRB approval will be obtained at each PBRN for approval for patient contact, informed consent and participation in this study.

All patients who meet all inclusion and no exclusion criteria at the participating PBRN clinical site will be eligible for participation. Research coordinators will work with participating practices to identify and approach potential participants. Recruitment strategies may vary depending on the practice.

Enrollment of participants will depend on the gender, ethnic and racial makeup of those that are being recruited from the practices included in this trial. No exclusion criteria apply specifically to women or to minorities. The Data Coordinating Center (DCC) will track enrollment of participants throughout the course of this study. If women and minorities are under-represented in the initial phase of recruitment, a commitment exists to develop recruitment strategies that target these populations so the final study group is a well-balanced representation of the studied population.

Recruitment and retention strategies for Aim 2

Clinician participants: Approximately 150 clinic participants are recruited by: 1) introductory telephone contact with the practice leadership by PBRN research coordinators and the aim 2 research team; 2) follow up letter, time commitment infographic and informed consent forms sent to interested practices outlining aim 2 clinician participant activities and responsibilities; and 3) in-person aim 2 study explanation to clinician participants at the committed practices during the introductory baseline study site visit.

Clinician participant recruitment draws from both prescribing (or "provider") staff and non-prescribing (or "clinical support") staff. The aim 2 research team will attempt to obtain an even mix of both clinician staff types from each practice. Retention incentive of clinician participants over 2 years includes provision of on-line COPD education to all clinician participants and monetary incentive to practices as determined by each individual PBRN.

Patient participants: 200 participants (40 from each PBRN) are recruited as a sub-set of the aim 1. Each of the 200 patient participants in aim 2 are asked to complete a one-time 10-minute written opinion survey. Their aim 2 participation is concluded at the end of the opinion survey completion.

The aim 2 research team and DCC will track enrollment and retention of all aim 2 participants throughout the course of the 2-year aim 2 study.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

The study intervention is applicable to Aims 2 and 3 and consists of healthcare provider education modules.

The practitioners at the 10 sites selected for Aim 2 will receive module 1, Basic COPD education, and may elect to take modules 3-5 for supplemental information on COPD.

For Aim 3, half of the practices will receive Basic COPD education (module 1) and half will receive Basic COPD Education and CAPTURE Education (modules 1 and 2). Practitioners at practices randomized to COPD only education must take module 1 and may elect to take modules 3-5; however, they will not take module 2. Practitioners at practices randomized to COPD+CAPTURE education must take modules 1 and 2, and may elect to take modules 3-5.

1 - Basic COPD Education will be provided in order for providers to optimally manage patients with COPD. The education will incorporate evidence-based recommendations using the 2018 update of the Global Obstructive Lung Disease Strategy(45).

A 40-minute overview will be presented in the most expeditious manner at each practice site, for example by webinar for all practice personnel over the lunch hour, or audiovisual presentation available on a dedicated CAPTURE web site. The PBRNs have indicated that this module should be no longer than 40 minutes. Topics will include: CAPTURE study description and rationale, importance of COPD in the region of the local practices, COPD definition and diagnosis, patient goals, and management approach. Attendance at this mandatory training will be documented and continuing education credits will be provided for physicians and nurse practitioners by National Jewish Health, an accredited CME provider.

2 - **CAPTURE education**. An online audiovisual module will be developed to explain CAPTURE interpretation and use in patient evaluation and diagnosis of COPD. This module will only be available to practices randomized to receive the results of CAPTURE for clinical use.

With the information provided in Aim 2 about practice preferences for education, the CAPTURE education module will be revised and made available to practices enrolled in Aim 1 after the completion of Aim 2.

3 - Online advanced COPD education will be available for all practices and continuing education credits will be provided to enhance practitioner participation. Practitioner attendance at each online audiovisual module will be collected including the amount of time spent on each education module, completion of each module with a post-test and evaluation, and CME will be provided. Education will be case-based and will include role playing where appropriate. Seven basic modules of 20 minutes or less will be available both to practices randomized to receive CAPTURE results for clinician use and to control practices that will not receive CAPTURE results and will cover:

1. Diagnosis of COPD: How to diagnose COPD in primary care including medical history, physical exam and role of spirometry, severity categorization
2. Spirometry overview: Basic clinical interpretation
3. Advanced spirometry: Test performance, evaluating quality, advanced case-based interpretation
4. Management overview: Patient goals, smoking cessation, vaccination, patient education, shared decision-making
5. Pharmacotherapy: Inhaled bronchodilators, inhaled corticosteroids
6. Other therapies: Oxygen, pulmonary rehabilitation, surgical approaches

7. Inhalation devices: Patient education

4 – On-site COPD education. Additional funds will be sought to provide on-site COPD education. We have experience in successfully providing half-day on-site education to primary care practices to enhance their management of COPD.

5 – Social media and case conferences. We will use social media (Facebook and Twitter) to provide ongoing education about COPD. Facebook and Twitter posts will provide tips on managing COPD. Online conferences will be scheduled to discuss cases submitted by primary care providers.

6.2 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

For Aims 1 and 3, this study will use randomization and blinding as two of the cardinal principles of clinical trials to minimize bias.

Randomization. Practices will be randomized into one of the two interventions, COPD education or COPD education + CAPTURE education, in a 1:1 manner, stratified by PBRN. Randomization will occur at the time of site activation and each site will be assigned a unique randomization number. The DCC will prepare the randomization schedule, using computer-generated block randomization with the block size(s) known only by the DCC. A secure web-based application will be built that will be used by the central study coordinators to enter site information (e.g., site ID, stratification factor) and to obtain the randomization number. The information can be printed and sent and/or emailed directly to the study coordinator.

Blinding. This is a single-blind study with the participants blinded to whether their practitioners have received CAPTURE education and patient-level CAPTURE results. Practitioners at sites that are randomized to the control arm (COPD education alone) will be blinded to the CAPTURE questionnaire and PEF results. All practitioners and participants will be blinded to the baseline COPD status of the participants (i.e., blinded to spirometry results), except for safety reasons. In this situation, participants and their clinician will be notified if a participant's post-bronchodilator FEV_1 is less than 30% predicted. For all other participants, they and their practitioners will be blinded to research spirometry results. The coordinator should make every effort to conceal the spirometry results from the participants in these latter cases. Study coordinators should also make every effort to conceal the administration of a post-bronchodilator spirometry test from the practice staff so as not to unblind the physicians to abnormal spirometry.

6.3 STUDY INTERVENTION COMPLIANCE

In practices randomized to share the CAPTURE results with the clinician, the goal is to share results with the clinician at the time of the CAPTURE study visit. Providing results at the time of the clinical visit will allow the clinician to act on the CAPTURE results as soon as possible when the participant is in front of the clinician. Based on the workflow at each of the practices, this may not always be possible.

Sharing of the CAPTURE results with the participant's primary care clinician will be tracked by the study coordinator enrolling patients at sites randomized to receive CAPTURE results. The sharing of CAPTURE results will be recorded on the study eCRF form. The eCRF will collect the timing of when the results

were provided to the practitioner - whether the results were provided to the clinician at the time of the enrollment visit prior to the clinician visit with the patient, or were provided at another time.

If results were not shared at the time of the CAPTURE study visit, then the date of sending the CAPTURE results will be recorded on the appropriate eCRF by filling in the date (day/month/year) the results were sent to the clinician through inter–clinic email or other HIPPA-compliant method. The goal is to communicate the results to the clinician within 3 business days. The DCC will monitor review all participants' eCRFs to assure that all those enrolled from practices randomized to CAPTURE results have been shared with clinicians in the specified timeframe.

6.4 CONCOMITANT THERAPY

Practitioners will treat participants using their own clinical judgment. No medications are prohibited. This is not an interventional therapeutic trial.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

In this cluster randomized controlled trial (Aim 3), where practices are the recipients of the intervention and where the interventions are based upon education and access to CAPTURE and PEF results, it is not anticipated that study intervention will be discontinued at the practice level. However, one of the CO-PIs will review safety data, especially SAEs related to baseline spirometry and PEF procedures, to ensure there are no untoward effects of the study on participants.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in Aims 1 and 3 of the study at any time upon request.

Clinician participants in Aim 2 are free to withdraw from participation in the study at any time upon request. If a clinician is no longer working at the participating practice then their involvement in Aim 2 activities will end and no further attempt will be made to include them in the remaining questionnaires or focus groups.

7.3 LOST TO FOLLOW-UP

If a participant selected for longitudinal follow up does not respond to the 12-month questionnaires, coordinators will attempt to contact participants first by the participant’s preferred method of communication, either phone or email. At least three attempts will be made. If no response is obtained, the participant’s alternate contact method will be attempted three times. Phone calls will be made at different times of the day. If there is no response, a registered letter will be sent to the participant. If the participant cannot be reached, the alternate contact will be called and/or emailed. If no response is received, a registered letter will be sent to the alternate contact. If after all of these methods are

employed and no contact with the participant results, the participant will be considered lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 BASELINE ASSESSMENTS AND DATA COLLECTION

Efficacy data will be collected by patient-reported outcomes and medical record review.

For Aim 1, CAPTURE, PEF results, acute respiratory event history and spirometry will be considered efficacy assessments. They are collected at the baseline visit.

CAPTURE. Participants will complete the 5-item *self-administered* questionnaire and measurement of Peak Expiratory Flow (PEF).

Peak Expiratory Flow (PEF). PEF using the Vitalograph® AsmaPlan® mechanical PEF meter with SafeTway® disposable mouthpieces (Vitalograph LTD, UK) will be measured for all participants. Ideally, PEF should be prior to the participant's physician appointment. The participant will perform three PEF tests. All three measurements will be recorded.

Spirometry. Pre-bronchodilator spirometry will be performed for measurement of forced vital capacity (FVC), forced expiratory volume in one-second (FEV_1), and calculation of FEV_1/FVC (using EasyOne® Spirometer, ndd Medical Technologies Inc., Andover, MA). Testing will be performed in accordance with established American Thoracic Society/European Thoracic Society (ATS/ERS) standards.

A Spirometry post-bronchodilator will only be performed if pre-bronchodilator spirometry FEV_1/FVC is less than 0.70 or FEV_1 is less than 80% predicted. Post-bronchodilator spirometry will be performed within 15 to 20 minutes after inhalation of 2 puffs of albuterol 180 mcg HFA using an AeroChamber Plus* Flow-Vu® spacer with one minute between the first and the second inhalation. A separate AeroChamber will be provided for each participant's testing. A standing order for albuterol administration may be used if necessary.

Spirometry is a valid, reproducible means of documenting the presence and severity of airflow limitation. When properly performed with maximum effort and attention to the details of calibration of the instrument, spirometry maneuvers are among the most reproducible of biomedical measures. In the setting of a highly trained, experienced therapist, a coefficient of variation of 2-3% is not unusual. Spirometry will be performed in a standardized manner in accordance with the ATS guidelines, as described in the manual of procedures (MOP). Spirometry is the timed-based measurement of the amount of air that can be forcefully exhaled from the lungs after a full inspiration. In the forced expiratory vital capacity maneuver, a person inhales as big a breath as possible and then blows it out as fast and as long as possible until no more air can leave the lungs. The volume of air leaving the lungs is recorded continuously throughout the maneuver in order to allow calculation of important measures of lung function.

NHANES prediction equations, which are programmed into the Easy On PC spirometers, will be used to calculate the predicted lung function levels. These require the input of age, height, and race/ethnicity

(White, Black, Hispanic). For people of mixed or unknown race the White prediction equations will be used.

PBRN Research Coordinators will be trained and certified in the performance of spirometry testing. Spirometry will be sent for central review for quality control assurance.

Height and weight
Height and weight will be recorded in order to determine appropriate prediction equations for spirometry and possible effect of obesity on spirometry. Height will be recorded and weight will be measured prior to spirometry testing.

Demographic Data Collection
Demographic data including date of birth, gender, ethnicity, race, educational level achieved, daily work schedule, living arrangement and health insurance will be entered into the EDC system.

Contact information including address, phone numbers and email address will be obtained. Alternate contact information will be obtained for two other people, family members not living with the participant or close contacts, who may be knowledgeable about the participant in the event that the participant cannot be contacted for subsequent longitudinal follow-up. Alternate contact information will include name, address, phone numbers and email addresses. All contact information will be stored securely at the clinical site or in a database separate from that developed for the clinical data.

Medical History
Previous medical diagnoses will include comorbidities such as cardiovascular, respiratory and malignant disorders. Influenza vaccination history will also be recorded. This questionnaire will be completed under supervision of the coordinator.

Concomitant Medication Review
Respiratory medications will be recorded at baseline for all participants. This questionnaire will be completed under supervision of the coordinator.

COPD Assessment Test (CAT)
Participants will complete the 8-item *self-administered* questionnaire.

Respiratory symptoms, smoke exposure and exacerbation like events
History of respiratory symptoms and exacerbation like events over the past year as well as smoke exposure (including e-cigarette or equivalent) will be recorded. This questionnaire will be completed under supervision of the coordinator.

Whenever possible, informed consent, eligibility review, CAPTURE Questionnaire and PEF will be performed prior to the participant's clinic appointment, so that CAPTURE results may be provided to the physician at the time of his/her appointment if the patient is cared for in a clinical center randomized to CAPTURE+ education.

Adverse events
Adverse events related to study procedures will be recorded by the coordinator.

8.2 LONGITUDINAL FOLLOW-UP ASSESSMENTS AND DATA COLLECTION

For Aim 3, the follow-up efficacy assessments are collected from the time of baseline to 12 months in selected cohorts (as described in section 4.1). Medical chart abstractions and participant questionnaires are used.

Data collected from medical record include:

All participants undergoing 12-month follow-up as described in section 4.1	Current Smokers Only
Clinical spirometry ordered or administered	Smoking cessation counseling
Referral to specialist for respiratory evaluation/treatment	New prescription for smoking cessation medication
New recorded clinical diagnosis of COPD	Formal smoking cessation program referral/completion
New prescription for respiratory medication (long acting bronchodilator, inhaled steroids, oral anti-inflammatory)	
Exacerbation like event assessment (hospital, ED, minute clinic, antibiotic/steroid prescription/administration)	
Vaccination status	
Formal pulmonary rehabilitation program referral/completion*	

*only collected in relevant participants

Data from clinical visits to be collected at follow-up by telephone, secure web-based server, or mail-based methodologies directly from participants include:

All participants undergoing 12-month follow-up as described in section 4.1	Current Smokers Only
Spirometry	Smoking cessation counseling
New diagnosis of COPD	Smoking cessation medications (including OTC)
Referral to pulmonologist or other respiratory specialist	
Exacerbation like event assessment	
New prescription for respiratory medication (long acting bronchodilator, inhaled steroids, oral anti-inflammatory)	
CAT score	

Attendance of pulmonary rehabilitation*	

*only collected in relevant participants

8.3 AIM 2 ASSESSMENTS AND DATA COLLECTION

Practice study introduction and participation confirmation: After PBRN practice selection, the CAPTURE study Aim 2 lead together with the local PBRN Aim 2 coordinator conduct a 15-minute participation confirmation and introduction phone call with the key PBRN contact at each of the two selected practices. The study specifics and timeline are reviewed. After practice participation is confirmed, the on-site practice assessment date is scheduled. Informed consent forms for clinical staff are mailed to each confirmed practice. To reduce practice burden, completed clinical staff informed consent forms (up to 15 clinical staff per practice) can be returned by mail to the University of Michigan School of Public Health office, addressed to Dr. Randall Brown, or saved for completion and picked up at the on-site practice assessment site visit. Following the confirmation phone call, the PBRN Aim 2 coordinator completes a short (15 minute) qualitative questionnaire detailing the selected and confirmed practice demographics and PBRN parameter of practice choice for each of the two practices. The completed PBRN Practice Selection Questionnaire is returned to the Aim 2 data team and stored securely.

On-site Practice Assessment (OSPA): The OSPA is an in-person on-site practice workflow assessment. It includes 2 practice clinicians per practice choice, the PBRN Aim 2 coordinator (if available), the CAPTURE study Aim 2 lead and the CAPTURE Aim 2 research specialist (if the PBRN Aim 2 coordinator is not present). The objective of the visit is to detail specifics of practice workflow, practice physical characteristics, staff roles, clinical information gathering patterns for respiratory patients, electronic health record communication, continuing education structure, and quality improvement structure. The assessment takes place in three parts; the pre-observation practice overview (conducted with the 2 practice clinicians – 60 minutes), the ½ day practice workflow observation (observation by one member of the Aim 2 research team of common and testing areas used for the respiratory patient). There is no patient engagement and no collection of patient-specific identification or health information), and the post-observation practice summary (conducted with the same 2 practice clinicians – 30 minutes).

The 3 OSPA assessment tools are:

i) The Pre-workflow Observation Practice Assessment Review Questionnaire
ii) Respiratory Workflow Assessment Review
iii) The Post-workflow Observation Practice Assessment Review Questionnaire

Also at the OSPA, informed consent is obtained from all remaining participating staff (up to 15 clinical staff per practice) by the CAPTURE Aim 2 team and returned to the Aim 2 data team for secure storage.

Clinical Staff Questionnaires (Baseline/6/12 months). Written or on-line questionnaires are provided to participating and consented staff personnel at two practice levels -- Non-Prescribing clinical (also known as “support”) staff and Prescribing (PR) clinical (also known as “provider”) staff.

Non-Prescribing (NPR) clinical staff are clinical practice personnel involved in clinical workflow (including registered nurses, licensed practical nurses, medical assistants, medical assistants and receptionists), yet not having the role to make final and official medical diagnostic and management disposition plan decisions for and with patients. Prescribing (PR) clinical staff are prescribing clinical practice personnel involved in clinical workflow (including doctors, nurse practitioners, and physician assistants) who may

independently make final medical diagnostic and management disposition plan decisions for and with patients.

Questionnaire items explore clinician demographics, including past education, duration of current employment and currently held clinical position. COPD knowledge, attitudes, beliefs, practice patterns and self-efficacy regarding COPD diagnosis, management, spirometry testing and interpretation, practice workflow and communication in the clinical primary practice care of adult patients with respiratory disease. Additional questions include preferred continuing education method and clinical staff quality improvement modalities for respiratory disease management. Specific examples of past practice chronic disease diagnostic changes and the individual and practice-wide levers of success and challenge associated with those changes are explored.

Each of the 3 (baseline, 6-month and 12-month) questionnaires are completed within 30 minutes. No identifying patient data is collected. Online questionnaires are collected and secured by the CAPTURE DCC and Aim 2 research team. The participants who complete written questionnaires (per their preference) mail completed questionnaires via pre-addressed stamped envelope to the CAPTURE DCC and Aim 2 research team.

Patient Opinion Surveys:
200 patient participants, 40 from each PBRN, are recruited as a sub-sample from Aim 1 practices. Patient participants fulfill all inclusion and exclusion criteria and receive informed consent for survey participation as part of aim 1.

Eligible participants complete a written one-time 5 to 10 minute CAPTURE opinion survey. Patient survey data is collected by Aim 1 research coordinators and is processed with Aim 1 baseline patient data. Patients receive a $10 gift card for completion of the survey Aim 2 patient participation ends at the completion on the lone opinion survey.

Participants who prefer to complete the 5 to 10-minute survey online via Qualtrics will be sent a secure, Qualtrics link via email. The Qualtrics survey will include a brief, introductory screen affirming consent, describing the survey and instructions about participation. Once the survey is complete, participants will see a screen with instructions about how to obtain their $10 gift card and how to contact study staff with questions regarding the survey.

Modular online COPD education. Access to free, COPD on-line, continuing education is provided for all clinical staff at each practice. Each module will take 20 minutes or less. Modular components of and access to COPD education is described in the protocol. Aim 2 clinician participant access and completion of COPD education modules is assessed by clinician questionnaires and focus group item response over 12 months (between months 2 and 14 of Aim 2 timeline).

COPD in Primary Care/CAPTURE Introduction Focus Groups:
Two 45 to 60-minute focus group discussions occur at each Aim 2 practice. Focus groups are informed by practice demographics, practice assessment data – including respiratory workflow, baseline clinical staff questionnaire data regarding respiratory knowledge, attitudes, beliefs and practice preference for the diagnosis and care of adult patients with respiratory disease as well as patient opinion from CAPTURE surveys and past CAPTURE study (46, 47). Focus group candidate themes and prompts are developed for non-prescribing clinical staff (NPR) and prescribing clinical staff (PR) and are presented at separate on-site focus group sessions to allow more detailed discussion of role responsibility in the

context of daily practice workflow, generating a more abundant qualitative data sample. Separation of and PR clinical staffing implementation themes into two focus groups also limits potential for hierarchical work-related discussion suppression described in other short duration focus group studies (48-52).

The focus group moderator introduces the CAPTURE tool utilizing CAPTURE education components described in Section 6.1.1. The focus group moderator follows RE-AIM prompts for CAPTURE implementation planning discussion throughout the focus group. Targeted COPD self-efficacy limitation themes from questionnaire data (including awareness and/or use of validated respiratory assessment questionnaires, spirometry, COPD guidelines, inhaled medication patient education, oxygen therapy, smoking cessation education, vaccination recommendation, pulmonology specialty care and pulmonary rehabilitation referral) are explored. Questions will probe clinicians to identify and explain levers that may maximize uptake of CAPTURE use in their practices as well as potential barriers to implementation. The Aim 2 research team will record each focus group using audio and written note-taking that will allow an abridged yet detailed tape-based micro-interlocutor analysis of focus group emergent themes, questions, answers and interactions. Key themes informing consensus discussion, program modifications and key elements of the CAPTURE RE-AIM implementation dimensions will be identified. Audio-recordings will be professionally transcribed and codes will be generated for the interview topics and key research questions. Reviewing the transcripts line-by-line, all substantive information will be assigned a priori codes as relevant for CAPTURE RE-AIM implementation planning, COPD diagnosis and CAPTURE intra-office clinical communication and COPD/CAPTURE education preference assessment. Additional codes will be developed for sub-themes and emergent themes.

Development of Practice-Based CAPTURE Implementation PBL Cases:
From analyses of the 2 NPR and 2 PR CAPTURE Introduction focus groups per PBRN, baseline clinical staff questionnaire data, online CAPTURE opinion surveys, and on-site practice assessments, 1 primary care practice CAPTURE implementation case per PBRN (total implementation cases = 5) is created by the Aim 2 research team. Given local knowledge of chronic disease management quality improvement history, effort, challenge and successes, each PBRN's participation in case creation will be instrumental. The Aim 2 research team will lead case creation using evidence-based problem based learning (PBL) techniques (53-57). The Center for Research on Learning and Teaching (CRLT) at the University of Michigan will serve as research reference for PBL case development qualification (58). Each local PBRN PBL case will be distributed to the Aim 2 clinical staff at the 2 participating PBRN practices 2 weeks prior to the CAPTURE Implementation focus groups, giving Aim 2 participants an opportunity to read the case introductions prior to the focus group session. Also, each practice will receive one additional non-PBRN case for focus group discussion as selected by the Aim 2 research team. Therein, each of the 5 CAPTURE implementation PBL cases will receive 2 comprehensive focus group reviews (see below).

CAPTURE Implementation PBL Case Presentation Focus Groups:
Each practice participates in a final pooled (NPRs and PRs together) on-site focus group. Two CAPTURE implementation cases (described above) are discussed at each focus group. The focus will explore, discuss, glean and create optimal 1) CAPTURE implementation, 2) CAPTURE clinical communication, 3) CAPTURE/COPD education and 4) CAPTURE primary care quality improvement recommendations pooled from all clinical practice levels for each of the 2 presented cases.

The Aim 2 research team will record each focus group using audio and written note-taking that will allow an abridged yet detailed tape-based micro-interlocutor analysis of focus group emergent themes, questions, answers and interactions. Key themes informing consensus discussion, program

modifications and key elements of the CAPTURE RE-AIM implementation dimensions will be identified. Audio-recordings will be professionally transcribed and codes will be generated for the interview topics and key research questions. Reviewing the transcripts line-by-line, all substantive information will be assigned a priori codes as relevant for CAPTURE RE-AIM implementation planning, COPD diagnosis, CAPTURE intra-office clinical communication, and COPD and CAPTURE education preference, and COPD diagnosis quality improvement assessment. Additional codes will be developed for sub-themes and emergent themes.

8.4 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.4.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.4.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.4.2.1 SEVERITY OF EVENT

The following guidelines will be used to describe severity of AEs.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.4.2.2 RELATIONSHIP TO STUDY INTERVENTION

All AEs must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.

- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.
- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the study intervention). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.4.2.3 EXPECTEDNESS

The Principal Investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.4.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

Adverse events (AE)s that occur during the baseline visit will be recorded.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed.

8.4.4 ADVERSE EVENT REPORTING

All AEs that occur at baseline visit will be recorded in the case report form and reported to the DCC. We anticipate few adverse events due to the non-invasive nature of the study procedures. Participants will only be enrolled if they meet the study eligibility criteria, including assessment for contraindications for spirometry. Targeted safety questions will be asked of all patient participants prior to albuterol to exclude those with a previous adverse event with the medication and others at high risk due to cardiac abnormalities.

8.4.5 SERIOUS ADVERSE EVENT REPORTING

SAEs will be reported to the IRB at the institution where the event occurred and the University of Michigan IRB will be notified of any serious adverse experience within 7 calendar days of occurrence. These will be reported to the DSMB.

Follow-up of serious adverse events

All SAEs will be followed up until resolution or permanent outcome of the event. All follow-up information will be included in the case report form. The DSMB will make recommendations to ensure data integrity and the safety of study participants.

8.5 UNANTICIPATED PROBLEMS

8.5.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.5.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing IRB and to the DCC. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the DCC within 7 calendar days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC within 14 calendar days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within one month of the IRB's receipt of the report of the problem from the investigator.

8.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a DSMB (physicians with the appropriate expertise, including non-involved pulmonologists, primary care physicians, and independent statisticians with clinical experience). Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the Principal Investigators.

9 STATISTICAL AND ANALYTICAL PLANS

9.1 SAMPLE SIZE AND POWER

9.1.1 PRIMARY OBJECTIVES

Define the sensitivity and specificity of CAPTURE for identifying previously undiagnosed patients with clinically significant COPD in a broad range of primary care settings. We will also explore clinical practice implementation approaches to and acceptance of CAPTURE case finding for clinically significant COPD in a range of primary care practices. Further, we will define the impact of CAPTURE information provided to clinicians in identifying and managing patients with respiratory symptoms (CAPTURE+) across a broad range of primary care settings.

9.1.1.1 SENSITIVITY AND SPECIFICITY OF THE CAPTURE TOOL

Primary Hypothesis 1. *The CAPTURE tool will exhibit excellent sensitivity and specificity in diagnosing clinically significant COPD as defined by post-bronchodilator $FEV_1/FVC < 0.70$ in addition to either >1 exacerbation-like event (ECOPD) within the past 12 months or an $FEV_1 < 60\%$ predicted.* Approximately 5000 patients will be enrolled in the study with the expectation that 300-800 of these will have previously undiagnosed clinically significant COPD, identified through research spirometry and documentation of prior respiratory events. Amongst cases, we will calculate the proportion of individuals who are at high risk for clinically significant COPD based on CAPTURE (sensitivity). Similarly, amongst non-cases, we will calculate the proportion of individuals not classified as having clinically significant COPD based on CAPTURE (specificity). Corresponding 95% confidence intervals will be calculated.

Based on our preliminary data drawn from a research setting, we noted 89.7% sensitivity and 93.1% specificity for CAPTURE. Table 9-1 shows the range of sensitivity and specificity 95% confidence interval widths that would result if the true sensitivity or specificity is 85%, 90% or 95% across a range of sample sizes. For instance, if we find 500 individuals with confirmed clinically significant COPD and CAPTURE has 90% sensitivity, then the 95% confidence interval for sensitivity would be 90% ± 2.6%. Similarly, if 4,000 individuals are confirmed to have no evidence of clinically significant COPD and CAPTURE has 90% specificity, then the 95% confidence interval for specificity would be 90% ± 0.9%.

Table 9-1 Projected Confidence Interval Widths for Various Sensitivity/Specificity Percentages (Columns) and Sample Sizes (Rows).

	Sensitivity or Specificity		
Sample Size	**85%**	**90%**	**95%**
5000	± 1.0%	± 0.8%	± 0.6%
4000	± 1.1%	± 0.9%	± 0.7%
1000	± 2.2%	± 1.9%	± 1.4%
500	± 3.1%	± 2.6%	± 1.9%
250	± 4.4%	± 3.7%	± 2.7%
100	± 7.0%	± 5.9%	± 4.3%
50	± 9.9%	± 8.3%	± 6.0%

9.1.1.2 ADOPTION AND IMPLEMENTATION OF THE CAPTURE TOOL IN PRIMARY CARE PRACTICE

Primary Hypothesis 2: *A COPD case finding methodology using a validated one-page, five-item questionnaire with selective PEF measurement (CAPTURE) can be incorporated into the clinical practice patterns, clinical workflow, communication and practice-based quality improvement paradigms of a variety of primary care clinical settings.*

Aim 2 is a qualitative study to determine the efficacy of workflow integration of the CAPTURE tool. Statistical analysis of the clinician questionnaire will involve simple sums of each item and reviewing answers across practices and region. Standard frequencies for questions will be developed to examine patterns in responses.

The clinician focus groups will be conducted on-site at each practice at a time convenient for the participating clinicians. The number of prescribing and non-prescribing clinicians will equal 15 per practice and is based on interest with a maximum of 8 prescribing clinicians/practice. The sample size will follow a basic qualitative sampling standard of interviewing to redundancy or saturation. The number of clinicians to be interviewed (up to n=15 in each practice) is estimated based on achieving concept saturation. Reflecting regional primary care practice norms and to bolster concept saturation, PBRN Aim 2 coordinator focus group discussion participation is encouraged for very small practices where the participating prescribing and non-prescribing clinician total is less than or equal to 4. For all practice focus groups questions will explore the described Aim 2 CAPTURE RE-AIM concepts, barriers to implementation of the CAPTURE tool at other practice sites, standard processes for COPD and respiratory care diagnosis and management for each clinical role within the practice, and perception of quality improvement methods at each practice. Clinician focus groups are conducted on-site at each of the 10 practices.

Transcripts of clinician focus groups will all be digital and entered into a qualitative data analysis program, NVivo for Mac. This program allows for an investigation of the salience, patterning, and contexts of key discourse items. Grounded theory methods will be used to identify and label recurrent themes and concepts within textual materials. Texts will be examined line-by-line, key phrases assigned tentative category labels, and coded passages grouped under the themes of feasibility, barrier and utility. The analyses will look for “traces” in dialogue, including repetitions, key words, evaluation statements, and metaphors. Change in salience, patterning, or content of key themes will provide further empirical evidence regarding the efficacy of our program’s efforts to impact community norms and behaviors. An audit trail will be maintained to document the position of text material from which codes and themes are developed. We will use word/code counts of repetitive themes and concepts to

indicate patterns. By allowing for open-ended responses, the narratives and notes will allow us to capture significant changes in participants' attitudes or behaviors. Codes and themes will be discussed iteratively with the research team members to hone definitions and assure consistency of interpretation. We will establish a coding dictionary and all interviews will be coded using the complete set of themes. Two independent coders will code each document to assure inter-coder reliability. Preliminary results will be shared with our Aim 2 research team and will inform the development of the case studies for the latter part of the project.

9.1.1.3 PRACTICE BEHAVIOR IN SITES WITH VERSUS WITHOUT CAPTURE EDUCATION AND PATIENT LEVEL CAPTURE DATA PROVIDED

Primary Hypothesis 3: *Sites where basic COPD and CAPTURE education are provided to clinicians, along with patient level CAPTURE data, will have a higher probability than control sites (i.e., those receiving only basic COPD education) of meeting the composite endpoint in their CAPTURE+ patients within 12 months of baseline.* From chart review, the composite endpoint is met if one of the following is recorded: (1) referral for clinical spirometry testing, 2) new clinical diagnosis of COPD, 3) newly prescribed respiratory medication (long acting bronchodilator or anti-inflammatory for respiratory condition), or 4) referral to a specialist for respiratory evaluation/ treatment.

The study will enroll 50 CAPTURE practices and 50 control practices; each practice will enroll 50 patients (for a total of 5,000 patients). We project that within each practice, there will be at least 5 patients previously undiagnosed with COPD who have a CAPTURE+ screening result. The primary analysis will be to compare the average proportion of CAPTURE+ patients per practice that meet the composite endpoint in the two intervention arms. For power and sample sizes computations, this is a cluster randomized trial of n=50 clusters (practices) per intervention arm with 5 CAPTURE+ patients per cluster (practice). The primary power calculation is based on comparing the average cluster sample proportion (average proportion of CAPTURE+ patients per practice meeting composite endpoint) between intervention arms. Table 9-2 displays power for a two-sample test comparing average cluster sample proportions, accounting for possible intra-cluster correlation coefficient (ICC) values of 0.05, 0.10 and 0.15 that are typically seen in cluster randomized trials of behavioral interventions (https://www.abdn.ac.uk/hsru/research/research-tools/study-design/). These calculations assume a type I error of 5% and that the control arm meets the composite endpoint in 5% of CAPTURE+ patients and the CAPTURE arm meets the composite endpoint in higher percentages (columns of Table 9-2). There will be variability in the actual number of CAPTURE+ patients per practice. It is standard practice to inflate the number of needed clusters by 12% to account for this extra source of variability. Therefore, our power calculations are based on 44 clusters per intervention arm.

Table 9-2. Overall power to detect a difference in rate of meeting primary endpoint in CAPTURE group (50 practices/clusters) vs usual care (50 practices/clusters), assuming 5% performance rate in usual care; 50 patients total / practice; assuming 10% prevalence gives 5 CAPTURE+/practice

Improvement over usual care	+7.5%	+10%	+15%	+25%	+50%
ICC=0.05	0.72	0.89	0.99	>0.99	>0.99
ICC=0.10	0.65	0.84	0.98	>0.99	>0.99
ICC=0.15	0.59	0.79	0.97	>0.99	>0.99

9.1.2 SECONDARY OBJECTIVES

9.1.2.1 SENSITIVITY AND SPECIFICITY IN PREDEFINED SUBGROUPS

We will also examine several subgroups of interest that are key to addressing our overall goal of defining the value of CAPTURE across a broad range on individuals. These will include sex, ethnic groups, rural and urban location, and educational level, among individuals with clinically significant COPD, spirometrically defined COPD and individuals with "mild" COPD as defined in this protocol. We have specifically chosen clinical sites with a diverse gender, racial and ethnic mix, and rural and urban mix with the expected prevalence of clinically significant COPD cases and controls by subgroup outlined in

Table 9-3. Projected numbers of clinically significant COPD cases and non-cases we expect by subgroup of interest assuming prevalence of obstructed individuals is between 6-16%. (*Non-Hispanic) This table assumes prevalence of non-clinically significant COPD similar to clinically significant COPD (not included in this table).

	Total	**Men (50%)**	**Women (50%)**	**White* (62%)**	**Black* (15%)**	**Hispanic (18%)**	**Rural (46%)**	**Urban (54%)**	**Ever-Smokers (40%)**	**Never-smokers (60%)**
Projected # confirmed clinically significant COPD by subgroup	300-800	150-400	150-400	186-496	45-120	54-144	138-368	162-432	120-320	180-480
Projected # confirmed no COPD by subgroup	3,400-4,400	1,700-2,200	1,700-2,200	2,108-2,728	510-660	612-792	1,564-2,024	1,836-2,376	1,360-1,760	2,040-2,640

Table 9-3, again with corresponding sensitivity and specificity confidence interval widths in Table 9-1. For example, if sensitivity of CAPTURE in Hispanic individuals is 90%, then a sample size of approximately 100 would give a confidence interval of 90% ± 5.9%. We believe that with an overall sample size of 5,000 recruited patients we will have adequately sized subgroups to assess the operating characteristics of CAPTURE in the subgroups of interest.

9.1.2.2 FURTHER ANALYSIS OF ASSOCIATIONS BETWEEN MEETING COMPOSITE ENDPOINT AND INDIVIDUAL AND PRACTICE LEVEL OUTCOMES

Secondary analyses for evaluating practice behavior are exploratory, and therefore not included in a formal power and sample size analysis. These analyses are described further in Section 9.3.2.

9.2 POPULATIONS FOR ANALYSES

Aim 1

Population used for sensitivity calculations are all enrolled patients with clinically significant COPD as defined by post-bronchodilator $FEV_1/FVC < 0.70$ in addition to either >1 exacerbation-like event (ECOPD) within the past 12 months or an $FEV_1 < 60\%$ predicted.

Population used for specificity calculations are all enrolled patients with no demonstrable COPD as determined by research spirometry conducted upon study entry, $FEV_1/FVC \geq 0.70$.

Aim 2
Clinician participants: enrolled clinicians are from 2 primary care practices in each of five US PBRN regions that do not engage in Aims 1 or 3 investigation. Eligible clinicians include primary care providers and primary care clinical non-provider support personnel.

Patient participants: enrolled as a sub-sample of Aim 1 participants at baseline. One CAPTURE patient opinion survey is administered at baseline.. Aim 2 participants fulfill the inclusion, exclusion and population analysis criteria of aim 1.

Aim 3
Populations used in 2-sample comparisons of the average proportion of CAPTURE+ patients per practice that meet the composite endpoint in the two intervention arms will be based on randomization group (intent-to-treat analysis).

9.3 STATISTICAL ANALYSES

9.3.1 SENSITIVITY AND SPECIFICITY (AIM 1)

SAS version 9.4 PROC LOGISTIC will be used for computations. Calculations of sensitivity and specificity along with their corresponding 95% confidence intervals assume independent Bernoulli outcomes for each patient. Clinically significant COPD+ and COPD- populations selected for these analyses are described in Section 9.2. CAPTURE+ patients are those with a baseline CAPTURE score $\geq$ 5 or with a baseline CAPTURE score of 2, 3, or 4 with a low PEF (defined as <350 L/min for males, <250 L/min for females).

In addition to the primary sensitivity/specificity calculations, sensitivity/specificity and associated 95% confidence intervals will be calculated in predefined subgroups: sex, ethnic subgroups, rural and urban location, and educational status. As part of secondary analyses, receiver operating characteristic (ROC) curve analyses will evaluate different thresholds of the CAPTURE questionnaire score in defining a positive clinically significant + COPD screen, separately and in combination with low PEF characteristics, and the 12 additional CAPTURE questions. As part of this exploration, participant and practice level data as well as interactions with the CAPTURE tool results, will be considered as predictors of clinically significant COPD using multivariable logistic regression. Corresponding positive and negative predictive values will be estimated across the range of prevalence percentages seen at the enrolled practices. Model selection in secondary logistic regression analyses will be based on forward selection using maximum likelihood theory, with entry into the model dependent on statistical significance at the 0.05 level. Exploration of this nature has the potential to produce artificially high operating characteristics (area under the curve [AUC], sensitivity and specificity) based on overfitting the data. SAS 9.4 PROC LOGISTIC includes a cross-validation approach to ROC curve analysis [ROCOPTIONS(CROSSVALIDATE)] that we will use when assessing operating characteristics for any new prediction tool that goes beyond the original CAPTURE metric considered in primary analyses. Once a final logistic regression model has been selected, classification thresholds for predicting clinically significant COPD will be described by the investigative team from the cross-validated ROC curve. Calibration plots of observed versus predicted sensitivity, and observed versus predicted specificity, will be conducted across previously specified subgroups of interest (sex, ethnic subgroups, rural and urban location, and educational status).

All of the above analyses will be applied to these additional populations: (1) patients with spirometrically defined COPD and (2) patients with mild COPD.

9.3.2 PRACTICE BEHAVIOR (AIM 3)

The primary analysis will be to compare the average cluster sample proportion (average proportion of CAPTURE+ patients per practice meeting composite endpoint) between intervention arms. Practices that do not identify any CAPTURE + subjects will not contribute to the primary analysis, although this is felt to be an unlikely occurrence. A two-sample test comparing average cluster sample proportions will be used that explicitly takes into account correlation between individuals treated within the same practice. A two-sided p-value < 0.05 will be considered statistically significant. This analysis corresponds to a generalized estimating equation (GEE) regression analysis with (1) individual-level binary composite outcome data, (2) CAPTURE intervention group as a covariate, (3) practice id used to identify correlated outcomes, (4) exchangeable correlation matrix that assumes similar correlation between all composite outcome results for patients within the same practice, and (5) a logistic link function. The primary analysis would then correspond to a test for the CAPTURE intervention group parameter. There are no planned interim analyses for the primary endpoint, the rationale being that this is not a pharmaceutical or device trial that would benefit from standard stopping rules for efficacy. A DSMB will be monitoring the study for safety and study integrity.

Secondary analyses on meeting the composite outcome for participants who are CAPTURE+ will employ the GEE analysis framework with individual and practice level predictors in addition to the CAPTURE intervention group. Interactions will be assessed. We will also use the GEE framework to study and describe each of the individual components of the composite outcome as they relate to individual and practice level outcomes. In the subset of smoking patients, we will use GEE regression analysis to study additional binary outcomes, such as incidence of physician referral to a formal smoking cessation program, prescribed smoking cessation medication in participants who are smokers, and referral to pulmonary rehabilitation program.

In participants who are CAPTURE+, change in CAT score will be analyzed using mixed models with a random effect for practice. The average cluster sample proportion of patients who experience exacerbations will be compared between intervention groups using methodology similar to that used for the primary endpoint. Survival analysis allowing for correlation of endpoints within cluster (practice) will be used to compare mortality between intervention groups and perform multivariable analysis. We will explore differences between intervention groups in the average cluster sample rate of hospitalizations again using GEE. All additional secondary analyses will also be applied to patients with clinically significant and spirometrically defined COPD. Practices that do not have any clinically significant COPD or spirometrically defined COPD will not contribute to analyses of these secondary endpoints, respectively.

Model selection in GEE secondary analyses will be based on statistical significance at the 0.05 level using robust sandwich estimation of variability within clusters. Model fit will be checked by comparing observed versus predicted values within predefined subgroups of interest (sex, ethnic subgroups, rural and urban location, and educational status).

9.3.3 CAPTURE IMPLEMENTATION RECOMMENDATIONS (AIM 2)

Site-specific practice information, clinician knowledge and behavioral questionnaires, as well as patient opinion survey responses are recorded primarily to populate focus group themes for qualitative analysis. Secondary analyses of individual clinician and patient response using frequencies, means, ranking and dispersion by clinician type, practice and PBRN is accomplished using SAS version 9.4. Correlation with implementation recommendation is determined using GEE variance models.

Audio transcripts of clinician focus groups will all be digital and entered into a qualitative data analysis program, NVivo for Mac. This program allows for an investigation of the salience, patterning, and contexts of key discourse items. Grounded theory methods will be used to identify and label recurrent themes and concepts within textual materials. Texts will be examined line-by-line, key phrases assigned tentative category labels, and coded passages grouped under the themes of feasibility, barrier and utility. The analyses will look for "traces" in dialogue, including repetitions, key words, evaluation statements, and metaphors. Micro-interlocutor analysis of focus group emergent themes, questions, answers and interactions will account for individual gaps in focus group participation. Change in salience, patterning, or content of key themes will provide further empirical evidence regarding the efficacy of our program's efforts to impact clinician community norms and behaviors. An audit trail will be maintained to document the position of text material from which codes and themes are developed. We will use word/code counts of repetitive themes and concepts to indicate patterns. By allowing for open-ended responses, the narratives and notes will allow us to capture significant changes in participants' attitudes or behaviors. Codes and themes will be discussed iteratively with the research team members to hone definitions and assure consistency of interpretation. We will establish a coding dictionary and all interviews will be coded using the complete set of themes. Reviewing the transcripts line-by-line, all substantive information will be assigned a priori codes as relevant for CAPTURE RE-AIM implementation planning, COPD diagnosis, CAPTURE intra-office clinical communication, and COPD and CAPTURE education preference, and COPD diagnosis quality improvement assessment. Two independent coders will code each document to assure inter-coder reliability. Preliminary results will be shared with the Aim 2 data team and will inform the development of the CAPTURE case studies and primary care practice implementation recommendations.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise.

A HIPPA waiver will be submitted to each IRB to prescreen clinic schedules and patient panels for recruitment purposes. The PHI reviewed by the coordinator in the electronic health record (EHR) will

include age, date of birth, diagnosis of COPD, respiratory medications, and other medical conditions that are contraindicated for spirometry. A waiver of written consent will be submitted to each IRB to pre-screen potential participants for eligibility criteria prior to informed consent. The pre-screening will either be by telephone prior to an upcoming clinic visit, or in person at the time of the visit. An IRB-approved telephone/in-person screening script will be submitted to each IRB.

A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. Participants will additionally have the opportunity to review the study and informed consent prior to providing consent for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

All PBRN research coordinators and other clinical investigators will be certified by their local IRB in informed consent and human studies research.

Clinicians interested in participating in the qualitative, minimal risk study for Aim 2, will be given the opportunity to review the consent form below and sign it. This can happen once their practice agrees to participate in Aim 2 activities or during the first in person site visit with Dr. Brown.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

When a study is prematurely terminated, refer to Section 7, Study Intervention Discontinuation and Participant Discontinuation/Withdrawal, for handling of enrolled study participants.

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. In addition, it may be transmitted and stored at the DCC in a database separate from the clinical database (used for statistical analysis and scientific reporting) and with study coordinator access to aid in contacting participants at the 12-month follow-up. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the DCC. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by DCC research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the DCC.

For the online Aim 2 patient opinion survey, Qualtrics is used. Qualtrics is a secure University of Michigan (U-M) contracted-for cloud service that can be used to maintain or share the university's sensitive unregulated data, as well as some kinds of sensitive regulated data.

U-M's agreement with Qualtrics includes a Business Associate Agreement. This means individuals may use this service to maintain Protected Health Information (PHI) regulated by HIPAA. Complying with HIPAA's requirements is a *shared responsibility*. Users sharing and storing PHI in Qualtrics are responsible for complying with HIPAA safeguards, including:

- Using and disclosing only the minimum necessary PHI for the intended purpose.
- Obtaining all required authorizations for using and disclosing PHI.
- Ensuring that PHI is seen only by those who are authorized to see it.
- Obtaining all necessary data-sharing agreements and Business Associate Agreements for using and disclosing PHI.
- Following any additional steps required by your unit to comply with HIPAA.

Sensitive data, including PHI, may be collected and stored in Qualtrics for non-clinical, academic purposes only (for example, research and hospital quality improvement initiatives). Qualtrics cannot be used for any clinical applications, no matter the sensitivity level of the data

11 STUDY ADMINISTRATION AND OVERSIGHT

11.1 STUDY LEADERSHIP

11.1.1 PRINCIPAL INVESTIGATORS

The principal investigators are responsible for providing direction and oversight of all study activities.

Principal Investigators	
Fernando Martinez, MD, MS	MeiLan Han, MD, MS
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11.1.2 PRACTICE BASED RESEARCH NETWORKS (PBRN)

Patient participants and staff participants will be recruited from the PBRNs.

PBRN	**Location**	**Director**
Carolinas HealthCare System	North Carolina	Hazel Tapp, PhD
LA Net Community Health Network	Southern California	Lyndee Knox, PhD
High Plains Network	Colorado	Linda Zittleman, MD
Duke Primary Care Research Consortium	North Carolina	Rowena Dolor, MD
Oregon Rural Practice-Based Research Network	Oregon	Lyle J. Fagnan, MD

11.1.3 SPIROMETRY CORE

Led by Dr. David Mannino, the Spirometry Core will maintain quality of the research spirometry that is integral to the success of the study. The work will be done in conjunction with a research assistant. This includes the following functions:

1. Development of the operation manual for the sites
2. Training of the site staff in the use of the spirometry equipment (including travel to training and sites as needed)
3. Certification of staff in spirometry
4. Assessing staff adherence to protocols for the use of bronchodilators
5. Grading and adjudication of spirometry
6. Importing processed spirometry into spreadsheets
7. Uploading processed data to data coordinating center
8. Working with data coordinating center to verify and clean data

In addition, Dr. Mannino will be a critical part of the team that evaluates the data both from spirometry and the other components of this study (the CAPTURE tool, quality of life measures, etc.), in addition to being part of the writing team that analyzes data and disseminates the findings from this study.

11.1.4 PBRN ROLES AND RESPONSIBILITIES

PBRNs will have the following roles and responsibilities:

CAPTURE Study Preparation

1. Review protocol to help identify operational details
2. Submit final protocol and informed consents to all IRBs necessary for the participating sites
3. Complete and maintain current human participants training for all main study personnel as required by the IRB
4. Attendance of PBRN coordinators at in person training, spirometry certification for all coordinators, update of spirometry quality assessments and training
5. Identify and recruit local practice sites to participate in the study

CAPTURE Study Implementation

1. Facilitate COPD and when appropriate CAPTURE education
2. Maintain regular contact with participating PBRN practice sites during their period of patient enrollment
3. Supervise and send PBRN Research Coordinators to enroll patients, perform study visits including completion of the CAPTURE questions, peak flow, spirometry, and collect other information on all enrolled patients
4. Complete pre bronchodilator spirometry on all participants
5. Complete post bronchodilator spirometry on participants with abnormal pre-bronchodilator spirometry as defined by study algorithm (e.g. those with pre bronchodilator results consistent with obstruction)
6. Facilitate completion of data entry to the data coordinating center
7. Follow up by research coordinator for patients failing to respond to the follow up questionnaires
8. Collect practice outcome data related to enrolled patients at close of study from either electronic medical records or if practice does not have EMR, by manual chart review

11.1.5 IMPLEMENTATION CORE

Dr. Randall Brown will lead the qualitative Aim 2 activities which assess the implementation strategy and acceptance recommendations for CAPTURE use in primary care practice. His team includes an Aim 2 project manager and dedicated research assistant. Led by Dr. Brown the Aim 2 team coordinates with PBRNs and their selected Aim 2 practices and will conduct qualitative site visits and focus groups in addition to administering clinical practice behavioral questionnaires. Drs. Barbara Yawn, Barry Make, Bruce Bender and Julia Houfek will contribute to the development of the web based educational modules and the qualitative efforts on this project.

11.1.6 DATA COORDINATING CENTER (DCC)

Dr. Cathie Spino directs the DCC, housed at the University of Michigan within the Statistical Analysis of Biomedical & Educational Research (SABER) Unit of the Department of Biostatistics in the School of Public Health. The DCC staff will include a Database programmer, Data manager, Senior Unblinded Statistician, Statistical Analyst, Project Manager, Clinical Monitor, Web Programmer/Designer, and a Research Administrator. In addition, the blinded senior statistician, Dr. Susan Murray, is located at the University of Michigan. The DCC plays a pivotal role in the design, implementation, execution and administration of the study. The DCC will be responsible for randomization, eCRFs and online reporting systems, preparation of the manual of operations for data entry, addressing questions regarding entry and analysis, monitoring recruitment, follow-up and adherence to protocol, and scheduling and arranging meetings of the Executive Committee, Steering Committee, and Medical Monitor. The DCC will prepare all of the routine study reports for the Executive Committee, Operations Committee, and Medical Monitor. The DCC will interact with all of the Cores and other Committees, as needed. The DCC will compile data tables and listing for DSMB reports.

11.1.7 CLINICAL COORDINATING CENTER

The Clinical Coordinating Center (CCC) will be led by Principal Investigators Fernando Martinez, MD, MS at Weill Cornell Medicine, and MeiLan Han, MD, MS at the University of Michigan. Dr. Martinez will be responsible for overall study oversight as well as fiscal management of the overall project and capitation payments to sites for work performed. He will also be responsible for communication with NIH and submission of annual reports. Dr. Han will work with the Data Coordinating Center to oversee clinical trial enrollment and, along with her statistical team, be responsible for coordinating statistical analysis. The process for making decisions on scientific direction and allocation of resources will be made by both Drs. Martinez and Han, with input from the rest of the investigative team as needed.

Additional Clinical Coordinating Center (CCC) responsibilities:

- Establish subcontracts with enrolling sites, central laboratories, imaging service providers, and others as appropriate
- Protocol development and scientific design oversight
- Statistical analysis
- Participating study site selection
- Review of serious adverse events and unanticipated problems involving risk to participants or others, reporting to participating centers and regulatory reporting
- Prepare and maintain Clinical Coordinating Center IRB submissions
- Analyze and present data to DSMB

Clinical Coordinating Center Personnel

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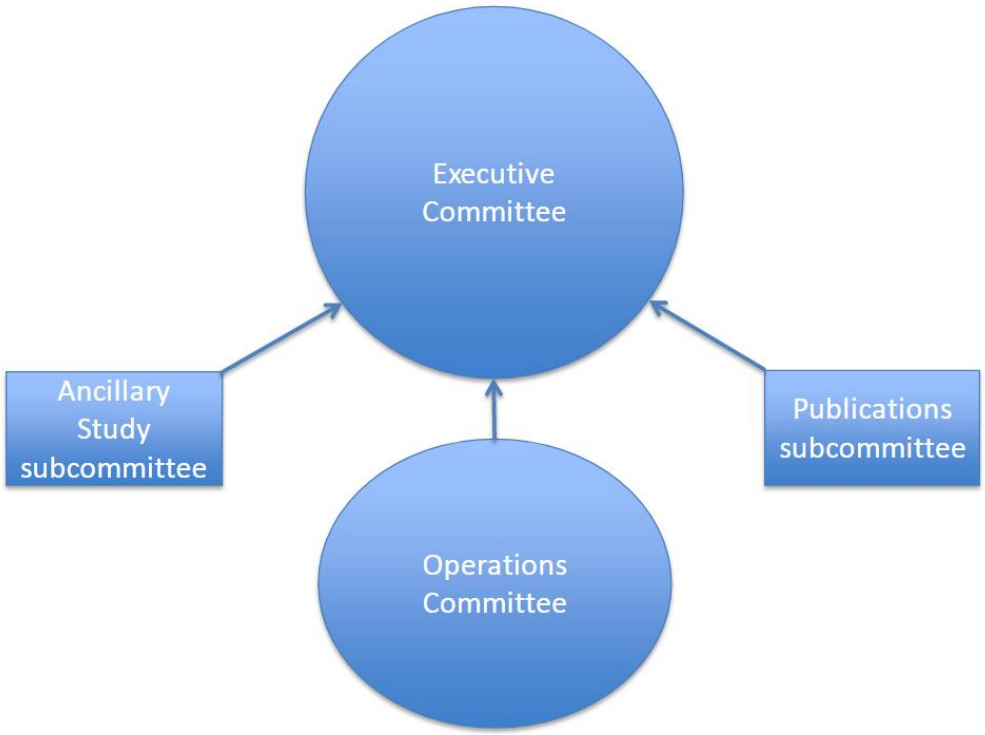
11.2 ORGANIZATIONAL STRUCTURE

The Executive Committee will be led by the Principal Investigators and will consist of the 2 elected PBRN Directors, Co-Investigators, Data Coordinating Center PI and Project Manager, NIH official and Clinical Coordinating Center Project Managers. The Executive Committee will meet every one-to-two weeks to administratively direct and monitor the progress of the study and to respond to any design, implementation or administrative issues that arise during the study.

The Operations Committee will consist of Overall Principal Investigators, PBRN Directors and lead coordinators, DCC Project Managers, and Co-Investigators. It will address implemental and administration faced by the PBRN practices that arise during the study.

Other subcommittees, such as the Publications and Ancillary Studies Subcommittees, will be constituted to support maximizing the utility of the CAPTURE study to the scientific community.



12 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data, documentation and completion. An individualized quality management plan will be developed.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

13 DATA HANDLING AND RECORD KEEPING

13.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Comprehensive data coordinating center (DCC) functions for this clinical trial, including clinical monitoring, database development, web-based data entry and management, as well as the creation and export of study reports for the DSMB will be provided by the University of Michigan Statistical Analysis of Biomedical and Education Research (SABER) group. Housed in the top nationally ranked Department of Biostatistics, SABER, in its 17-year existence, has served as the DCC for over 50 studies, including multiple NIH-sponsored networks.

The DCC will use OpenClinica® (OpenClinica Clinical Trial Software; OpenClinica, LLC, Waltham, MA), a clinical trial software platform for electronic remote (i.e., site-based entry) data capture and clinical data management, as the basis for our custom-designed data entry and management system. The majority of data will be collected via electronic Case Report Forms (CRFs); however, other data sources, such as laboratory data from the central laboratory, may be used. In these circumstances, the DCC will also utilize electronic data transfer. Protocols for the transfer of data, with careful attention to data integrity, will be written by experienced programmers and stored in the OpenClinica database or data mart.

The DCC has established a set of standard operating procedures (SOPs) governing the processes used to ensure patient privacy and data confidentiality, including the use of anonymous participant IDs on CRFs and in reports. OpenClinica® enables compliance with Good Clinical Practice (GCP) and regulatory requirements by providing differentiated user roles and privileges, password and user authentication security, electronic signatures, SSL encryption, and comprehensive auditing to record and monitor access and data changes.

Data collection is the responsibility of the central study staff at the PBRN under the supervision of the PBRN Director (investigator). The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. In addition to the protocol, the DCC will prepare a Manual of Procedures which provides additional detail on data collection procedures, including source documentation, eCRF completion guidelines, data handling procedures and procedures for data monitoring and quality control that ensure these data are accurate, consistent, complete and reliable and in accordance with ICH 36.

13.2 STUDY RECORDS RETENTION

Study documents should be retained as required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

13.3 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation or scheduled protocol-required activity. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

13.4 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers after the completion of the primary endpoint by contacting Drs. Martinez and Han.

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The CAPTURE Study: Validating a unique COPD case finding tool in primary care

Protocol Number: 1R01HL136682

National Clinical Trial (NCT) Identified Number:

Principal Investigators:

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Funder:

National Heart, Lung, and Blood Institute (NHLBI)

Version Number: v. 2.0

14 December 2018

Protocol Amendment 2.0 - Summary of Changes				
Location	**Page Number**	**Type of Change**	**Description**	**Rationale**
Cover Page	---	*Administrative*	Update Protocol Version to 2.0 and update version date to	Amendment version and date
Cover Page	---	*Administrative*	Add NCT # for each AIM	Add all 3 numbers to protocol since each AIM is registered in clinicaltrials.gov
Table of Contents	---	*Administrative*	Corrected page numbers for new version	Updating Table of Contents to reflect any page number shifts due to reformat
Multiple Sections	Multiple	*Administrative*	Changed Medical Chart Review to Medical Record Review throughout the protocol	Changed Medical Chart Review to Medical Record Review throughout the protocol
1.2 Schema Table 1	9	*Clarification*	Concomitant medications revised to read Respiratory Medications	Further clarification since these are limited to respiratory medication not all medications
1.2 Schema Table 1	9	*Clarification*	Foot note 3 moved to 12 month to reflect the data that will be collected for subjects who qualify for 12 month follow-up w	Clarification that 12 month column is for indicating what data will be collected for subjects who meet 12 month follow-up criteria
1.2 Schema Table 1	9	*Clarification*	X in last column for 12 month spirometry was deleted. This was originally meant to be footnote that post bronchodilator spirometry would be performed at baseline for those subjects that qualified	Further clarification that spirometry will not be done at 12 month follow-up, the footnote was meant to reflect post bronchodilator spirometry at baseline for those subjects who qualify
Section 2.3.1 Known Potential Risks	14	*Revision*	For Albuterol: A targeted safety questionnaire will be administered to all participants prior to albuterol to exclude those with a previous adverse event with the medication ~~and others at high risk due to cardiac abnormalities.~~	Subjects are excluded who have had MI and therefore not necessary
Section 4.1 Overall Study Design	21	*Clarification*	Patient-reported data will be collected by telephone, secure web-based server, and mail-based methodologies <u>based on participant preference and completed by the COPD Foundation.</u>~~, as well as medical record abstraction, depending upon practice site preferences and feasibility.~~	The COPD Foundation will be collecting participant 12 month follow-up subject questionnaires
Section 4.1 Overall Study Design	21	*Clarification*	~~Clinic site data will also be collected from the~~Subject medical ~~record~~ data will be collected from the medical record to assess for changes in practice-level care.	Further clarification that this data will be collected from medical record

Section 6.3 Study Intervention Compliance	27	*New*	If results were not shared at the time of the CAPTURE study visit, then the date of sending the CAPTURE results will be recorded on the appropriate eCRF by filling in the date (day/month/year) the exact copy of the CAPTURE Tool~~results~~ were sent to the clinician through a ~~inter- clinic email or other~~ HIPPA-compliant method and placed in the medical record. The goal is to communicate the results to the clinician in a timely manner ~~within 3 business days~~. The DCC will monitor review all participants' eCRFs to assure that all those enrolled from practices randomized to CAPTURE results have been shared with clinicians. ~~in the specified timeframe.~~	The study team wanted to clarify that the exact copy of the CAPTURE tool should be shared with clinician. Also wanted to make timing of sharing less restrictive and the team recognized that restrictive parameters cannot always be realized in clinical practice setting
Section 8.2 Longitudinal Follow-up Assessment and Data Collection	30	*Clarification*	Medical chart abstractions <u>completed by PBRN coordinators</u> and participant questionnaires <u>administered by study team members from the COPD Foundation are used.</u>	Clarification that medical chart reviews will be done by PBRN coordinators and COPD Foundation will administer participant questionnaires at 12 months
Section 8.2 Longitudinal Follow-up Assessment and Data Collection	30	*Clarification*	Data from clinical visits to be collected at follow-up by telephone, secure web-based server, or mail-based methodologies directly from participants <u>and administered by COPD Foundation study personnel</u>	Clarification that COPD Foundation will administer participant questionnaires at 12 months
Section 10.1.1 Informed Consent Process	45	*New*	All PBRN research coordinators, <u>COPD Foundation study staff</u> and other clinical investigators will be certified by their local IRB in informed consent and human studies research.	The COPD Foundation has attained IRB approval as their team will be interacting with participants
Section 10.1.3 Confidentiality and Privacy	46	*Clarification*	In addition, it may be transmitted and stored at the DCC in a database separate from the clinical database (used for statistical analysis and scientific reporting) and with <u>COPD Foundation study team</u> ~~study coordinator~~ access to aid in contacting participants at the 12-month follow-up.	COPD Foundation will have access to participant contact information from a separate database in order to contact participants for follow-up questionnaire completion
Section 11.1.2 Practice Based Research Networks (PBRN)	47	*Administrative*	Moved Roles and Responsibilities to section 11.1.2	Moved Roles and Responsibilities to section 11.1.2

Section 11.1.2 Practice Based Research Networks (PBRN)	47	*Revision*	Change Carolinas HealthCare System to Atrium Health and add new PI for Oregon Rural Practice-Based Research Network	Carolinas HealthCare System is now Atrium Health and the new PI at Oregon, Dr. Lyle Fagnan is retiring and Dr. Nancy Elder will take his place as director and site PI for CAPTURE
Section 11.1.7 Clinical Coordinating Center	49	*Clarification*	Update titles for COPD Foundation study members	Adminstrative change to include titles for Dr. Yawn
Section 11.1.8 12 Month Survey Coordinating Center	50	*New*	Add 12 Month Survey Coordinating Center to Study Leadership, Section 11.	The COPD Foundation study team will be coordinating outreach to 12 month follow-up subjects and administering surveys
Section 11.2 Organizational Structure	51	*Clarification*	Includes 1 representative of the COPD Foundation in the Executive Committee Organization description.	COPD Foundation representatives are part of the Executive Committee currently
Section 4.1 Overall Study Design	9, 10, 21	*New*	Deletion of CAT Score ≥ 10 and CAPTURE Score ≥ 2 and return to CAPTURE+ and abnormal spirometry as longitudinal follow-up criteria	The study team proposes to defer longitudinal follow-up based solely on an isolated, baseline CAT or CAPTURE scores as it is outside the scope of the current CAPTURE program. The study team is also proposing to return to the original scientific approach to follow CAPTURE+ (as defined in the protocol) subjects along with abnormal post-BD spirometry and 5% random sample of those subjects that meet neither of these criteria. Those subjects already selected under the current algorithm would still be followed longitudinally (and noted as selected under the initial follow-up selection criteria) and would use data as appropriate. Importantly, the primary care clinician colleagues within the CAPTURE program do not feel there is a safety issue in not following this population as there are no data defining a negative impact of an isolated, elevated CAT score in primary care patients.

Section 1.1 Synopsis, Section 4.1 Overall Study Design, Section 8.1 Baseline Assessments and Data Collection	3, 20, 29	*New*	Addition of adjudication of the presence of obstruction on post-bronchodilator spirometry	As the study commenced, several instances of the faulty spirometry software reading incomplete or participant refusal of post-bronchodilator occurred and led to the need for spirometry core to determine review process in these instances and validity of pre-bronchodilator spirometry. The rationale for this is that in other databases where all patients had both pre and post-bronchodilator spirometry, those who had a pre-bronchodilator FEV1/FVC less than 0.65 had a post-bronchodilator FEV1/FVC less than 0.70 more than 95% of the time.
8.1 Baseline Assessments and Data Collection	28	*New*	Addition of spirometry instructions if participant has taken a medicine they breathed into lungs from puffer or inhaler within two hours of spirometry test	Since study start, one participant reported taking albuterol shortly before the visit. The study clinicians confirmed this scenario would constitute the participant being in a post-bronchodilator state already with no further need to proceed after initial spirometry. The data collection process has been updated to assure these values would be placed in post-bronchodilator data. Coordinators are instructed to ask this question before spirometry should this scenario occur again during the study.

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STATEMENT OF COMPLIANCE

This study will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CAO	Chronic Airflow Obstruction
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
ECOPD	Exacerbation of Chronic Obstructive Pulmonary Disease
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FEV1	Forced Expiratory Volume in 1 second
FFR	Federal Financial Report
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practice
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act

IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PBRN	Practice-Based Research Network
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
RE-AIM	Reach, Effectiveness, Adoption, Implementation, Maintenance
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States
USPSTF	United States Preventive Services Task Force

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	The CAPTURE Study: Validating a unique Chronic Obstructive Pulmonary Disease (COPD) case finding tool in primary care
Study Description:	**Aims 1 and 3**. A prospective, multicenter study including a cross-sectional validation to define sensitivity and specificity of CAPTURE and its impact on clinical care across a broad range of primary care settings in a cluster randomized controlled clinical trial. The CAPTURE tool consists of a 5-item self-administered questionnaire and peak expiratory flow (PEF) measurement, designed to identify undiagnosed patients with Chronic Obstructive Pulmonary Disease (COPD). **Aim 2.** This study delivers a qualitative assessment of clinical practice acceptance of and implementation strategy for CAPTURE case finding within 10 varied primary care practices across 5 US PBRN regions. We evaluate primary care practice attitudes, beliefs and recommendations about CAPTURE's potential to feasibly integrate into clinical practice patterns, workflow and quality improvement paradigm planning in a variety of primary care clinical settings.
Definitions:	**CAPTURE+ =** Participants with • CAPTURE score $\geq$ 5, or • CAPTURE score of 2, 3, or 4 with a low PEF, defined as <350 L/min for males and <250 L/min for females **CAPTURE-** = Participants with CAPTURE score < 2 or scores 2-4 with normal PEF, defined as >350 L/min for males and > 250 L/min for females **Spirometrically defined COPD =** Participants with abnormal spirometry, defined as post-bronchodilator FEV_1/FVC <0.7. If a participant is unable to complete a post-bronchodilator spirometry (refusal, technical error on the part of coordinator, etc.), and the pre-bronchodilator FEV1/FVC is less than 0.65, the participant will be considered to have COPD for the purpose of follow-up in this study. **Clinically significant COPD =** Participants with abnormal spirometry, defined as post-bronchodilator FEV_1/FVC <0.7, plus one of the following: • FEV_1 < 60% predicted, or • > 1 exacerbation-like event within the past 12 months. **Mild COPD =** Participants with abnormal spirometry, defined as post-bronchodilator FEV_1/FVC<0.7 plus both of the following: • $FEV_1 \geq$ 60% and • No prior history of ECOPD
Objectives:	**Aims 1 and 3 Primary Objectives:** • **Aim 1 -** Define the sensitivity and specificity of CAPTURE for identifying previously undiagnosed patients with clinically significant COPD in a broad range of primary care settings.

	• **Aim 3 –** Define the impact of CAPTURE information provided to clinicians in identifying and managing patients with respiratory symptoms (CAPTURE+) across a broad range of primary care settings.
	
	Aim 2 Primary Objective:
	Explore clinical practice implementation approaches to and acceptance of CAPTURE case finding for clinically significant COPD in a range of primary care practices.
	
	Aims 1 and 3 Secondary Objectives:
	• **Aim 1 –**
	  • Define the sensitivity and specificity of CAPTURE for patients with COPD across a broad range of racial and ethnic groups in a range of primary care settings.
	  • Determine positive and negative predictive values (PPV and NPV) in different practice settings.
	  • Verify the optimal use (cutoff threshold) of the CAPTURE tool in combination with PEF measurements for identifying undiagnosed COPD.
	  • Determine patient and site characteristics that, with the CAPTURE assessment, will best identify persons with undiagnosed COPD.
	  • Determine whether CAPTURE is useful in identifying other definitions of undiagnosed COPD including:
	  1) spirometry-defined COPD, and
	  2) mild COPD
	
	• **Aim 3 -**
	  • Define the impact of CAPTURE clinician education, and patient-level CAPTURE information to clinicians (“CAPTURE education”) on selected additional therapeutic interventions in previously undiagnosed patients with clinically significant COPD.
	  • Assess impact of CAPTURE education on clinician interventions specific to smokers.
	  • Determine the impact of CAPTURE education on patient symptoms, exacerbations, hospitalizations, and mortality.
	  • Determine the impact of CAPTURE education when COPD is defined spirometrically.
	
	Aim 2 Secondary Objectives:
	• Qualitatively assess primary care clinical staff COPD practice behavior – including COPD screening and diagnostic perceptions, beliefs and knowledge – that will inform strategies to improve CAPTURE RE-AIM (reach, impact, adoption, implementation and maintenance of use) characteristics.
	• Qualitatively assess primary care patient opinion of CAPTURE COPD case finding that will inform strategies to improve CAPTURE RE-AIM

	(reach, impact, adoption, implementation and maintenance of use) characteristics.
Endpoints:	**Aims 1 and 3 Primary Endpoints:** • Aim 1 – o Sensitivity and specificity of CAPTURE to identify previously undiagnosed patients with clinically significant COPD at baseline. • Aim 3 – o Proportion of CAPTURE+ participants who meet at least one of the following within 12 months of study baseline (composite endpoint): 1) referral for or completion of clinical spirometry testing, 2) new diagnosis of COPD, 3) newly prescribed respiratory medication (long acting bronchodilator or anti-inflammatory for respiratory condition), or 4) referral to a specialist for respiratory evaluation/treatment **Aim 2 Primary Endpoints:** • Primary care clinician recommendations that inform CAPTURE RE-AIM strategies at both provider and clinical support levels of primary care practice. • Primary clinician recommendations that inform CAPTURE-associated COPD education models for primary care clinicians. • Primary care clinician recommendations that inform CAPTURE-associated COPD clinical quality improvement designs across a variety of primary care practice types. **Aims 1 and 3 Secondary Endpoints:** • Aim 1 – o Sensitivity and specificity of CAPTURE to identify previously undiagnosed patients with COPD across sex, ethnic groups, urban vs rural location, and educational level. o Positive and negative predictive values (PPV and NPV) in different practice settings. o Areas under the receiving operator characteristic curve (AUC) for various cutpoints of CAPTURE and PEF_1 measurements to determine the best cutpoint for COPD+ screen. o AUC to identify the combination of patient/site characteristics which best discriminates those with clinically significant COPD. o All primary and secondary endpoints as applied to 1) spirometry-defined COPD and 2) mild COPD • Aim 3 – o Proportion of CAPTURE+ patients who meet the components of the composite endpoint. o Proportion of patients with clinically significant COPD who meet the composite endpoint. o In participants with clinically significant COPD who are current smokers, the incidence of physician referral to a formal smoking cessation program, prescribed smoking cessation medication, and referral to pulmonary rehabilitation program.

	o In participants with clinically significant COPD, change in CAT score, and proportion of patients who experience exacerbations, hospitalizations, or mortality. o All of the above endpoints for Aim 3, with the patient population defined as those who have COPD defined spirometrically. **Aim 2 Secondary Endpoints:** • Existing COPD screening and diagnostic and case finding processes within a variety of primary care practices. • Primary care practice belief about capacity to change from existing COPD screening and diagnostic assessment strategies. • Practice-specific COPD screening and diagnostic continuing education preference.
Study Population:	**Aims 1 and 3.** Adults 45-80 years old without a prior diagnosis of COPD (total N = 5000; approximately 1000 participants per PBRN) **Aim 2.** - 10 primary care practices: 2 practices per PBRN with up to 15 clinical staff participants per practice; clinician N = up to 150 (up to 30 clinician participants per PBRN). - Aim 1 patient opinion survey population; patient N = 200 (40 patients from each PBRN; adults 45-80 years old, without a prior diagnosis of COPD). - Total N = up to 350
Phase:	N/A
Description of Sites/Facilities Enrolling Participants:	**Aims 1 and 3.** Enrollment will occur in approximately 100 primary care practices affiliated with 5 primary care based practice networks (PBRN) across the United States who exhibit a broad range of gender, ethnic, racial, socioeconomic, and regional diversity. **Aim 2.** • Two primary care practices chosen by each of the same 5 PBRN co-investigator teams make up the 10 aim 2 practices from which clinician participants are enrolled. These 10 practices are separate from the 100 chosen practices in aims 1 and 3. • Patient participants are a sub-sample of those participants enrolled in aims 1 and 3.
Description of Study Intervention:	**Aims 1 and 3.** Primary care practices will be randomized to either receive basic COPD education and patient-level CAPTURE information with CAPTURE education (initially basic then later enhanced based on data collected in Aim 2) versus COPD education only. **Aim 2.** Participating primary care clinicians from 10 varied practices are surveyed at three different time points and participate in two focus groups qualitatively assessing CAPTURE implementation strategy and COPD case finding approaches in primary care. Participating patients complete one 10-minute written opinion survey about CAPTURE.
Study Duration:	**Aim 1 and 3.** 4 years **Aim 2.** 2 years

Participant Duration:	**Aims 1 and 3.** Up to 12 months **Aim 2.** • Primary care practice clinicians: questionnaires and focus groups (total 3 hours/participant) over 16 months. • Primary care patients: one 10-minute questionnaire/participant over 14 months.

1.2 SCHEMA

FIGURE 1. OVERALL STRUCTURE OF AIMS

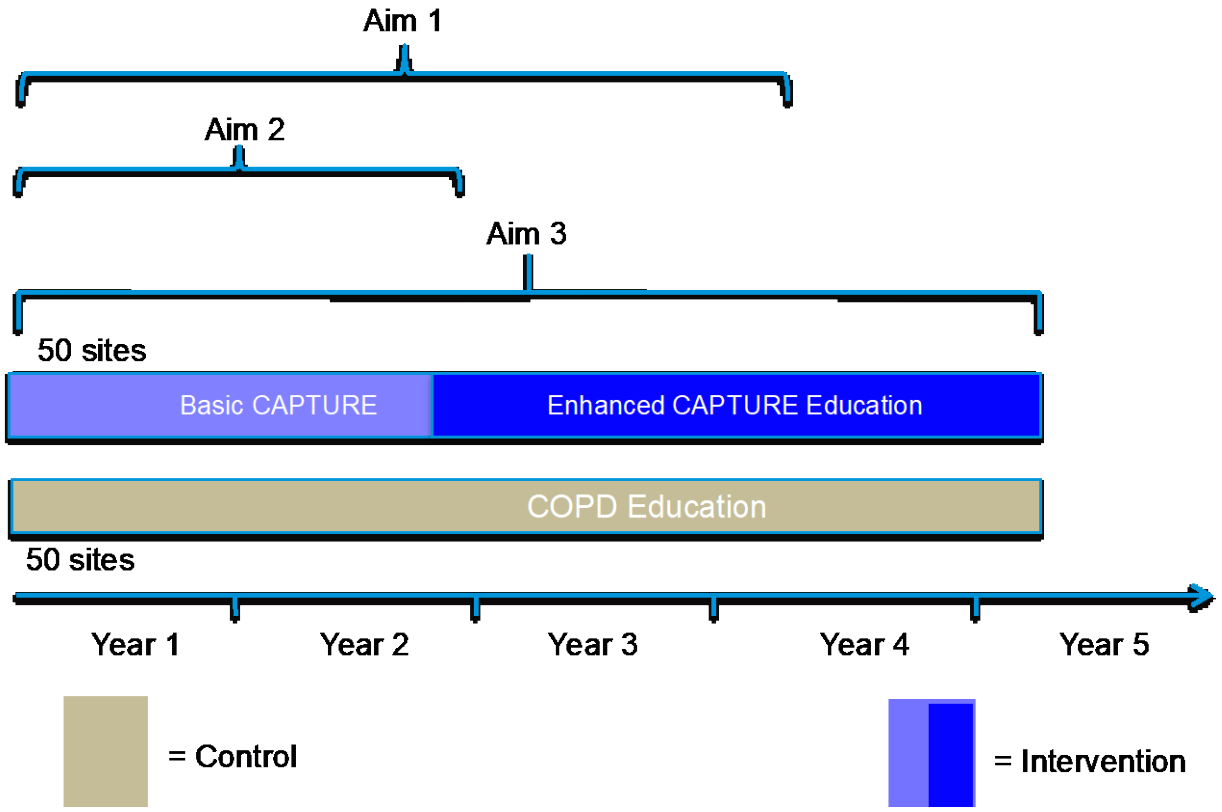
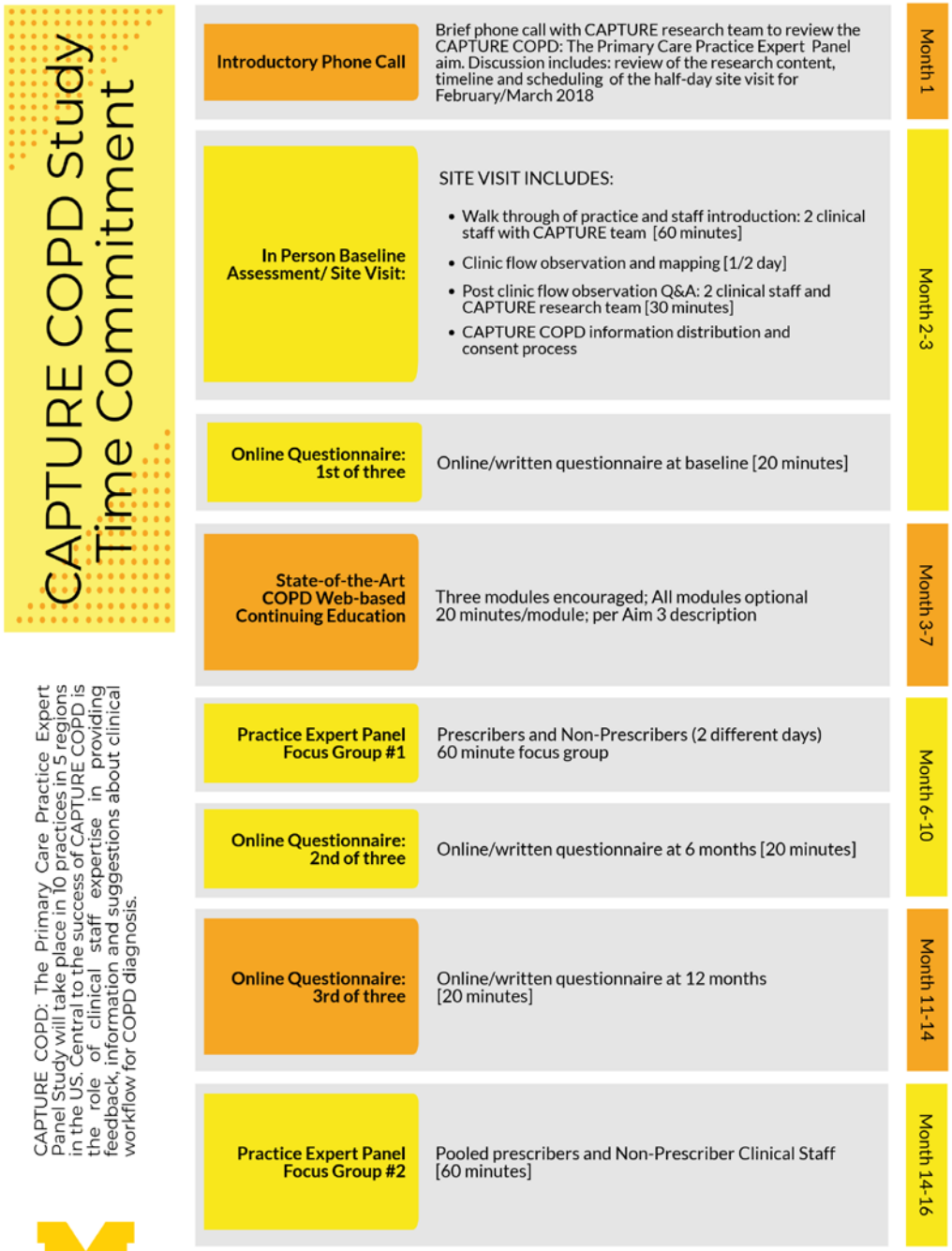


FIGURE 2. STRUCTURE OF AIM 2


CAPTURE COPD Study
Time Commitment
Introductory Phone Call
Brief phone call with CAPTURE research team to review the CAPTURE COPD: The Primary Care Practice Expert Panel aim. Discussion includes: review of the research content, timeline and scheduling of the half-day site visit for February/March 2018
Month 1
In Person Baseline Assessment/ Site Visit:
SITE VISIT INCLUDES:
• Walk through of practice and staff introduction: 2 clinical staff with CAPTURE team [60 minutes]
• Clinic flow observation and mapping [1/2 day]
• Post clinic flow observation Q&A: 2 clinical staff and CAPTURE research team [30 minutes]
• CAPTURE COPD information distribution and consent process
Online Questionnaire: 1st of three
Online/written questionnaire at baseline [20 minutes]
Month 2-3
State-of-the-Art COPD Web-based Continuing Education
Three modules encouraged; All modules optional 20 minutes/module; per Aim 3 description
Month 3-7
Practice Expert Panel Focus Group #1
Prescribers and Non-Prescribers (2 different days) 60 minute focus group
Online Questionnaire: 2nd of three
Online/written questionnaire at 6 months [20 minutes]
Month 6-10
Online Questionnaire: 3rd of three
Online/written questionnaire at 12 months [20 minutes]
Month 11-14
Practice Expert Panel Focus Group #2
Pooled prescribers and Non-Prescriber Clinical Staff [60 minutes]
Month 14-16
CAPTURE COPD: The Primary Care Practice Expert Panel Study will take place in 10 practices in 5 regions in the US. Central to the success of CAPTURE COPD is the role of clinical staff expertise in providing feedback, information and suggestions about clinical workflow for COPD diagnosis.
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1.3 SCHEDULE OF ACTIVITIES (SOA)

Table 1: Schedule of Activities (Aims 1 and 3)

	Pre-Visit Contact[1]	**Baseline**	**12 Months[3]**
Contact (C)/ Visit (V)/Medical Record Review (MRR)	**C1**	**V1**	**C2/MRR[5]**
Time point, days (Visit window)	**Prior to outpatient visit (≤-1)**	**Within 30 days of pre-visit contact**	**365 ±30 (C2)**
Contact patient re: interest in study visit[1]	X		
Informed consent		X	
Demographics		X	
Medical history (Co-morbidities)[2]		X	
Vaccination status		X	X
CAPTURE 5-item questionnaire		X	X
CAPTURE 12-item additional questionnaire		X	
Peak Expiratory Flow (PEF)		X	
Height and weight		X	
Respiratory medications review		X	X
Spirometry[4]		X*	
Respiratory symptoms, exacerbation assessment		X	X
Smoking exposure history		X	
Smoking cessation review[6]			X
COPD Assessment Test (CAT)		X	X
Adverse Events		X	
Medical record review			X

1. Optional per site recruitment preferences
2. Comorbidities including cardiovascular, respiratory and malignant disorders
3. Recorded for a subset of participants who meet any of the following criteria: 1) CAPTURE+ subjects defined as CAPTURE Score ≥ 5 or CAPTURE score of 2, 3, or 4 with a low PEF, defined as <350 L/min for males and <250 L/min for females 2) abnormal spirometry defined as $FEV_1/FVC < 0.70$ or $FEV_1 < 80\%$ predicted at baseline; and, 3) a random sample of approximately 5% of those who do not meet criteria 1 and 2. For participants meeting criteria 1 and 2 who cannot or choose not to complete the 12-month assessment, medical record review will still be completed. For participants meeting criteria 1 and 2 who change medical practices and medical record review cannot be completed, patients will be contacted for completion of patient reported data. For

participants meeting criterion 3 where all of the protocol-specified 12-month assessments cannot be made, another participant will be selected at random to replace this participant.

4. Pre-bronchodilator spirometry will be done for all participants. Post-bronchodilator spirometry will be performed for participants with abnormal spirometry ($FEV_1/FVC < 0.70$ or $FEV_1 < 80\%$ predicted) *If the participant has taken a bronchodilator within a 2-hour window of spirometry the spirometry will be considered post-bronchodilator and a pre-bronchodilator spirometry will not be done.
5. The 12-month assessment consists of patient reported data, collected by the COPD Foundation, and medical record review completed by site coordinators.
6. This will be completed in those that are smoking at V1.

2 INTRODUCTION

2.1 STUDY RATIONALE

Undiagnosed COPD is a leading cause of morbidity and mortality. Spirometry, the 'gold standard' for diagnosis, is not recommended for screening in asymptomatic individuals or untargeted case finding and remains widely underutilized in primary care settings. Targeted case finding approaches have been strongly advocated but currently available approaches generally identify patients across the spectrum of mild to severe disease without reference to potential therapeutic benefit or exacerbation risk, thereby limiting clinical impact and acceptance in primary care. There is an urgent need to develop and implement simple case finding approaches that can identify patients with clinically significant COPD in primary care settings.

Through a multi-stage, iterative process we developed a simple case finding tool using five questions combined with selective peak expiratory flow **(PEF)** measurement that identifies individuals with 1) an $FEV_1 < 60\%$ predicted and/or 2) at risk for ECOPD. We call this tool CAPTURE (**C**OPD **A**ssessment in **P**rimary Care **T**o Identify **U**ndiagnosed **R**espiratory Disease and **E**xacerbation Risk)(1). As clinical trials have demonstrated benefit and therapeutic guidelines recommend therapy for these individuals we have labeled these patients as suffering from 'clinically significant' COPD. The long-term goal of this project is to identify these patients so that they can be treated and result in improved health status, reduced exacerbations, and decreased morbidity.

The *overall objectives* of Aims 1 and 3 of this project are to 1) validate the sensitivity, specificity, and predictive value of CAPTURE to identify undiagnosed, clinically significant COPD patients in a diverse primary care population; and explore whether identifying these patients results in improved COPD specific care and health status. Our *principal hypothesis* is that CAPTURE can effectively and efficiently identify primary care patients with undiagnosed, clinically significant COPD. We objectively test our principal hypothesis by completing to two separate and linked aims:

Aim 1 – Determine the sensitivity and specificity of CAPTURE in identifying clinically significant COPD patients in a broad range of primary care outpatient practices.

Working hypothesis - A simple case finding methodology using a five-item questionnaire with selective PEF measurement will identify undiagnosed patients with clinically significant COPD.

We will conduct a 5,000 participant cohort study in 100 primary care practices affiliated with five

primary care based research networks **(PBRN)** that provide access to previously undiagnosed patients with clinically significant COPD who exhibit gender, ethnic, racial, socioeconomic and regional diversity.

Aim 3 – Define the impact of CAPTURE screening in a broad range of primary care outpatient practices and evaluate practice and patient characteristics that are associated with care implementation and clinical outcomes for patients with respiratory symptoms (CAPTURE+).

Working hypothesis – Provision of patient specific CAPTURE data to practicing clinicians will result in improved management of patients with respiratory symptoms (CAPTURE+).

We will provide basic COPD education and patient level CAPTURE information and education to site clinicians at 50 of the sites and prospectively follow selective, pre-defined subgroups of patients to define relevant outcomes. Care at the other 50 clinical sites will follow standard of care with basic COPD education to clinicians.

Assessing the potential clinical impact of a novel COPD case finding strategy includes confirmation of validity in a diverse primary care patient population and a quantitative research evaluation of its impact on clinical decision-making and COPD patient outcomes, as found in aims 1 and 3 above. Equally important is exploration through validated implementation methods that the newly designed CAPTURE tool, even if valid and impactful, can provide real-world utility within a variety of primary care practice settings. While we find no evidence in previous COPD screening studies of such detailed appraisal, ascertaining the feasibility of clinical testing is a vital component of assuring that new approaches address potential clinical practice need, capacity, knowledge and diagnostic gaps. As much as possible, clinical respiratory innovations should align with busy workflow at all practice staff levels to more effectively identify primary care patients with undiagnosed, clinically significant COPD.

To maximize success of the CAPTURE adoption, education and implementation in this study and in future work, Aim 2 is introduced to assess practice experience, need and preference that can inform clinical COPD case finding and education in primary care settings:

Aim 2 – Explore clinical practice implementation approaches to and acceptance of CAPTURE case finding for clinically significant COPD in a range of primary care practices.

The *overall objective* of this aim is to qualitatively explore primary care clinical practice acceptance of COPD case finding implementation and define education and feasibility strategies to enhance adoption in primary care practice. This assessment includes understanding clinician and clinical staff COPD practice and perceptions in addition to the feasibility of case finding integration into existent clinical work patterns. To attain this objective, we address one *working hypothesis* – a COPD case finding methodology using a validated one-page, five-item questionnaire with selective PEF measurement (CAPTURE) can be incorporated into the clinical practice patterns, clinical workflow, communication and practice-based quality improvement paradigms in a variety of primary care clinical settings. The *rationale* for this objective reflects the importance of establishing if an innovative approach to COPD case finding (CAPTURE) is considered a pragmatic tool with potential utility for primary care clinicians within real-world clinical practice settings. With the completion of this aim we anticipate confirming that future validated approaches to COPD case finding can be adopted in a broad variety of clinical care settings thereby providing further impetus for the rigorous evaluation of a) case finding guided patient outcomes as part of routine primary care clinical practice; b) case finding use in a range of primary care health professional COPD-related education approaches, clinical quality improvement models and

diagnostic guidelines; and c) the capacity of clinical case finding with informed follow-up to enhance future COPD clinical care therapeutic paradigms used in primary care practice.

2.2 BACKGROUND

Aims 1 and 3.

COPD remains a major cause of morbidity and mortality. COPD results in substantial morbidity and mortality worldwide.(2-4) Globally, the prevalence of COPD and years lived with disability increased from 1990 to 2013.(5) This is particularly evident in older individuals.(6) These well-designed population based studies confirm the growing impact of COPD.

COPD is frequently undiagnosed. We recently documented that only 28% of participants with chronic airway obstruction **(CAO)** had physician diagnosed disease.(7) Importantly, an FEV_1 <50% predicted was noted in 10% of those with undiagnosed CAO; this is similar to other cohorts or population based surveys.(8-11) There is consistency in these well-conducted studies that confirm most COPD patients are undiagnosed.

Spirometry is underutilized. The U.S. Preventive Services Task Force **(USPSTF)** recently recommended against the use of spirometry for routine, general population or practice-based screening in asymptomatic individuals.(12) An editorial by the PI of this application highlighted the limitations of this conclusion.(13) Within primary care spirometry is often viewed as time consuming and difficult to implement and interpret.(14) As such, it is not routinely used.(15-19) Even the availability of less expensive and easily used spirometers(20) has not resulted in increased utilization.(21, 22)

Undiagnosed COPD is associated with a negative clinical impact. In a robust, population based study we confirmed that undiagnosed patients experienced impaired health status and a higher risk for all-cause mortality compared to those without CAO; this was particularly evident with more severe CAO.(7) Others have confirmed increased mortality,(23) health status impairment,(24) exacerbation-like respiratory events,(11) and increased health care costs.(25, 26) As such, there are consistent data suggesting that undiagnosed COPD patients experience negative clinical events and impaired health status.

Therapeutic interventions improve COPD clinical outcomes. Well designed, randomized controlled trials confirm that COPD therapy is effective, particularly in patients with an FEV_1 < 60% predicted who are symptomatic or at risk for ECOPD.(27, 28) Despite limited data, some have suggested that earlier detection of patients with previously undiagnosed, yet clinically significant COPD, in primary care settings could improve short- and long-term patient outcomes and may be cost-effective. (29, 30)

COPD case finding approaches to date have generally been methodologically limited. Several COPD case finding tools have been created based on existing epidemiologic literature or expert opinion.(31, 32) This includes tools created by investigators in this study.(33, 34) In general, current approaches were designed to identify COPD patients without reference to disease severity or ECOPD risk, resulting in the identification of a high proportion of patients with mild or minimally symptomatic disease.(21, 33-39) Several studies have tested the accuracy of handheld flow meters for case identification with varying sensitivity and specificity.(40) Although informative in terms of CAO, PEF meters have been unable to systematically identify patients at risk of ECOPD. We tested a three-staged approach (risk-factor questionnaire, PEF, and spirometry) for identifying moderate to severe COPD (FEV_1<60% predicted) in a convenience sample of the general population.(41) This study was limited by the nature of the population screened and the screening questionnaire used but supported the concept that PEF can facilitate COPD case finding.

A systematic analysis of existing databases provides insight into the best variables for COPD Case Identification. To identify potential items that could be useful in the identification of undiagnosed COPD we interrogated three robust datasets of populations in which the investigators on this application had major roles [COPD Foundation Peak Flow Study Cohort (n=5761); Burden of Obstructive Lung Disease Kentucky site (n=508); and COPDGene® (n=10,214)].(42) We utilized the machine learning statistical method of random forests to identify and validate variables most important in identifying patients with clinically significant COPD. COPD case finding candidate content included items reflecting exposure, personal and family history, respiratory symptoms, recent health history, activity limitation and demographics.

A comprehensive, qualitative study identified key constructs for identifying recently diagnosed patients with clinically significant COPD. We completed a two phase study that included focus groups followed by cognitive interviews to refine the key constructs for identifying patients with clinically significant COPD.(43) Fifty participants were recruited including those with mild airflow obstruction, diagnosed within the previous six months and without previous ECOPD; those diagnosed within the previous six months and with a history of at least one ECOPD within the prior year; those with 2-3 risk factors for COPD but without CAO; and those with $\geq$ 4 risk factors for COPD but without CAO. Using a content analysis approach, key themes and constructs were identified and integrated with the content of the previous literature review and data mining. We identified 44 candidate items that resonated with patients and provided important insights into a case finding instrument.

A five-item questionnaire exhibits excellent operating characteristics to identify clinically significant COPD patients. We completed a prospective, multi-site, case-control study of four groups: cases with clinically significant COPD – COPD with > 1 ECOPD in the previous year (n=97) and COPD with no ECOPD but an FEV_1 < 60% predicted (n=89); controls – no known COPD (n=87) and COPD with an FEV_1 > 60% predicted and no ECOPD in the previous year (n=74). Using random forest analyses the 44 candidate items were reduced to 34-item, 21-item, 8-item and two different five-item sets. Through-out the item reduction process, the item sets maintained good performance, consistently misclassifying fewer than 27% of cases and controls, and with sensitivity greater than 80% and specificity greater than 70%. A five-item questionnaire exhibited good operating characteristics for separating COPD cases from controls. These characteristics were even better when separating COPD from controls without COPD.

Selective PEF measurement enhances the operating characteristics of a COPD case finding strategy. In the above case control study PEF was measured using a mechanical PEF meter with disposable mouthpieces. To optimize sensitivity and specificity, the following cut-off scores were selected, based on our data, for identifying cases of clinically significant COPD using PEF alone: males: <350 L/min; females: <250 L/min. The best method for predicting cases was a combination of the questionnaire and PEF **(CAPTURE)**, where PEF is used only for mid-range scores. Under this scoring scenario, patients with scores of 0 or 1 are not considered at risk of clinically significant COPD; they would not require further evaluation. Those with a score of 5 or 6 are considered to be at high risk of clinically significant COPD and should be referred directly for further evaluation, including clinical spirometry. Patients scoring in the middle range (2 to 4) would undergo PEF testing, applying the 350/250 interpretation thresholds. In our sample, 52% of the participants required PEF to determine if spirometry was indicated. The other 48% needed only the five-item questionnaire. This approach provided 90% sensitivity, 93% specificity and an overall error rate of 9%.

CAPTURE exhibits similar operating characteristics in a Spanish speaking population. To broaden our target population, the five-item questionnaire was methodically translated to Spanish using previously validated, rigorous methods(44) to yield an instrument that is equivalent to the English questionnaire

and linguistically and culturally applicable to persons of diverse Spanish-speaking backgrounds residing in the US. In a subset of Spanish speaking participants CAPTURE exhibited excellent sensitivity (88%), specificity (92%) and overall error rate (10%) for identifying patients with clinically significant COPD.

Aim 2.

Consistent with national criteria for preventive and chronic disease care quality, feasibility science is designed to assist clinical and health education evaluators plan for assessing and evaluating specific implementation factors essential to the success of new diagnostic, therapeutic and programmatic options in real-world clinical practice. This aim's analysis of primary care clinical practice COPD case finding feasibility includes an initial evaluation of existing COPD diagnostic and case finding processes within the practices, assessment of practices' capacity to change from existing respiratory symptom assessment strategies and an understanding of practice-specific learning preferences associated with new diagnostics in chronic disease diagnosis and management. The aim addresses through the RE-AIM feasibility approach how a new tool might a) identify target populations (Reach); b) appraise optimal targeted respiratory history and symptoms consistent with clinically significant COPD (Effectiveness or Impact); c) integrate into practice workflow (Adoption); d) deliver changes and improvements to COPD care within the scope of real-world clinical practice (Implementation); and e) persist in use and quality over time (Maintenance) (45-53).

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Potential risks associated with Aims 1 and 3 of this study are outlined below.

Spirometry: Participants may become short of breath. Syncope, light-headedness and fainting may develop during this test. These are uncommon.

Albuterol: Tremulousness, feeling of a strong, rapid heartbeat, and palpitations can occur with inhaled albuterol. A targeted safety questionnaire will be administered to all participants prior to albuterol to exclude those with a previous adverse event with the medication.. Note that albuterol is only administered to those with abnormal spirometry on the baseline spirometry assessment (defined as $FEV_1/FVC < 0.70$ or $FEV_1 < 80\%$ predicted).

Peak Expiratory Flow: Participants may become short of breath. Syncope, light-headedness and fainting may develop during this test. These are uncommon.

Other non-physical risks of the study include those from economic loss from participation in the study; this will be minimized by scheduling tests and evaluations in a timely manner in the fewest number of visits possible. Patient and physician participants will be provided a modest fee to cover their time to participate in the study.

We anticipate few adverse events due to the non-invasive nature of the study procedures and the rarity of such events encountered during the initial visits and longitudinal follow-up. Medical care will be available at each Clinical Center to treat participants who develop adverse events during in-person study visits.

Potential risks associated with Aim 2 of this study include:

No more than minimal risk exists for participants within aim 2.

Confidentiality of information and identification are the risks associated with this project. Based on previous research and the protocols that have been developed, we believe that the likelihood of these risks to the participants would be minimal, i.e. "rare".

Potential risks associated with the study (all Aims) include:

Loss of confidentiality of study data: This is unlikely since data collected will be stored in locked file cabinets in locked rooms at the Clinical Centers. In addition, only participant IDs are used to identify participants in the secure server at the Data Coordinating Center.

Poor quality data: If the data collected are of poor quality such that it is not useable to achieve study aims, participants will have unnecessarily been exposed to other risks in the study.

2.3.2 KNOWN POTENTIAL BENEFITS

For Aims 1 and 3 of this study, participants could receive direct benefit as a result of their participation in this research. Current state-of-the-art COPD education is offered to all clinicians at participating PBRN sites (see aim 3 protocol) that could result in improved care for their COPD patients. At the conclusion of the study, both patients and their care providers will have received the results of the CAPTURE screening tool and research spirometry that could result in further diagnostic testing leading to a diagnosis of COPD or other respiratory disorder. Some participants, however, will not have respiratory disease and therefore may not benefit. For Aims 1, 2 and 3, physician participants may benefit in learning how better to identify COPD participants in clinic.

Known potential benefits for each participating clinical staff include critical review their clinical respiratory practice. In general, aim 2 offers the ability to assess and address CAPTURE-specific primary care practice feasibility issues which could augment or hamper clinical communication or implementation of COPD case-finding in real-world primary care clinical practice.

Potential benefits to society include improved understanding of how best to identify individuals with COPD in the primary care setting. This could ultimately lead to better treatments and lower morbidity and mortality for patients with COPD.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The demonstrated and potential future benefits to improved understanding of COPD case finding outweigh the minimal risks of the procedures performed.

Increased understanding of how best to diagnose individuals at risk for COPD in the primary care population has the potential to benefit both patients with COPD and society at large. The risk to individuals associated with this study protocol is small and the knowledge to be gained is substantial.

3 OBJECTIVES AND ENDPOINTS

Aims 1 and 3.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Aim 1: Define the sensitivity and specificity of CAPTURE for identifying previously undiagnosed patients with *clinically significant COPD* in a broad range of primary care settings	Sensitivity and specificity of CAPTURE to identify previously undiagnosed patients with clinically significant COPD at baseline.	Standard methodology for COPD diagnosis will be used (1).
Aim 3: Define the impact of CAPTURE information provided to clinicians in identifying and managing patients with respiratory symptoms (*CAPTURE+*) across a broad range of primary care settings.	Proportion of CAPTURE+ participants who meet at least one of the following within 12 months of study baseline (composite endpoint): 1) referral for or completion of clinical spirometry testing, 2) new diagnosis of COPD, 3) newly prescribed respiratory medication (long acting bronchodilator or anti-inflammatory for respiratory condition), or 4) referral to a specialist for respiratory evaluation/treatment.	The composite endpoint is clinically relevant and consistent with published data (45). This will test the impact of CAPTURE on clinician behavior.
Secondary		
Aim 1: Define the sensitivity and specificity of CAPTURE for patients with COPD across a broad range of racial and ethnic subgroups in a range of primary care settings	Sensitivity and specificity of CAPTURE to identify previously undiagnosed patients with COPD across sex, ethnic groups, urban vs rural location, and educational status.	Patient characteristics will be used to assess the robustness of CAPTURE.
Aim 1: Determine positive and negative predictive values (PPV and NPV) in different practice settings.	Positive and negative predictive values (PPV and NPV) in different practice settings.	PPV and NPV will be used to assess the robustness and usefulness of CAPTURE in various settings.
Aim 1: Verify the optimal use (cutoff threshold) of the CAPTURE tool in combination with FEV_1 measurements for identifying undiagnosed COPD.	AUC for various cutpoints of CAPTURE and PEF measurements to determine the best cutpoint for clinically significant COPD screen.	The best discrimination for CAPTURE combined with FEV_1 will indicate the optimal usage of the tool.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Aim 1: Determine patient and site characteristics that, with the CAPTURE assessment, will best identify persons with undiagnosed COPD.	AUC to identify the combination of patient/site characteristics which best discriminates those with clinically significant COPD.	The best discrimination will determine which site and patient characteristics best predicted undiagnosed COPD in combination with the CAPTURE tool.
Aim 1: Determine whether CAPTURE is useful in identifying other definitions of undiagnosed COPD: 1) spirometry-defined COPD, and 2) mild COPD	All primary and secondary endpoints as applied to 1) spirometry-defined COPD and 2) mild COPD	This will determine the robustness of the CAPTURE tool.
Aim 3: Define the impact of CAPTURE clinician education, and patient-level CAPTURE information to clinicians ("CAPTURE education") on selected additional therapeutic interventions in previously undiagnosed patients with *clinically significant COPD.*	Proportion of CAPTURE+ participants who meet the components of the composite endpoint.	Each endpoint is clinically relevant and consistent with published data. (45) This will test the impact of CAPTURE on clinician behavior.
Aim 3: Assess impact of CAPTURE education on clinician interventions specific to smokers.	In participants with clinically significant COPD who are current smokers, the incidence of physician referral to a formal smoking cessation program, prescribed smoking cessation medication, and referral to pulmonary rehabilitation program.	Certain outcomes are specific to only smokers and should be assessed.
Aim 3: Determine the impact of CAPTURE education on patient symptoms, exacerbations, hospitalizations, and mortality.	In participants with clinically significant COPD, change in CAT score, and proportion of patients who experience exacerbations, hospitalizations, or mortality.	This endpoint is important for quality of life, and long-term patient outlook.
Aim 3: Determine the impact of CAPTURE education when COPD is defined spirometrically.	All of the above endpoints for Aim 3, with the patient population defined as those who have COPD defined spirometrically.	This will determine the robustness of the CAPTURE tool

Aim 2.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Explore clinical practice implementation approaches to and acceptance of CAPTURE case finding for clinically significant COPD in a range of primary care practices.	Primary care clinician recommendations that inform CAPTURE RE-AIM strategies at both provider and clinical support levels of primary care practice. Primary clinician recommendations that inform CAPTURE-associated COPD education models for primary care clinicians. Primary care clinician recommendations that inform CAPTURE-associated COPD clinical quality improvement designs across a variety of primary care practice types.	Clinical improvement models that introduce new testing must investigate practice opinion and behavior and incorporate clinician recommendation.
Secondary		
Qualitatively assess primary care clinical staff COPD practice behavior – including COPD screening and diagnostic perceptions, beliefs and knowledge – that will inform strategies to improve CAPTURE RE-AIM (reach, impact, adoption, implementation and maintenance of use) characteristics.	Existing COPD screening and diagnostic and case-finding processes within a variety of primary care practices. Primary care practice beliefs about capacity to change from existing COPD screening and diagnostic assessment strategies. Practice-specific COPD screening and diagnostic continuing education preference.	Awareness of existing clinician knowledge and behavior can influence workflow implementation and overall effectiveness of new clinical tools.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Qualitatively assess primary care patient opinion of CAPTURE COPD case finding that will inform strategies to improve CAPTURE RE-AIM (reach, impact, adoption, implementation and maintenance of use) characteristics.	CAPTURE opinion survey ascertaining participant comprehension of CAPTURE instructions and testing and ease of completion.	Patient satisfaction, understanding and ease of test completion affects staff implementation and workflow decision. Participant opinion survey results will seed CAPTURE implementation planning practice staff focus groups.

4 STUDY DESIGN

4.1 OVERALL DESIGN

A prospective, multicenter study that includes three key aims: 1) cross-sectional validation to define sensitivity and specificity of CAPTURE; 2) *qualitative* research exploration engaging clinical staff at all levels from primary care practices serving US patient populations of differing gender, racial, ethnic, urban/rural and socio-economic blends, and 3) explore the impact of CAPTURE on clinical care and patient outcomes across a broad range of primary care settings in a cluster randomized controlled clinical trial. The CAPTURE tool consists of a 5-item self-administered questionnaire and selected use of peak expiratory flow (PEF) measurement, designed to identify clinically significant Chronic Obstructive Pulmonary Disease (COPD).

For Aim 1, approximately 5,000 patients will be recruited at the time of their regularly-scheduled appointment across 100 participating primary care clinics associated with practice-based research networks (PBRNs). Eligible participants will undergo a baseline visit during which the CAPTURE tool and spirometry will be obtained, as well as PEF and other participant characteristics.

For Aim 2, approximately 150 clinicians from 10 participating primary care practices across 5 US PBRNs will undergo detailed implementation investigation of the CAPTURE case finding model for clinically significant COPD. In addition, 200 primary care patients recruited as part of Aim 1 will complete a 10-minute written CAPTURE opinion survey.

To address Aim 3, participating primary care practices will be randomized in a 1:1 fashion to one of the following interventions:

- Arm 1: Practice clinicians will receive basic COPD education, and patient-level CAPTURE information with CAPTURE interpretation education (CAPTURE+ COPD education). As the second aim addresses the optimal format for delivering practice CAPTURE education this will be incorporated at the sites randomized to this arm (see Enhanced CAPTURE education in Figure 1).
- Arm 2: Practice clinicians will receive basic COPD education only (COPD education).

Basic COPD and CAPTURE specific education will use an interactive, web-based education program which will be provided to all practice personnel, including physicians, nurse practitioners, physician assistants, nurses, medical assistants, clerical staff and administrative staff. Practitioners at sites randomized to the CAPTURE+COPD education intervention will receive the CAPTURE score from the central study coordinators soon after the baseline assessments have been completed.

Addressing Aims 1 and 3 will include a baseline visit for all participants and for Aim 3 longitudinal follow-up over 12 months for a predefined cohort of participants. Determination of the participants included in the longitudinal follow-up cohorts will be made after the baseline visit.

Baseline Data

Practices and/or study staff will pre-screen patients according to local guidelines to identify potential participants based on the following criteria: no prior COPD diagnoses, between 45 and 80 years old, and speak and read either English or Spanish. The timing of the pre-screening and the method to approach these patients for participation in the study (e.g., at the next outpatient visit, via telephone) will be flexible, depending upon site recruitment preferences. Patients who are eligible based on the pre-screening questions and agree to participate in the study will sign informed consent. After signing the consent, they will complete the CAPTURE questionnaire, PEF testing, spirometry testing, other respiratory questionnaires, and provide past medical history and demographic information. Local/PBRN study coordinators for each of the 5 PBRNs will perform the study procedures and record baseline information into the electronic data capture (EDC) system.

The EDC system will calculate a CAPTURE score for each participant, based on his/her CAPTURE questionnaire answers and PEF measurement. A binary score (positive or negative CAPTURE) will be emailed to the central study coordinator only for participants randomized to CAPTURE+COPD education intervention practices. The coordinator will communicate this information to these practitioners. Practitioners at sites randomized to the COPD education only intervention will be blinded to CAPTURE scores. Practitioners in both intervention arms will be blinded to research spirometry results.

Analyses will include a comparison of CAPTURE scores with data from spirometry testing and participant reported data to determine sensitivity and specificity of the CAPTURE tool. *The hypothesis is that a simple case finding methodology using a five-item questionnaire with selective PEF measurement will identify undiagnosed patients with clinically significant COPD.*

Based on the data collected at baseline, participants will be classified into the following groups for analyses:

Cohort	**Definition**
CAPTURE+	Participants with • CAPTURE score $\geq$ 5, or • CAPTURE score of 2, 3, or 4 with a low PEF, defined as <350 L/min for males and <250 L/min for females
CAPTURE-	Participants with • CAPTURE score < 2 or scores 2-4 with normal PEF (defined as $\geq$350 L/min for males and $\geq$250 L/min for females)
Spirometrically defined COPD	Participants with abnormal spirometry, defined as post-bronchodilator FEV_1/FVC <0.7. If a participant is unable to complete a post-bronchodilator spirometry (refusal, technical error on the part of coordinator, etc.), and the pre-bronchodilator

	FEV1/FVC is less than 0.65, the participant will be considered to have COPD for the purpose of follow-up in this study.
Clinically significant COPD	Participants with abnormal spirometry, defined as post-bronchodilator FEV_1/FVC <0.7, plus one of the following: 1) FEV_1 < 60% predicted or > 1 exacerbation like event within the past 12 months.
Mild COPD	Participants with abnormal spirometry, defined as post-bronchodilator FEV_1/FVC<0.7 plus both of the following: • FEV_1 ≥ 60% and • No prior history of ECOPD

Longitudinal Follow-up
A pre-defined subgroup of enrolled participants, who meet any of the below criteria will undergo longitudinal follow-up at 12 months,

1. Participants with a CAPTURE Score ≥ 5 or CAPTURE score of 2, 3, or 4 with a low PEF, defined as <350 L/min for males and <250 L/min for females
2. Participants who have abnormal spirometry results, defined as post-bronchodilator FEV_1/FVC < 0.7 or FEV_1 < 80% predicted at baseline. If a participant is unable to complete a post-bronchodilator spirometry (refusal, technical error on the part of coordinator, etc.), and the pre-bronchodilator FEV1/FVC is less than 0.65, the participant will be considered to have COPD for the purpose of follow-up in this study.
3. A random sample of approximately 5% who do not meet criteria 1 - 2

Participants who meet the criteria for follow-up will be sent notification/reminder letters within the first 3 weeks of enrollment and at 3, 6, and 9 months. Patient-reported data will be collected by COPD Foundation via telephone, secure web-based server, or mail-based methodologies, based on participant preference...

Subject medical data will be collected from the medical record to assess for changes in practice-level care.

The hypothesis for Aim 3 is that sites where COPD and CAPTURE education and patient-level CAPTURE data are provided to clinicians will exhibit improved COPD diagnosis and COPD-related care compared to sites where COPD education is provided to clinicians.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Aims 1 and 3

The totality of the published data confirms the clinical and economic impact of undiagnosed COPD, continuing under-diagnosis, and incomplete application of spirometric testing in the primary care community. It suggests that there is value in COPD case-finding that targets COPD patients most likely to benefit from available therapies. These points identify a pressing health care problem that requires an innovative approach to facilitate identifying these individuals. Our preliminary studies enumerated in section 2.2 extend these concepts by demonstrating that:

- Six key domains identify patients with clinically significant COPD.

- Forty-four distinct items resonate with patients and provide important insights for COPD case-finding.
- Five items exhibit excellent sensitivity and specificity in identifying patients with clinically significant COPD.
- PEF provides incremental value in a case-finding strategy.
- The combination of a five-item questionnaire and PEF optimizes a COPD case-finding strategy in English and Spanish speaking patients.

Our proposed study will provide crucial data to address the operating characteristics and clinical translation to our COPD case-finding strategy into the primary care setting. It will also provide an important initial evaluation of the potential clinical impact of the systematic identification of previously undiagnosed COPD patients.

Aim 2

The rationale for this aim reflects the importance of establishing if an innovative approach to COPD case finding is considered a pragmatic tool with potential utility for primary care clinicians within real-world clinical practice settings. With the completion of this aim we anticipate confirming that future validated approaches to COPD case finding can be adopted in a broad variety of clinical care settings thereby providing further impetus for the rigorous evaluation of a) case finding guided patient outcomes as part of routine primary care clinical practice; b) case finding use in a range of primary care health professional COPD-related education approaches, clinical quality improvement models and diagnostic guidelines; and c) the capacity of clinical case finding and informed follow-up to enhance future COPD clinical care therapeutic paradigms used in primary care practice.

Consistent with Institute of Medicine criteria and US health quality standards for preventive and chronic disease care, the feasibility science qualitative research framework is designed to assist clinical and health education evaluators prepare, assess and evaluate specific implementation factors essential to the success of new diagnostic, therapeutic, educational and programmatic options in real-world clinical practice. This aim's analysis of primary care clinical practice COPD case finding feasibility considerations for CAPTURE includes an initial evaluation of existing COPD diagnostic and case finding processes within the practices, assessment of practices' capacity to change from existing respiratory symptom assessment strategies and an understanding of practice-specific learning preferences associated with new diagnostics and chronic disease diagnosis and management. Patient perceptions of the CAPTURE case-finding process are also obtained to provide a holistic perspective of the clinical feasibility of CAPTURE implementation in primary care practice. Borrowing from the RE-AIM implementation science approach, this aim explores how real-word primary care practices might potentially use CAPTURE to: a) identify target populations (Reach); b) refine current practice appraisal of patient respiratory history, symptoms and diagnostics used to identify clinically significant COPD (Effectiveness/Impact); c) change or integrate COPD case finding into practice workflow (Adoption); d) alter practice communication, education and/or care quality improvement planning for COPD diagnosis and management (Implementation); and e) use COPD case finding consistently over time (Maintenance).

Ten primary care practices will undergo detailed implementation investigation of the CAPTURE case finding model designed to identify patients with COPD most likely to benefit from available therapeutic options. CAPTURE, a one-page questionnaire with selective PEF measurement, is presented to the clinicians of ten practices not participating in aims 1 and 3 as a prospective COPD case finding option awaiting validation. By representing CAPTURE as a model—and not introducing it into actual practice—aim 2 gains recommendation from primary care clinical practice experience with sufficient feasibility

generality to circumvent interdependence between the operating characteristic exploration (aim 1) and qualitative feasibility understanding (aim 2) components of our study. The aim 2 results, that include the pooled CAPTURE clinical communication, education and implementation recommendations from real-world primary care practice, are analyzed and applied in concert with local and national research team expertise to enhance the potential impact of CAPTURE's introduction into clinical care in aim 3. Aim 2 results also provide previously unexplored qualitative information necessary for future long-term patient outcome studies of COPD case finding approaches in primary care.

4.3 END OF STUDY DEFINITION

Participants that do not meet the criteria for, or are not selected for, longitudinal follow-up will be considered to have completed the study after completion of the baseline visit.

Participants included in the longitudinal follow-up phase will be considered to have completed the study after completion of the Month 12 Assessment as shown in the Schedule of Activities (SoA), Section 1.3.

Clinician participants in aim 2 will have completed the study after participation on their second focus group between months 14 and 16 as shown in the Figure 2, Structure of Aim 2.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Inclusion criteria for Aims 1 and 3
In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Male or female, aged 45 – 80 years

Inclusion criteria for Aim 2

Two Aim 2 practices are selected by each of their 5 affiliated PBRNs based upon willingness to participate and variability of primary care practice type within the PBRN. Differences in practice size, staffing, ownership, prior quality improvement engagement, geography, patient population socioeconomic status (SES) or languages spoken are among the among the selection criteria the PBRNs will utilize to choose.

Clinician participants (10 practices with up to 15 clinicians per practice):
1. Provision of signed and dated informed consent form.
2. Stated willingness to comply with availability and all study procedures for the duration of aim 2 by the 10 practices (through PBRN recruitment) and their up to 15 clinicians within (through informed consent).

Patient participants [200 patients (approximately 40 from each PBRN)] for CAPTURE survey:
1. Provision of signed and dated informed consent form.

2. Stated willingness to comply with all study procedures and availability for the duration of the study.
3. Male or female, aged 45 – 80 years.

5.2 EXCLUSION CRITERIA

Exclusion criteria for Aims 1 and 3

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Previous clinician provided diagnosis of COPD
2. Treated respiratory infection (with antibiotics and/or systemic steroids) in the past 30 days of baseline
3. Participants unable to perform spirometry due to any of the following conditions within the past 30 days of baseline
    a) Chest surgery
    b) Abdominal surgery
    c) Eye surgery
    d) Heart attack
    e) Stroke

Exclusion criteria for Aim 2

1. Clinician participants: current employment at practices participating in aims 1 and/or 3
2. Clinician participants: from practices providing fewer than 2 clinician participants
3. Patient participants: meeting the exclusion criteria for aims 1 and 3 (above)

5.3 SCREEN FAILURES

PBRN coordinators, in conjunction with clinical study site personnel, will pre-screen individuals who are unlikely to be able to complete research spirometry. These individuals will be considered *pre-screen failures*.

Participants who are consented to participate but have a prior clinician diagnosis of COPD will be considered *screen failures*.

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment and retention strategies for Aims 1 and 3

Approximately 5,000 participants will be recruited from 100 primary care clinics affiliated with five PBRNs. Each PBRN has centrally-based research coordinators with a history of success working in PBRN practices, documented expertise in previous large diagnostic or therapeutic trials, and personnel experienced in recruitment and data collection.

IRB approval will be obtained at each PBRN for approval for patient contact, informed consent and participation in this study.

All patients who meet all inclusion and no exclusion criteria at the participating PBRN clinical site will be eligible for participation. Research coordinators will work with participating practices to identify and approach potential participants. Recruitment strategies may vary depending on the practice.

Enrollment of participants will depend on the gender, ethnic and racial makeup of those that are being recruited from the practices included in this trial. No exclusion criteria apply specifically to women or to minorities. The Data Coordinating Center (DCC) will track enrollment of participants throughout the course of this study. If women and minorities are under-represented in the initial phase of recruitment, a commitment exists to develop recruitment strategies that target these populations so the final study group is a well-balanced representation of the studied population.

Recruitment and retention strategies for Aim 2

Clinician participants: Approximately 150 clinic participants are recruited by: 1) introductory telephone contact with the practice leadership by PBRN research coordinators and the aim 2 research team; 2) follow up letter, time commitment infographic and informed consent forms sent to interested practices outlining aim 2 clinician participant activities and responsibilities; and 3) in-person aim 2 study explanation to clinician participants at the committed practices during the introductory baseline study site visit.

Clinician participant recruitment draws from both prescribing (or "provider") staff and non-prescribing (or "clinical support") staff. The aim 2 research team will attempt to obtain an even mix of both clinician staff types from each practice. Retention incentive of clinician participants over 2 years includes provision of on-line COPD education to all clinician participants and monetary incentive to practices as determined by each individual PBRN.

Patient participants: 200 participants (40 from each PBRN) are recruited as a sub-set of the aim 1. Each of the 200 patient participants in aim 2 are asked to complete a one-time 10-minute written opinion survey. Their aim 2 participation is concluded at the end of the opinion survey completion.

The aim 2 research team and DCC will track enrollment and retention of all aim 2 participants throughout the course of the 2-year aim 2 study.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

The study intervention is applicable to Aims 2 and 3 and consists of healthcare provider education modules.

The practitioners at the 10 sites selected for Aim 2 will receive module 1, Basic COPD education, and may elect to take modules 3-5 for supplemental information on COPD.

For Aim 3, half of the practices will receive Basic COPD education (module 1) and half will receive Basic COPD Education and CAPTURE Education (modules 1 and 2). Practitioners at practices randomized to COPD only education must take module 1 and may elect to take modules 3-5; however, they will not take module 2. Practitioners at practices randomized to COPD+CAPTURE education must take modules 1 and 2, and may elect to take modules 3-5.

1 - Basic COPD Education will be provided in order for providers to optimally manage patients with COPD. The education will incorporate evidence-based recommendations using the 2018 update of the Global Obstructive Lung Disease Strategy(45).

A 40-minute overview will be presented in the most expeditious manner at each practice site, for example by webinar for all practice personnel over the lunch hour, or audiovisual presentation available on a dedicated CAPTURE web site. The PBRNs have indicated that this module should be no longer than 40 minutes. Topics will include: CAPTURE study description and rationale, importance of COPD in the region of the local practices, COPD definition and diagnosis, patient goals, and management approach. Attendance at this mandatory training will be documented and continuing education credits will be provided for physicians and nurse practitioners by National Jewish Health, an accredited CME provider.

2 - **CAPTURE education**. An online audiovisual module will be developed to explain CAPTURE interpretation and use in patient evaluation and diagnosis of COPD. This module will only be available to practices randomized to receive the results of CAPTURE for clinical use.

With the information provided in Aim 2 about practice preferences for education, the CAPTURE education module will be revised and made available to practices enrolled in Aim 1 after the completion of Aim 2.

3 - Online advanced COPD education will be available for all practices and continuing education credits will be provided to enhance practitioner participation. Practitioner attendance at each online audiovisual module will be collected including the amount of time spent on each education module, completion of each module with a post-test and evaluation, and CME will be provided. Education will be case-based and will include role playing where appropriate. Seven basic modules of 20 minutes or less will be available both to practices randomized to receive CAPTURE results for clinician use and to control practices that will not receive CAPTURE results and will cover:

1. Diagnosis of COPD: How to diagnose COPD in primary care including medical history, physical exam and role of spirometry, severity categorization
2. Spirometry overview: Basic clinical interpretation
3. Advanced spirometry: Test performance, evaluating quality, advanced case-based interpretation
4. Management overview: Patient goals, smoking cessation, vaccination, patient education, shared decision-making
5. Pharmacotherapy: Inhaled bronchodilators, inhaled corticosteroids
6. Other therapies: Oxygen, pulmonary rehabilitation, surgical approaches
7. Inhalation devices: Patient education

4 – On-site COPD education. Additional funds will be sought to provide on-site COPD education. We have experience in successfully providing half-day on-site education to primary care practices to enhance their management of COPD.

5 – Social media and case conferences. We will use social media (Facebook and Twitter) to provide ongoing education about COPD. Facebook and Twitter posts will provide tips on managing COPD. Online conferences will be scheduled to discuss cases submitted by primary care providers.

6.2 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

For Aims 1 and 3, this study will use randomization and blinding as two of the cardinal principles of clinical trials to minimize bias.

Randomization. Practices will be randomized into one of the two interventions, COPD education or COPD education + CAPTURE education, in a 1:1 manner, stratified by PBRN. Randomization will occur at the time of site activation and each site will be assigned a unique randomization number. The DCC will prepare the randomization schedule, using computer-generated block randomization with the block size(s) known only by the DCC. A secure web-based application will be built that will be used by the central study coordinators to enter site information (e.g., site ID, stratification factor) and to obtain the randomization number. The information can be printed and sent and/or emailed directly to the study coordinator.

Blinding. This is a single-blind study with the participants blinded to whether their practitioners have received CAPTURE education and patient-level CAPTURE results. Practitioners at sites that are randomized to the control arm (COPD education alone) will be blinded to the CAPTURE questionnaire and PEF results. All practitioners and participants will be blinded to the baseline COPD status of the participants (i.e., blinded to spirometry results), except for safety reasons. In this situation, participants and their clinician will be notified if a participant's post-bronchodilator FEV_1 is less than 30% predicted. For all other participants, they and their practitioners will be blinded to research spirometry results. The coordinator should make every effort to conceal the spirometry results from the participants in these latter cases. Study coordinators should also make every effort to conceal the administration of a post-bronchodilator spirometry test from the practice staff so as not to unblind the physicians to abnormal spirometry.

6.3 STUDY INTERVENTION COMPLIANCE

In practices randomized to share the CAPTURE results with the clinician, the goal is to share results with the clinician at the time of the CAPTURE study visit. Providing results at the time of the clinical visit will allow the clinician to act on the CAPTURE results as soon as possible when the participant is in front of the clinician. Based on the workflow at each of the practices, this may not always be possible.

Sharing of the CAPTURE results with the participant's primary care clinician will be tracked by the study coordinator enrolling patients at sites randomized to receive CAPTURE results. The sharing of CAPTURE results will be recorded on the study eCRF form. The eCRF will collect the timing of when the results were provided to the practitioner - whether the results were provided to the clinician at the time of the enrollment visit prior to the clinician visit with the patient, or were provided at another time.

If results were not shared at the time of the CAPTURE study visit, then the date of sending the CAPTURE results will be recorded on the appropriate eCRF by filling in the date (day/month/year) the exact copy of the CAPTURE Toolwere sent to the clinician through a HIPPA-compliant method and placed in the medical record. The goal is to communicate the results to the clinician. The DCC will monitor review all participants' eCRFs to assure that all those enrolled from practices randomized to CAPTURE results have been shared with clinicians..

6.4 CONCOMITANT THERAPY

Practitioners will treat participants using their own clinical judgment. No medications are prohibited. This is not an interventional therapeutic trial.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

In this cluster randomized controlled trial (Aim 3), where practices are the recipients of the intervention and where the interventions are based upon education and access to CAPTURE and PEF results, it is not anticipated that study intervention will be discontinued at the practice level. However, one of the CO-PIs will review safety data, especially SAEs related to baseline spirometry and PEF procedures, to ensure there are no untoward effects of the study on participants.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in Aims 1 and 3 of the study at any time upon request.

Clinician participants in Aim 2 are free to withdraw from participation in the study at any time upon request. If a clinician is no longer working at the participating practice then their involvement in Aim 2 activities will end and no further attempt will be made to include them in the remaining questionnaires or focus groups.

7.3 LOST TO FOLLOW-UP

If a participant selected for longitudinal follow up does not respond to the 12-month questionnaires, coordinators will attempt to contact participants first by the participant's preferred method of communication, either phone or email. At least three attempts will be made. If no response is obtained, the participant's alternate contact method will be attempted three times. Phone calls will be made at different times of the day. If there is no response, a registered letter will be sent to the participant. If the participant cannot be reached, the alternate contact will be called and/or emailed. If no response is received, a registered letter will be sent to the alternate contact. If after all of these methods are employed and no contact with the participant results, the participant will be considered lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 BASELINE ASSESSMENTS AND DATA COLLECTION

Efficacy data will be collected by patient-reported outcomes and medical record review.

For Aim 1, CAPTURE, PEF results, acute respiratory event history and spirometry will be considered efficacy assessments. They are collected at the baseline visit.

CAPTURE. Participants will complete the 5-item *self-administered* questionnaire and measurement of Peak Expiratory Flow (PEF).

Peak Expiratory Flow (PEF). PEF using the Vitalograph® AsmaPlan® mechanical PEF meter with SafeTway® disposable mouthpieces (Vitalograph LTD, UK) will be measured for all participants. Ideally, PEF should be prior to the participant's physician appointment. The participant will perform three PEF tests. All three measurements will be recorded.

Spirometry. Before spirometry is performed, participants will be asked if they have taken a medicine which they breathed into their lungs from any puffer or inhaler within the past two hours. If participant answers yes, then spirometry will be performed but considered a post-bronchodilator spirometry test. No further spirometry will be needed. If participant answers no, then pre-bronchodilator spirometry will be performed for measurement of forced vital capacity (FVC), forced expiratory volume in one-second (FEV_1), and calculation of FEV_1/FVC (using EasyOne® Spirometer, ndd Medical Technologies Inc., Andover, MA). Testing will be performed in accordance with established American Thoracic Society/European Thoracic Society (ATS/ERS) standards.
A Spirometry post-bronchodilator will only be performed if pre-bronchodilator spirometry FEV_1/FVC is less than 0.70 or FEV_1 is less than 80% predicted. Post-bronchodilator spirometry will be performed within 15 to 20 minutes after inhalation of 2 puffs of albuterol 180 mcg HFA using an AeroChamber Plus* Flow-Vu® spacer with one minute between the first and the second inhalation. A separate AeroChamber will be provided for each participant's testing. A standing order for albuterol administration may be used if necessary.

Spirometry is a valid, reproducible means of documenting the presence and severity of airflow limitation. When properly performed with maximum effort and attention to the details of calibration of the instrument, spirometry maneuvers are among the most reproducible of biomedical measures. In the setting of a highly trained, experienced therapist, a coefficient of variation of 2-3% is not unusual. Spirometry will be performed in a standardized manner in accordance with the ATS guidelines, as described in the manual of procedures (MOP). Spirometry is the timed-based measurement of the amount of air that can be forcefully exhaled from the lungs after a full inspiration. In the forced expiratory vital capacity maneuver, a person inhales as big a breath as possible and then blows it out as fast and as long as possible until no more air can leave the lungs. The volume of air leaving the lungs is recorded continuously throughout the maneuver in order to allow calculation of important measures of lung function.

NHANES prediction equations, which are programmed into the Easy On PC spirometers, will be used to calculate the predicted lung function levels. These require the input of age, height, and race/ethnicity (White, Black, Hispanic). For people of mixed or unknown race the White prediction equations will be used.

PBRN Research Coordinators will be trained and certified in the performance of spirometry testing. Spirometry will be sent for central review for quality control assurance.

Adjudication of the Presence of Obstruction on Post-Bronchodilator Spirometry

The presence of obstruction is determined by the presence of an FEV_1/FVC ratio less than 0.70 after the administration of a bronchodilator. A bronchodilator will be administered to study subjects whose baseline FEV_1/FVC is less than 0.70 or whose FEV_1 is less than 80% of the predicted value.

If a subject is unable to complete a post-bronchodilator spirometry (refusal, technical error on the part of coordinator, etc.), and the pre-bronchodilator FEV_1/FVC is less than 0.65, the patient will be considered to have COPD for the purpose of follow-up in this study.

Height and weight
Height and weight will be recorded in order to determine appropriate prediction equations for spirometry and possible effect of obesity on spirometry. Height will be recorded and weight will be measured prior to spirometry testing.

Demographic Data Collection
Demographic data including date of birth, gender, ethnicity, race, educational level achieved, daily work schedule, living arrangement and health insurance will be entered into the EDC system.

Contact information including address, phone numbers and email address will be obtained. Alternate contact information will be obtained for two other people, family members not living with the participant or close contacts, who may be knowledgeable about the participant in the event that the participant cannot be contacted for subsequent longitudinal follow-up. Alternate contact information will include name, address, phone numbers and email addresses. All contact information will be stored securely at the clinical site or in a database separate from that developed for the clinical data.

Medical History
Previous medical diagnoses will include comorbidities such as cardiovascular, respiratory and malignant disorders. Influenza vaccination history will also be recorded. This questionnaire will be completed under supervision of the coordinator.

Concomitant Medication Review
Respiratory medications will be recorded at baseline for all participants. This questionnaire will be completed under supervision of the coordinator.

COPD Assessment Test (CAT)
Participants will complete the 8-item *self-administered* questionnaire.

Respiratory symptoms, smoke exposure and exacerbation like events
History of respiratory symptoms and exacerbation like events over the past year as well as smoke exposure (including e-cigarette or equivalent) will be recorded. This questionnaire will be completed under supervision of the coordinator.

Whenever possible, informed consent, eligibility review, CAPTURE Questionnaire and PEF will be performed prior to the participant's clinic appointment, so that CAPTURE results may be provided to the physician at the time of his/her appointment if the patient is cared for in a clinical center randomized to CAPTURE+ education.

Adverse events
Adverse events related to study procedures will be recorded by the coordinator.

8.2 LONGITUDINAL FOLLOW-UP ASSESSMENTS AND DATA COLLECTION

For Aim 3, the follow-up efficacy assessments are collected from the time of baseline to 12 months in selected cohorts (as described in section 4.1). Medical record abstractions completed by PBRN coordinators and participant questionnaires administered by study team members from the COPD Foundation are used.

Data collected from medical record include:

All participants undergoing 12-month follow-up as described in section 4.1	Current Smokers Only
Clinical spirometry ordered or administered	Smoking cessation counseling
Referral to specialist for respiratory evaluation/treatment	New prescription for smoking cessation medication
New recorded clinical diagnosis of COPD	Formal smoking cessation program referral/completion
New prescription for respiratory medication (long acting bronchodilator, inhaled steroids, oral anti-inflammatory)	
Exacerbation like event assessment (hospital, ED, minute clinic, antibiotic/steroid prescription/administration)	
Vaccination status	
Formal pulmonary rehabilitation program referral/completion*	

*only collected in relevant participants

Data from clinical visits to be collected at follow-up by telephone, secure web-based server, or mail-based methodologies directly from participants and administered by COPD Foundation study personnel include:

All participants undergoing 12-month follow-up as described in section 4.1	Current Smokers Only
Spirometry	Smoking cessation counseling
New diagnosis of COPD	Smoking cessation medications (including OTC)
Referral to pulmonologist or other respiratory specialist	
Exacerbation like event assessment	
New prescription for respiratory medication (long acting bronchodilator, inhaled steroids, oral anti-inflammatory)	
CAT score	

Attendance of pulmonary rehabilitation*	

*only collected in relevant participants

8.3 AIM 2 ASSESSMENTS AND DATA COLLECTION

Practice study introduction and participation confirmation: After PBRN practice selection, the CAPTURE study Aim 2 lead together with the local PBRN Aim 2 coordinator conduct a 15-minute participation confirmation and introduction phone call with the key PBRN contact at each of the two selected practices. The study specifics and timeline are reviewed. After practice participation is confirmed, the on-site practice assessment date is scheduled. Informed consent forms for clinical staff are mailed to each confirmed practice. To reduce practice burden, completed clinical staff informed consent forms (up to 15 clinical staff per practice) can be returned by mail to the University of Michigan School of Public Health office, addressed to Dr. Randall Brown, or saved for completion and picked up at the on-site practice assessment site visit. Following the confirmation phone call, the PBRN Aim 2 coordinator completes a short (15 minute) qualitative questionnaire detailing the selected and confirmed practice demographics and PBRN parameter of practice choice for each of the two practices. The completed PBRN Practice Selection Questionnaire is returned to the Aim 2 data team and stored securely.

On-site Practice Assessment (OSPA): The OSPA is an in-person on-site practice workflow assessment. It includes 2 practice clinicians per practice choice, the PBRN Aim 2 coordinator (if available), the CAPTURE study Aim 2 lead and the CAPTURE Aim 2 research specialist (if the PBRN Aim 2 coordinator is not present). The objective of the visit is to detail specifics of practice workflow, practice physical characteristics, staff roles, clinical information gathering patterns for respiratory patients, electronic health record communication, continuing education structure, and quality improvement structure. The assessment takes place in three parts; the pre-observation practice overview (conducted with the 2 practice clinicians – 60 minutes), the ½ day practice workflow observation (observation by one member of the Aim 2 research team of common and testing areas used for the respiratory patient). There is no patient engagement and no collection of patient-specific identification or health information), and the post-observation practice summary (conducted with the same 2 practice clinicians – 30 minutes).

The 3 OSPA assessment tools are:

i) The Pre-workflow Observation Practice Assessment Review Questionnaire
ii) Respiratory Workflow Assessment Review
iii) The Post-workflow Observation Practice Assessment Review Questionnaire

Also at the OSPA, informed consent is obtained from all remaining participating staff (up to 15 clinical staff per practice) by the CAPTURE Aim 2 team and returned to the Aim 2 data team for secure storage.

Clinical Staff Questionnaires (Baseline/6/12 months). Written or on-line questionnaires are provided to participating and consented staff personnel at two practice levels -- Non-Prescribing clinical (also known as “support”) staff and Prescribing (PR) clinical (also known as “provider”) staff.

Non-Prescribing (NPR) clinical staff are clinical practice personnel involved in clinical workflow (including registered nurses, licensed practical nurses, medical assistants, medical assistants and receptionists), yet not having the role to make final and official medical diagnostic and management disposition plan decisions for and with patients. Prescribing (PR) clinical staff are prescribing clinical practice personnel involved in clinical workflow (including doctors, nurse practitioners, and physician assistants) who may

independently make final medical diagnostic and management disposition plan decisions for and with patients.

Questionnaire items explore clinician demographics, including past education, duration of current employment and currently held clinical position. COPD knowledge, attitudes, beliefs, practice patterns and self-efficacy regarding COPD diagnosis, management, spirometry testing and interpretation, practice workflow and communication in the clinical primary practice care of adult patients with respiratory disease. Additional questions include preferred continuing education method and clinical staff quality improvement modalities for respiratory disease management. Specific examples of past practice chronic disease diagnostic changes and the individual and practice-wide levers of success and challenge associated with those changes are explored.

Each of the 3 (baseline, 6-month and 12-month) questionnaires are completed within 30 minutes. No identifying patient data is collected. Online questionnaires are collected and secured by the CAPTURE DCC and Aim 2 research team. The participants who complete written questionnaires (per their preference) mail completed questionnaires via pre-addressed stamped envelope to the CAPTURE DCC and Aim 2 research team.

Patient Opinion Surveys:
200 patient participants, 40 from each PBRN, are recruited as a sub-sample from Aim 1 practices. Patient participants fulfill all inclusion and exclusion criteria and receive informed consent for survey participation as part of aim 1.

Eligible participants complete a written one-time 5 to 10 minute CAPTURE opinion survey. Patient survey data is collected by Aim 1 research coordinators and is processed with Aim 1 baseline patient data. Patients receive a $10 gift card for completion of the survey Aim 2 patient participation ends at the completion on the lone opinion survey.

Participants who prefer to complete the 5 to 10-minute survey online via Qualtrics will be sent a secure, Qualtrics link via email. The Qualtrics survey will include a brief, introductory screen affirming consent, describing the survey and instructions about participation. Once the survey is complete, participants will see a screen with instructions about how to obtain their $10 gift card and how to contact study staff with questions regarding the survey.

Modular online COPD education. Access to free, COPD on-line, continuing education is provided for all clinical staff at each practice. Each module will take 20 minutes or less. Modular components of and access to COPD education is described in the protocol. Aim 2 clinician participant access and completion of COPD education modules is assessed by clinician questionnaires and focus group item response over 12 months (between months 2 and 14 of Aim 2 timeline).

COPD in Primary Care/CAPTURE Introduction Focus Groups:
Two 45 to 60-minute focus group discussions occur at each Aim 2 practice. Focus groups are informed by practice demographics, practice assessment data – including respiratory workflow, baseline clinical staff questionnaire data regarding respiratory knowledge, attitudes, beliefs and practice preference for the diagnosis and care of adult patients with respiratory disease as well as patient opinion from CAPTURE surveys and past CAPTURE study (46, 47). Focus group candidate themes and prompts are developed for non-prescribing clinical staff (NPR) and prescribing clinical staff (PR) and are presented at separate on-site focus group sessions to allow more detailed discussion of role responsibility in the

context of daily practice workflow, generating a more abundant qualitative data sample. Separation of and PR clinical staffing implementation themes into two focus groups also limits potential for hierarchical work-related discussion suppression described in other short duration focus group studies (48-52).

The focus group moderator introduces the CAPTURE tool utilizing CAPTURE education components described in Section 6.1.1. The focus group moderator follows RE-AIM prompts for CAPTURE implementation planning discussion throughout the focus group. Targeted COPD self-efficacy limitation themes from questionnaire data (including awareness and/or use of validated respiratory assessment questionnaires, spirometry, COPD guidelines, inhaled medication patient education, oxygen therapy, smoking cessation education, vaccination recommendation, pulmonology specialty care and pulmonary rehabilitation referral) are explored. Questions will probe clinicians to identify and explain levers that may maximize uptake of CAPTURE use in their practices as well as potential barriers to implementation. The Aim 2 research team will record each focus group using audio and written note-taking that will allow an abridged yet detailed tape-based micro-interlocutor analysis of focus group emergent themes, questions, answers and interactions. Key themes informing consensus discussion, program modifications and key elements of the CAPTURE RE-AIM implementation dimensions will be identified. Audio-recordings will be professionally transcribed and codes will be generated for the interview topics and key research questions. Reviewing the transcripts line-by-line, all substantive information will be assigned a priori codes as relevant for CAPTURE RE-AIM implementation planning, COPD diagnosis and CAPTURE intra-office clinical communication and COPD/CAPTURE education preference assessment. Additional codes will be developed for sub-themes and emergent themes.

Development of Practice-Based CAPTURE Implementation PBL Cases:
From analyses of the 2 NPR and 2 PR CAPTURE Introduction focus groups per PBRN, baseline clinical staff questionnaire data, online CAPTURE opinion surveys, and on-site practice assessments, 1 primary care practice CAPTURE implementation case per PBRN (total implementation cases = 5) is created by the Aim 2 research team. Given local knowledge of chronic disease management quality improvement history, effort, challenge and successes, each PBRN's participation in case creation will be instrumental. The Aim 2 research team will lead case creation using evidence-based problem based learning (PBL) techniques (53-57). The Center for Research on Learning and Teaching (CRLT) at the University of Michigan will serve as research reference for PBL case development qualification (58). Each local PBRN PBL case will be distributed to the Aim 2 clinical staff at the 2 participating PBRN practices 2 weeks prior to the CAPTURE Implementation focus groups, giving Aim 2 participants an opportunity to read the case introductions prior to the focus group session. Also, each practice will receive one additional non-PBRN case for focus group discussion as selected by the Aim 2 research team. Therein, each of the 5 CAPTURE implementation PBL cases will receive 2 comprehensive focus group reviews (see below).

CAPTURE Implementation PBL Case Presentation Focus Groups:
Each practice participates in a final pooled (NPRs and PRs together) on-site focus group. Two CAPTURE implementation cases (described above) are discussed at each focus group. The focus will explore, discuss, glean and create optimal 1) CAPTURE implementation, 2) CAPTURE clinical communication, 3) CAPTURE/COPD education and 4) CAPTURE primary care quality improvement recommendations pooled from all clinical practice levels for each of the 2 presented cases.

The Aim 2 research team will record each focus group using audio and written note-taking that will allow an abridged yet detailed tape-based micro-interlocutor analysis of focus group emergent themes, questions, answers and interactions. Key themes informing consensus discussion, program

modifications and key elements of the CAPTURE RE-AIM implementation dimensions will be identified. Audio-recordings will be professionally transcribed and codes will be generated for the interview topics and key research questions. Reviewing the transcripts line-by-line, all substantive information will be assigned a priori codes as relevant for CAPTURE RE-AIM implementation planning, COPD diagnosis, CAPTURE intra-office clinical communication, and COPD and CAPTURE education preference, and COPD diagnosis quality improvement assessment. Additional codes will be developed for sub-themes and emergent themes.

8.4 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.4.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.4.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.4.2.1 SEVERITY OF EVENT

The following guidelines will be used to describe severity of AEs.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.4.2.2 RELATIONSHIP TO STUDY INTERVENTION

All AEs must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.

- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.
- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the study intervention). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.4.2.3 EXPECTEDNESS

The Principal Investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.4.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

Adverse events (AE)s that occur during the baseline visit will be recorded.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed.

8.4.4 ADVERSE EVENT REPORTING

All AEs that occur at baseline visit will be recorded in the case report form and reported to the DCC. We anticipate few adverse events due to the non-invasive nature of the study procedures. Participants will only be enrolled if they meet the study eligibility criteria, including assessment for contraindications for spirometry. Targeted safety questions will be asked of all patient participants prior to albuterol to exclude those with a previous adverse event with the medication and others at high risk due to cardiac abnormalities.

8.4.5 SERIOUS ADVERSE EVENT REPORTING

SAEs will be reported to the IRB at the institution where the event occurred and the University of Michigan IRB will be notified of any serious adverse experience within 7 calendar days of occurrence. These will be reported to the DSMB.

Follow-up of serious adverse events

All SAEs will be followed up until resolution or permanent outcome of the event. All follow-up information will be included in the case report form. The DSMB will make recommendations to ensure data integrity and the safety of study participants.

8.5 UNANTICIPATED PROBLEMS

8.5.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.5.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing IRB and to the DCC. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the DCC within 7 calendar days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC within 14 calendar days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within one month of the IRB's receipt of the report of the problem from the investigator.

8.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a DSMB (physicians with the appropriate expertise, including non-involved pulmonologists, primary care physicians, and independent statisticians with clinical experience). Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the Principal Investigators.

9 STATISTICAL AND ANALYTICAL PLANS

9.1 SAMPLE SIZE AND POWER

9.1.1 PRIMARY OBJECTIVES

Define the sensitivity and specificity of CAPTURE for identifying previously undiagnosed patients with clinically significant COPD in a broad range of primary care settings. We will also explore clinical practice implementation approaches to and acceptance of CAPTURE case finding for clinically significant COPD in a range of primary care practices. Further, we will define the impact of CAPTURE information provided to clinicians in identifying and managing patients with respiratory symptoms (CAPTURE+) across a broad range of primary care settings.

9.1.1.1 SENSITIVITY AND SPECIFICITY OF THE CAPTURE TOOL

Primary Hypothesis 1. *The CAPTURE tool will exhibit excellent sensitivity and specificity in diagnosing clinically significant COPD as defined by post-bronchodilator $FEV_1/FVC < 0.70$ in addition to either >1 exacerbation-like event (ECOPD) within the past 12 months or an $FEV_1 < 60\%$ predicted.* Approximately 5000 patients will be enrolled in the study with the expectation that 300-800 of these will have previously undiagnosed clinically significant COPD, identified through research spirometry and documentation of prior respiratory events. Amongst cases, we will calculate the proportion of individuals who are at high risk for clinically significant COPD based on CAPTURE (sensitivity). Similarly, amongst non-cases, we will calculate the proportion of individuals not classified as having clinically significant COPD based on CAPTURE (specificity). Corresponding 95% confidence intervals will be calculated.

Based on our preliminary data drawn from a research setting, we noted 89.7% sensitivity and 93.1% specificity for CAPTURE. Table 9-1 shows the range of sensitivity and specificity 95% confidence interval widths that would result if the true sensitivity or specificity is 85%, 90% or 95% across a range of sample sizes. For instance, if we find 500 individuals with confirmed clinically significant COPD and CAPTURE has 90% sensitivity, then the 95% confidence interval for sensitivity would be 90% ± 2.6%. Similarly, if 4,000 individuals are confirmed to have no evidence of clinically significant COPD and CAPTURE has 90% specificity, then the 95% confidence interval for specificity would be 90% ± 0.9%.

Table 9-1 Projected Confidence Interval Widths for Various Sensitivity/Specificity Percentages (Columns) and Sample Sizes (Rows).

	Sensitivity or Specificity		
Sample Size	**85%**	**90%**	**95%**
5000	± 1.0%	± 0.8%	± 0.6%
4000	± 1.1%	± 0.9%	± 0.7%
1000	± 2.2%	± 1.9%	± 1.4%
500	± 3.1%	± 2.6%	± 1.9%
250	± 4.4%	± 3.7%	± 2.7%
100	± 7.0%	± 5.9%	± 4.3%
50	± 9.9%	± 8.3%	± 6.0%

9.1.1.2 ADOPTION AND IMPLEMENTATION OF THE CAPTURE TOOL IN PRIMARY CARE PRACTICE

Primary Hypothesis 2: *A COPD case finding methodology using a validated one-page, five-item questionnaire with selective PEF measurement (CAPTURE) can be incorporated into the clinical practice patterns, clinical workflow, communication and practice-based quality improvement paradigms of a variety of primary care clinical settings.*

Aim 2 is a qualitative study to determine the efficacy of workflow integration of the CAPTURE tool. Statistical analysis of the clinician questionnaire will involve simple sums of each item and reviewing answers across practices and region. Standard frequencies for questions will be developed to examine patterns in responses.

The clinician focus groups will be conducted on-site at each practice at a time convenient for the participating clinicians. The number of prescribing and non-prescribing clinicians will equal 15 per practice and is based on interest with a maximum of 8 prescribing clinicians/practice. The sample size will follow a basic qualitative sampling standard of interviewing to redundancy or saturation. The number of clinicians to be interviewed (up to n=15 in each practice) is estimated based on achieving concept saturation. Reflecting regional primary care practice norms and to bolster concept saturation, PBRN Aim 2 coordinator focus group discussion participation is encouraged for very small practices where the participating prescribing and non-prescribing clinician total is less than or equal to 4. For all practice focus groups questions will explore the described Aim 2 CAPTURE RE-AIM concepts, barriers to implementation of the CAPTURE tool at other practice sites, standard processes for COPD and respiratory care diagnosis and management for each clinical role within the practice, and perception of quality improvement methods at each practice. Clinician focus groups are conducted on-site at each of the 10 practices.

Transcripts of clinician focus groups will all be digital and entered into a qualitative data analysis program, NVivo for Mac. This program allows for an investigation of the salience, patterning, and contexts of key discourse items. Grounded theory methods will be used to identify and label recurrent themes and concepts within textual materials. Texts will be examined line-by-line, key phrases assigned tentative category labels, and coded passages grouped under the themes of feasibility, barrier and utility. The analyses will look for “traces” in dialogue, including repetitions, key words, evaluation statements, and metaphors. Change in salience, patterning, or content of key themes will provide further empirical evidence regarding the efficacy of our program’s efforts to impact community norms and behaviors. An audit trail will be maintained to document the position of text material from which codes and themes are developed. We will use word/code counts of repetitive themes and concepts to

indicate patterns. By allowing for open-ended responses, the narratives and notes will allow us to capture significant changes in participants' attitudes or behaviors. Codes and themes will be discussed iteratively with the research team members to hone definitions and assure consistency of interpretation. We will establish a coding dictionary and all interviews will be coded using the complete set of themes. Two independent coders will code each document to assure inter-coder reliability. Preliminary results will be shared with our Aim 2 research team and will inform the development of the case studies for the latter part of the project.

9.1.1.3 PRACTICE BEHAVIOR IN SITES WITH VERSUS WITHOUT CAPTURE EDUCATION AND PATIENT LEVEL CAPTURE DATA PROVIDED

Primary Hypothesis 3: *Sites where basic COPD and CAPTURE education are provided to clinicians, along with patient level CAPTURE data, will have a higher probability than control sites (i.e., those receiving only basic COPD education) of meeting the composite endpoint in their CAPTURE+ patients within 12 months of baseline.* From record review, the composite endpoint is met if one of the following is recorded: (1) referral for clinical spirometry testing, 2) new clinical diagnosis of COPD, 3) newly prescribed respiratory medication (long acting bronchodilator or anti-inflammatory for respiratory condition), or 4) referral to a specialist for respiratory evaluation/ treatment.

The study will enroll 50 CAPTURE practices and 50 control practices; each practice will enroll 50 patients (for a total of 5,000 patients). We project that within each practice, there will be at least 5 patients previously undiagnosed with COPD who have a CAPTURE+ screening result. The primary analysis will be to compare the average proportion of CAPTURE+ patients per practice that meet the composite endpoint in the two intervention arms. For power and sample sizes computations, this is a cluster randomized trial of n=50 clusters (practices) per intervention arm with 5 CAPTURE+ patients per cluster (practice). The primary power calculation is based on comparing the average cluster sample proportion (average proportion of CAPTURE+ patients per practice meeting composite endpoint) between intervention arms. Table 9-2 displays power for a two-sample test comparing average cluster sample proportions, accounting for possible intra-cluster correlation coefficient (ICC) values of 0.05, 0.10 and 0.15 that are typically seen in cluster randomized trials of behavioral interventions (https://www.abdn.ac.uk/hsru/research/research-tools/study-design/). These calculations assume a type I error of 5% and that the control arm meets the composite endpoint in 5% of CAPTURE+ patients and the CAPTURE arm meets the composite endpoint in higher percentages (columns of Table 9-2). There will be variability in the actual number of CAPTURE+ patients per practice. It is standard practice to inflate the number of needed clusters by 12% to account for this extra source of variability. Therefore, our power calculations are based on 44 clusters per intervention arm.

Table 9-2. Overall power to detect a difference in rate of meeting primary endpoint in CAPTURE group (50 practices/clusters) vs usual care (50 practices/clusters), assuming 5% performance rate in usual care; 50 patients total / practice; assuming 10% prevalence gives 5 CAPTURE+/practice

Improvement over usual care	+7.5%	+10%	+15%	+25%	+50%
ICC=0.05	0.72	0.89	0.99	>0.99	>0.99
ICC=0.10	0.65	0.84	0.98	>0.99	>0.99
ICC=0.15	0.59	0.79	0.97	>0.99	>0.99

9.1.2 SECONDARY OBJECTIVES

9.1.2.1 SENSITIVITY AND SPECIFICITY IN PREDEFINED SUBGROUPS

We will also examine several subgroups of interest that are key to addressing our overall goal of defining the value of CAPTURE across a broad range on individuals. These will include sex, ethnic groups, rural and urban location, and educational level, among individuals with clinically significant COPD, spirometrically defined COPD and individuals with "mild" COPD as defined in this protocol. We have specifically chosen clinical sites with a diverse gender, racial and ethnic mix, and rural and urban mix with the expected prevalence of clinically significant COPD cases and controls by subgroup outlined in

Table 9-3. Projected numbers of clinically significant COPD cases and non-cases we expect by subgroup of interest assuming prevalence of obstructed individuals is between 6-16%. (*Non-Hispanic) This table assumes prevalence of non-clinically significant COPD similar to clinically significant COPD (not included in this table).

	Total	**Men (50%)**	**Women (50%)**	**White* (62%)**	**Black* (15%)**	**Hispanic (18%)**	**Rural (46%)**	**Urban (54%)**	**Ever-Smokers (40%)**	**Never-smokers (60%)**
Projected # confirmed clinically significant COPD by subgroup	300-800	150-400	150-400	186-496	45-120	54-144	138-368	162-432	120-320	180-480
Projected # confirmed no COPD by subgroup	3,400-4,400	1,700-2,200	1,700-2,200	2,108-2,728	510-660	612-792	1,564-2,024	1,836-2,376	1,360-1,760	2,040-2,640

Table 9-3, again with corresponding sensitivity and specificity confidence interval widths in Table 9-1. For example, if sensitivity of CAPTURE in Hispanic individuals is 90%, then a sample size of approximately 100 would give a confidence interval of 90% ± 5.9%. We believe that with an overall sample size of 5,000 recruited patients we will have adequately sized subgroups to assess the operating characteristics of CAPTURE in the subgroups of interest.

9.1.2.2 FURTHER ANALYSIS OF ASSOCIATIONS BETWEEN MEETING COMPOSITE ENDPOINT AND INDIVIDUAL AND PRACTICE LEVEL OUTCOMES

Secondary analyses for evaluating practice behavior are exploratory, and therefore not included in a formal power and sample size analysis. These analyses are described further in Section 9.3.2.

9.2 POPULATIONS FOR ANALYSES

Aim 1

Population used for sensitivity calculations are all enrolled patients with clinically significant COPD as defined by post-bronchodilator $FEV_1/FVC < 0.70$ in addition to either >1 exacerbation-like event (ECOPD) within the past 12 months or an $FEV_1 < 60\%$ predicted.

Population used for specificity calculations are all enrolled patients with no demonstrable COPD as determined by research spirometry conducted upon study entry, $FEV_1/FVC \geq 0.70$.

Aim 2
Clinician participants: enrolled clinicians are from 2 primary care practices in each of five US PBRN regions that do not engage in Aims 1 or 3 investigation. Eligible clinicians include primary care providers and primary care clinical non-provider support personnel.

Patient participants: enrolled as a sub-sample of Aim 1 participants at baseline. One CAPTURE patient opinion survey is administered at baseline.. Aim 2 participants fulfill the inclusion, exclusion and population analysis criteria of aim 1.

Aim 3
Populations used in 2-sample comparisons of the average proportion of CAPTURE+ patients per practice that meet the composite endpoint in the two intervention arms will be based on randomization group (intent-to-treat analysis).

9.3 STATISTICAL ANALYSES

9.3.1 SENSITIVITY AND SPECIFICITY (AIM 1)

SAS version 9.4 PROC LOGISTIC will be used for computations. Calculations of sensitivity and specificity along with their corresponding 95% confidence intervals assume independent Bernoulli outcomes for each patient. Clinically significant COPD+ and COPD- populations selected for these analyses are described in Section 9.2. CAPTURE+ patients are those with a baseline CAPTURE score $\geq$ 5 or with a baseline CAPTURE score of 2, 3, or 4 with a low PEF (defined as <350 L/min for males, <250 L/min for females).

In addition to the primary sensitivity/specificity calculations, sensitivity/specificity and associated 95% confidence intervals will be calculated in predefined subgroups: sex, ethnic subgroups, rural and urban location, and educational status. As part of secondary analyses, receiver operating characteristic (ROC) curve analyses will evaluate different thresholds of the CAPTURE questionnaire score in defining a positive clinically significant + COPD screen, separately and in combination with low PEF characteristics, and the 12 additional CAPTURE questions. As part of this exploration, participant and practice level data as well as interactions with the CAPTURE tool results, will be considered as predictors of clinically significant COPD using multivariable logistic regression. Corresponding positive and negative predictive values will be estimated across the range of prevalence percentages seen at the enrolled practices. Model selection in secondary logistic regression analyses will be based on forward selection using maximum likelihood theory, with entry into the model dependent on statistical significance at the 0.05 level. Exploration of this nature has the potential to produce artificially high operating characteristics (area under the curve [AUC], sensitivity and specificity) based on overfitting the data. SAS 9.4 PROC LOGISTIC includes a cross-validation approach to ROC curve analysis [ROCOPTIONS(CROSSVALIDATE)] that we will use when assessing operating characteristics for any new prediction tool that goes beyond the original CAPTURE metric considered in primary analyses. Once a final logistic regression model has been selected, classification thresholds for predicting clinically significant COPD will be described by the investigative team from the cross-validated ROC curve. Calibration plots of observed versus predicted sensitivity, and observed versus predicted specificity, will be conducted across previously specified subgroups of interest (sex, ethnic subgroups, rural and urban location, and educational status).

All of the above analyses will be applied to these additional populations: (1) patients with spirometrically defined COPD and (2) patients with mild COPD.

9.3.2 PRACTICE BEHAVIOR (AIM 3)

The primary analysis will be to compare the average cluster sample proportion (average proportion of CAPTURE+ patients per practice meeting composite endpoint) between intervention arms. Practices that do not identify any CAPTURE + subjects will not contribute to the primary analysis, although this is felt to be an unlikely occurrence. A two-sample test comparing average cluster sample proportions will be used that explicitly takes into account correlation between individuals treated within the same practice. A two-sided p-value < 0.05 will be considered statistically significant. This analysis corresponds to a generalized estimating equation (GEE) regression analysis with (1) individual-level binary composite outcome data, (2) CAPTURE intervention group as a covariate, (3) practice id used to identify correlated outcomes, (4) exchangeable correlation matrix that assumes similar correlation between all composite outcome results for patients within the same practice, and (5) a logistic link function. The primary analysis would then correspond to a test for the CAPTURE intervention group parameter. There are no planned interim analyses for the primary endpoint, the rationale being that this is not a pharmaceutical or device trial that would benefit from standard stopping rules for efficacy. A DSMB will be monitoring the study for safety and study integrity.

Secondary analyses on meeting the composite outcome for participants who are CAPTURE+ will employ the GEE analysis framework with individual and practice level predictors in addition to the CAPTURE intervention group. Interactions will be assessed. We will also use the GEE framework to study and describe each of the individual components of the composite outcome as they relate to individual and practice level outcomes. In the subset of smoking patients, we will use GEE regression analysis to study additional binary outcomes, such as incidence of physician referral to a formal smoking cessation program, prescribed smoking cessation medication in participants who are smokers, and referral to pulmonary rehabilitation program.

In participants who are CAPTURE+, change in CAT score will be analyzed using mixed models with a random effect for practice. The average cluster sample proportion of patients who experience exacerbations will be compared between intervention groups using methodology similar to that used for the primary endpoint. Survival analysis allowing for correlation of endpoints within cluster (practice) will be used to compare mortality between intervention groups and perform multivariable analysis. We will explore differences between intervention groups in the average cluster sample rate of hospitalizations again using GEE. All additional secondary analyses will also be applied to patients with clinically significant and spirometrically defined COPD. Practices that do not have any clinically significant COPD or spirometrically defined COPD will not contribute to analyses of these secondary endpoints, respectively.

Model selection in GEE secondary analyses will be based on statistical significance at the 0.05 level using robust sandwich estimation of variability within clusters. Model fit will be checked by comparing observed versus predicted values within predefined subgroups of interest (sex, ethnic subgroups, rural and urban location, and educational status).

9.3.3 CAPTURE IMPLEMENTATION RECOMMENDATIONS (AIM 2)

Site-specific practice information, clinician knowledge and behavioral questionnaires, as well as patient opinion survey responses are recorded primarily to populate focus group themes for qualitative analysis. Secondary analyses of individual clinician and patient response using frequencies, means, ranking and dispersion by clinician type, practice and PBRN is accomplished using SAS version 9.4. Correlation with implementation recommendation is determined using GEE variance models.

Audio transcripts of clinician focus groups will all be digital and entered into a qualitative data analysis program, NVivo for Mac. This program allows for an investigation of the salience, patterning, and contexts of key discourse items. Grounded theory methods will be used to identify and label recurrent themes and concepts within textual materials. Texts will be examined line-by-line, key phrases assigned tentative category labels, and coded passages grouped under the themes of feasibility, barrier and utility. The analyses will look for "traces" in dialogue, including repetitions, key words, evaluation statements, and metaphors. Micro-interlocutor analysis of focus group emergent themes, questions, answers and interactions will account for individual gaps in focus group participation. Change in salience, patterning, or content of key themes will provide further empirical evidence regarding the efficacy of our program's efforts to impact clinician community norms and behaviors. An audit trail will be maintained to document the position of text material from which codes and themes are developed. We will use word/code counts of repetitive themes and concepts to indicate patterns. By allowing for open-ended responses, the narratives and notes will allow us to capture significant changes in participants' attitudes or behaviors. Codes and themes will be discussed iteratively with the research team members to hone definitions and assure consistency of interpretation. We will establish a coding dictionary and all interviews will be coded using the complete set of themes. Reviewing the transcripts line-by-line, all substantive information will be assigned a priori codes as relevant for CAPTURE RE-AIM implementation planning, COPD diagnosis, CAPTURE intra-office clinical communication, and COPD and CAPTURE education preference, and COPD diagnosis quality improvement assessment. Two independent coders will code each document to assure inter-coder reliability. Preliminary results will be shared with the Aim 2 data team and will inform the development of the CAPTURE case studies and primary care practice implementation recommendations.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise.

A HIPPA waiver will be submitted to each IRB to prescreen clinic schedules and patient panels for recruitment purposes. The PHI reviewed by the coordinator in the electronic health record (EHR) will

include age, date of birth, diagnosis of COPD, respiratory medications, and other medical conditions that are contraindicated for spirometry. A waiver of written consent will be submitted to each IRB to pre-screen potential participants for eligibility criteria prior to informed consent. The pre-screening will either be by telephone prior to an upcoming clinic visit, or in person at the time of the visit. An IRB-approved telephone/in-person screening script will be submitted to each IRB.

A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. Participants will additionally have the opportunity to review the study and informed consent prior to providing consent for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

All PBRN research coordinators, COPD Foundation study staff and other clinical investigators will be certified by their local IRB in informed consent and human studies research.

Clinicians interested in participating in the qualitative, minimal risk study for Aim 2, will be given the opportunity to review the consent form below and sign it. This can happen once their practice agrees to participate in Aim 2 activities or during the first in person site visit with Dr. Brown.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

When a study is prematurely terminated, refer to Section 7, Study Intervention Discontinuation and Participant Discontinuation/Withdrawal, for handling of enrolled study participants.

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. In addition, it may be transmitted and stored at the DCC in a database separate from the clinical database (used for statistical analysis and scientific reporting) and with COPD Foundation study team access to aid in contacting participants at the 12-month follow-up. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the DCC. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by DCC research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the DCC.

For the online Aim 2 patient opinion survey, Qualtrics is used. Qualtrics is a secure University of Michigan (U-M) contracted-for cloud service that can be used to maintain or share the university's sensitive unregulated data, as well as some kinds of sensitive regulated data.

U-M's agreement with Qualtrics includes a Business Associate Agreement. This means individuals may use this service to maintain Protected Health Information (PHI) regulated by HIPAA. Complying with HIPAA's requirements is a *shared responsibility*. Users sharing and storing PHI in Qualtrics are responsible for complying with HIPAA safeguards, including:

- Using and disclosing only the minimum necessary PHI for the intended purpose.
- Obtaining all required authorizations for using and disclosing PHI.
- Ensuring that PHI is seen only by those who are authorized to see it.
- Obtaining all necessary data-sharing agreements and Business Associate Agreements for using and disclosing PHI.
- Following any additional steps required by your unit to comply with HIPAA.

Sensitive data, including PHI, may be collected and stored in Qualtrics for non-clinical, academic purposes only (for example, research and hospital quality improvement initiatives). Qualtrics cannot be used for any clinical applications, no matter the sensitivity level of the data

11 STUDY ADMINISTRATION AND OVERSIGHT

11.1 STUDY LEADERSHIP

11.1.1 PRINCIPAL INVESTIGATORS

The principal investigators are responsible for providing direction and oversight of all study activities.

Principal Investigators	
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11.1.2 PRACTICE BASED RESEARCH NETWORKS (PBRN)

PBRNs will have the following roles and responsibilities:

CAPTURE Study Preparation

1. Review protocol to help identify operational details
2. Submit final protocol and informed consents to all IRBs necessary for the participating sites
3. Complete and maintain current human participants training for all main study personnel as required by the IRB
4. Attendance of PBRN coordinators at in person training, spirometry certification for all coordinators, update of spirometry quality assessments and training
5. Identify and recruit local practice sites to participate in the study

CAPTURE Study Implementation

1. Facilitate COPD and when appropriate CAPTURE education
2. Maintain regular contact with participating PBRN practice sites during their period of patient enrollment
3. Supervise and send PBRN Research Coordinators to enroll patients, perform study visits including completion of the CAPTURE questions, peak flow, spirometry, and collect other information on all enrolled patients
4. Complete pre bronchodilator spirometry on all participants
5. Complete post bronchodilator spirometry on participants with abnormal pre-bronchodilator spirometry as defined by study algorithm (e.g. those with pre bronchodilator results consistent with obstruction)
6. Facilitate completion of data entry to the data coordinating center
7. Follow up by research coordinator for patients failing to respond to the follow up questionnaires
8. Collect practice outcome data related to enrolled patients at close of study from either electronic medical records or if practice does not have EMR, by manual record review

Patient participants and staff participants will be recruited from the PBRNs.

PBRN	Location	Director
Atrium Health	North Carolina	Hazel Tapp, PhD
LA Net Community Health Network	Southern California	Lyndee Knox, PhD
High Plains Network	Colorado	Linda Zittleman, MD
Duke Primary Care Research Consortium	North Carolina	Rowena Dolor, MD
Oregon Rural Practice-Based Research Network	Oregon	Nancy Elder, MD

11.1.3 SPIROMETRY CORE

Led by Dr. David Mannino, the Spirometry Core will maintain quality of the research spirometry that is integral to the success of the study. The work will be done in conjunction with a research assistant. This includes the following functions:

1. Development of the operation manual for the sites
2. Training of the site staff in the use of the spirometry equipment (including travel to training and sites as needed)
3. Certification of staff in spirometry
4. Assessing staff adherence to protocols for the use of bronchodilators
5. Grading and adjudication of spirometry
6. Importing processed spirometry into spreadsheets
7. Uploading processed data to data coordinating center
8. Working with data coordinating center to verify and clean data

In addition, Dr. Mannino will be a critical part of the team that evaluates the data both from spirometry and the other components of this study (the CAPTURE tool, quality of life measures, etc.), in addition to being part of the writing team that analyzes data and disseminates the findings from this study.

11.1.4 IMPLEMENTATION CORE

Dr. Randall Brown will lead the qualitative Aim 2 activities which assess the implementation strategy and acceptance recommendations for CAPTURE use in primary care practice. His team includes an Aim 2 project manager and dedicated research assistant. Led by Dr. Brown the Aim 2 team coordinates with PBRNs and their selected Aim 2 practices and will conduct qualitative site visits and focus groups in addition to administering clinical practice behavioral questionnaires. Drs. Barbara Yawn, Barry Make, Bruce Bender and Julia Houfek will contribute to the development of the web based educational modules and the qualitative efforts on this project.

11.1.5 DATA COORDINATING CENTER (DCC)

Dr. Cathie Spino directs the DCC, housed at the University of Michigan within the Statistical Analysis of Biomedical & Educational Research (SABER) Unit of the Department of Biostatistics in the School of

Public Health. The DCC staff will include a Database programmer, Data manager, Senior Unblinded Statistician, Statistical Analyst, Project Manager, Clinical Monitor, Web Programmer/Designer, and a Research Administrator. In addition, the blinded senior statistician, Dr. Susan Murray, is located at the University of Michigan. The DCC plays a pivotal role in the design, implementation, execution and administration of the study. The DCC will be responsible for randomization, eCRFs and online reporting systems, preparation of the manual of operations for data entry, addressing questions regarding entry and analysis, monitoring recruitment, follow-up and adherence to protocol, and scheduling and arranging meetings of the Executive Committee, Steering Committee, and Medical Monitor. The DCC will prepare all of the routine study reports for the Executive Committee, Operations Committee, and Medical Monitor. The DCC will interact with all of the Cores and other Committees, as needed. The DCC will compile data tables and listing for DSMB reports.

11.1.6 CLINICAL COORDINATING CENTER

The Clinical Coordinating Center (CCC) will be led by Principal Investigators Fernando Martinez, MD, MS at Weill Cornell Medicine, and MeiLan Han, MD, MS at the University of Michigan. Dr. Martinez will be responsible for overall study oversight as well as fiscal management of the overall project and capitation payments to sites for work performed. He will also be responsible for communication with NIH and submission of annual reports. Dr. Han will work with the Data Coordinating Center to oversee clinical trial enrollment and, along with her statistical team, be responsible for coordinating statistical analysis. The process for making decisions on scientific direction and allocation of resources will be made by both Drs. Martinez and Han, with input from the rest of the investigative team as needed.

Additional Clinical Coordinating Center (CCC) responsibilities:

- Establish subcontracts with enrolling sites, central laboratories, imaging service providers, and others as appropriate
- Protocol development and scientific design oversight
- Statistical analysis
- Participating study site selection
- Review of serious adverse events and unanticipated problems involving risk to participants or others, reporting to participating centers and regulatory reporting
- Prepare and maintain Clinical Coordinating Center IRB submissions
- Analyze and present data to DSMB

Clinical Coordinating Center Personnel

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11.1.7 12 MONTH SURVEY COORDINATING CENTER

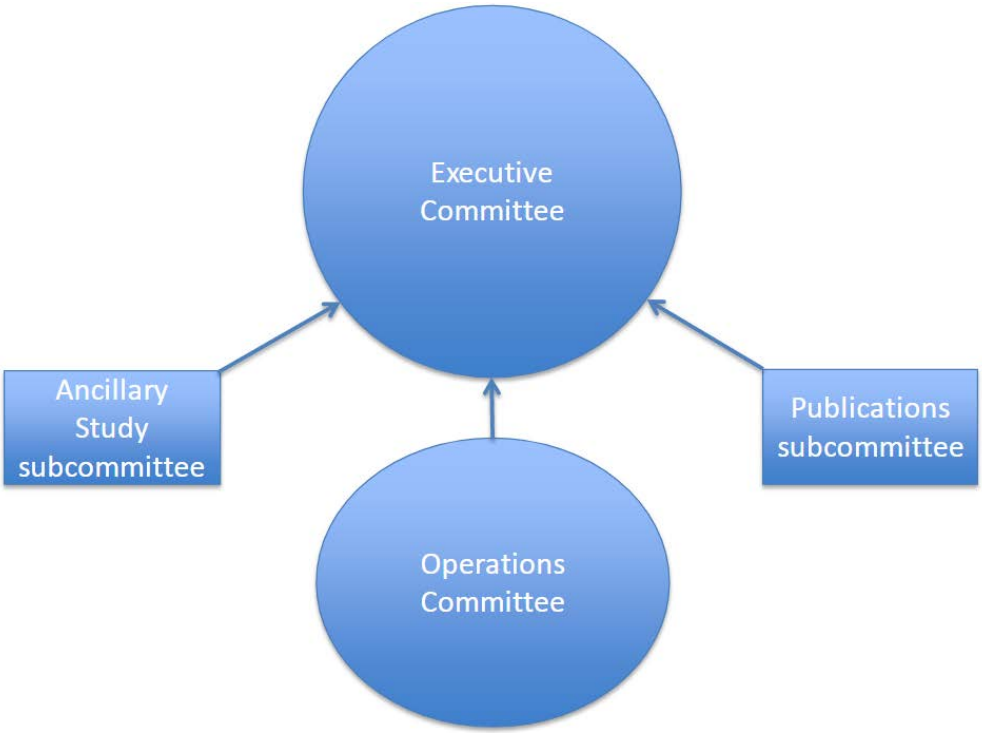
The 12 month Survey Coordinating Center will be led by Co-Investigator Barbara Yawn, MD MSc, Chief Science Officer at the COPD Foundation. Dr. Yawn will be responsible for oversight of the development and implementation of the reminder notices and 12 month survey administration by COPD Foundation study personnel for participants selected to complete the 12 month follow up survey.

11.2 ORGANIZATIONAL STRUCTURE

The Executive Committee will be led by the Principal Investigators and will consist of the 2 elected PBRN Directors, 1 representative of the COPD Foundation, Co-Investigators, Data Coordinating Center PI and Project Manager, NIH official and Clinical Coordinating Center Project Managers. The Executive Committee will meet every one-to-two weeks to administratively direct and monitor the progress of the study and to respond to any design, implementation or administrative issues that arise during the study.

The Operations Committee will consist of Overall Principal Investigators, PBRN Directors and lead coordinators, DCC Project Managers, and Co-Investigators. It will address implemental and administration faced by the PBRN practices that arise during the study.

Other subcommittees, such as the Publications and Ancillary Studies Subcommittees, will be constituted to support maximizing the utility of the CAPTURE study to the scientific community.



12 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data, documentation and completion. An individualized quality management plan will be developed.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

13 DATA HANDLING AND RECORD KEEPING

13.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Comprehensive data coordinating center (DCC) functions for this clinical trial, including clinical monitoring, database development, web-based data entry and management, as well as the creation and export of study reports for the DSMB will be provided by the University of Michigan Statistical Analysis of Biomedical and Education Research (SABER) group. Housed in the top nationally ranked Department of Biostatistics, SABER, in its 17-year existence, has served as the DCC for over 50 studies, including multiple NIH-sponsored networks.

The DCC will use OpenClinica® (OpenClinica Clinical Trial Software; OpenClinica, LLC, Waltham, MA), a clinical trial software platform for electronic remote (i.e., site-based entry) data capture and clinical data

management, as the basis for our custom-designed data entry and management system. The majority of data will be collected via electronic Case Report Forms (CRFs); however, other data sources, such as laboratory data from the central laboratory, may be used. In these circumstances, the DCC will also utilize electronic data transfer. Protocols for the transfer of data, with careful attention to data integrity, will be written by experienced programmers and stored in the OpenClinica database or data mart.

The DCC has established a set of standard operating procedures (SOPs) governing the processes used to ensure patient privacy and data confidentiality, including the use of anonymous participant IDs on CRFs and in reports. OpenClinica® enables compliance with Good Clinical Practice (GCP) and regulatory requirements by providing differentiated user roles and privileges, password and user authentication security, electronic signatures, SSL encryption, and comprehensive auditing to record and monitor access and data changes.

Data collection is the responsibility of the central study staff at the PBRN under the supervision of the PBRN Director (investigator). The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. In addition to the protocol, the DCC will prepare a Manual of Procedures which provides additional detail on data collection procedures, including source documentation, eCRF completion guidelines, data handling procedures and procedures for data monitoring and quality control that ensure these data are accurate, consistent, complete and reliable and in accordance with ICH 36.

13.2 STUDY RECORDS RETENTION

Study documents should be retained as required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

13.3 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation or scheduled protocol-required activity. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

13.4 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers after the completion of the primary endpoint by contacting Drs. Martinez and Han.

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The CAPTURE Study: Validating a unique COPD case finding tool in primary care

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Protocol Amendment 3.0 - Summary of Changes				
Location	**Page Number**	**Type of Change**	**Description**	**Rationale**
Cover Page	---	*Administrative*	Update Protocol Version to 3.0 and update version date to 24 September 2019	Amendment version and date updated
Cover Page	---	*Administrative*	Add NCT # for each AIM	Add all 3 numbers to protocol since each AIM is registered in clinicaltrials.gov
Multiple Sections	Multiple	*Revision*	Number of PBRNs participating in aims 1 and 2 revised to 6 PBRNs throughout protocol.	Additional PBRN added
1.2 Schema Table 1	9	*Revision*	CAPTURE ~~12~~ additional items questionnaire	The CAPTURE 12 item additional questionnaire was renamed.
Section 8.1 Baseline Assessments and Data Collection	30	*Clarification*	CAPTURE Additional Items Questionnaire administration instruction added to Study Assessments.	Further instruction for administration of CAPTURE Additional Items Questionnaire, as described in Section 1.2 Schema table, was added.
Section 11.1.2 Practice Based Research Networks (PBRN)	48	*Revision*	University of Illinois, Chicago added as a participating PBRN.	University of Illinois, Chicago added as an enrolling site in aims 1 and 3.

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STATEMENT OF COMPLIANCE

This study will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CAO	Chronic Airflow Obstruction
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
ECOPD	Exacerbation of Chronic Obstructive Pulmonary Disease
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FEV1	Forced Expiratory Volume in 1 second
FFR	Federal Financial Report
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practice
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act

IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PBRN	Practice-Based Research Network
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
RE-AIM	Reach, Effectiveness, Adoption, Implementation, Maintenance
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States
USPSTF	United States Preventive Services Task Force

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	The CAPTURE Study: Validating a unique Chronic Obstructive Pulmonary Disease (COPD) case finding tool in primary care
Study Description:	**Aims 1 and 3**. A prospective, multicenter study including a cross-sectional validation to define sensitivity and specificity of CAPTURE and its impact on clinical care across a broad range of primary care settings in a cluster randomized controlled clinical trial. The CAPTURE tool consists of a 5-item self-administered questionnaire and peak expiratory flow (PEF) measurement, designed to identify undiagnosed patients with Chronic Obstructive Pulmonary Disease (COPD). **Aim 2.** This study delivers a qualitative assessment of clinical practice acceptance of and implementation strategy for CAPTURE case finding within 10 varied primary care practices across 5 US PBRN regions. We evaluate primary care practice attitudes, beliefs and recommendations about CAPTURE's potential to feasibly integrate into clinical practice patterns, workflow and quality improvement paradigm planning in a variety of primary care clinical settings.
Definitions:	**CAPTURE+ =** Participants with • CAPTURE score $\geq$ 5, or • CAPTURE score of 2, 3, or 4 with a low PEF, defined as <350 L/min for males and <250 L/min for females **CAPTURE-** = Participants with CAPTURE score < 2 or scores 2-4 with normal PEF, defined as >350 L/min for males and > 250 L/min for females **Spirometrically defined COPD =** Participants with abnormal spirometry, defined as post-bronchodilator FEV_1/FVC <0.7. If a participant is unable to complete a post-bronchodilator spirometry (refusal, technical error on the part of coordinator, etc.), and the pre-bronchodilator FEV1/FVC is less than 0.65, the participant will be considered to have COPD for the purpose of follow-up in this study. **Clinically significant COPD =** Participants with abnormal spirometry, defined as post-bronchodilator FEV_1/FVC <0.7, plus one of the following: • FEV_1 < 60% predicted, or • > 1 exacerbation-like event within the past 12 months. **Mild COPD =** Participants with abnormal spirometry, defined as post-bronchodilator FEV_1/FVC<0.7 plus both of the following: • $FEV_1 \geq$ 60% and • No prior history of ECOPD
Objectives:	**Aims 1 and 3 Primary Objectives:** • **Aim 1 -** Define the sensitivity and specificity of CAPTURE for identifying previously undiagnosed patients with clinically significant COPD in a broad range of primary care settings.

	• **Aim 3 –** Define the impact of CAPTURE information provided to clinicians in identifying and managing patients with respiratory symptoms (CAPTURE+) across a broad range of primary care settings.
	
	Aim 2 Primary Objective:
	Explore clinical practice implementation approaches to and acceptance of CAPTURE case finding for clinically significant COPD in a range of primary care practices.
	
	Aims 1 and 3 Secondary Objectives:
	• **Aim 1 –**
	  • Define the sensitivity and specificity of CAPTURE for patients with COPD across a broad range of racial and ethnic groups in a range of primary care settings.
	  • Determine positive and negative predictive values (PPV and NPV) in different practice settings.
	  • Verify the optimal use (cutoff threshold) of the CAPTURE tool in combination with PEF measurements for identifying undiagnosed COPD.
	  • Determine patient and site characteristics that, with the CAPTURE assessment, will best identify persons with undiagnosed COPD.
	  • Determine whether CAPTURE is useful in identifying other definitions of undiagnosed COPD including:
	  1) spirometry-defined COPD, and
	  2) mild COPD
	
	• **Aim 3 -**
	  • Define the impact of CAPTURE clinician education, and patient-level CAPTURE information to clinicians (“CAPTURE education”) on selected additional therapeutic interventions in previously undiagnosed patients with clinically significant COPD.
	  • Assess impact of CAPTURE education on clinician interventions specific to smokers.
	  • Determine the impact of CAPTURE education on patient symptoms, exacerbations, hospitalizations, and mortality.
	  • Determine the impact of CAPTURE education when COPD is defined spirometrically.
	
	Aim 2 Secondary Objectives:
	• Qualitatively assess primary care clinical staff COPD practice behavior – including COPD screening and diagnostic perceptions, beliefs and knowledge – that will inform strategies to improve CAPTURE RE-AIM (reach, impact, adoption, implementation and maintenance of use) characteristics.
	• Qualitatively assess primary care patient opinion of CAPTURE COPD case finding that will inform strategies to improve CAPTURE RE-AIM

	(reach, impact, adoption, implementation and maintenance of use) characteristics.

Endpoints:	**Aims 1 and 3 Primary Endpoints:**
	• Aim 1 –
	  ○ Sensitivity and specificity of CAPTURE to identify previously undiagnosed patients with clinically significant COPD at baseline.
	• Aim 3 –
	  ○ Proportion of CAPTURE+ participants who meet at least one of the following within 12 months of study baseline (composite endpoint): 1) referral for or completion of clinical spirometry testing, 2) new diagnosis of COPD, 3) newly prescribed respiratory medication (long acting bronchodilator or anti-inflammatory for respiratory condition), or 4) referral to a specialist for respiratory evaluation/treatment
	Aim 2 Primary Endpoints:
	• Primary care clinician recommendations that inform CAPTURE RE-AIM strategies at both provider and clinical support levels of primary care practice.
	• Primary clinician recommendations that inform CAPTURE-associated COPD education models for primary care clinicians.
	• Primary care clinician recommendations that inform CAPTURE-associated COPD clinical quality improvement designs across a variety of primary care practice types.
	Aims 1 and 3 Secondary Endpoints:
	• Aim 1 –
	  ○ Sensitivity and specificity of CAPTURE to identify previously undiagnosed patients with COPD across sex, ethnic groups, urban vs rural location, and educational level.
	  ○ Positive and negative predictive values (PPV and NPV) in different practice settings.
	  ○ Areas under the receiving operator characteristic curve (AUC) for various cutpoints of CAPTURE and PEF_1 measurements to determine the best cutpoint for COPD+ screen.
	  ○ AUC to identify the combination of patient/site characteristics which best discriminates those with clinically significant COPD.
	  ○ All primary and secondary endpoints as applied to 1) spirometry-defined COPD and 2) mild COPD
	• Aim 3 –
	  ○ Proportion of CAPTURE+ patients who meet the components of the composite endpoint.
	  ○ Proportion of patients with clinically significant COPD who meet the composite endpoint.
	  ○ In participants with clinically significant COPD who are current smokers, the incidence of physician referral to a formal smoking cessation program, prescribed smoking cessation medication, and referral to pulmonary rehabilitation program.

	○ In participants with clinically significant COPD, change in CAT score, and proportion of patients who experience exacerbations, hospitalizations, or mortality. ○ All of the above endpoints for Aim 3, with the patient population defined as those who have COPD defined spirometrically. **Aim 2 Secondary Endpoints:** • Existing COPD screening and diagnostic and case finding processes within a variety of primary care practices. • Primary care practice belief about capacity to change from existing COPD screening and diagnostic assessment strategies. • Practice-specific COPD screening and diagnostic continuing education preference.
Study Population:	**Aims 1 and 3.** Adults 45-80 years old without a prior diagnosis of COPD (total N = 5000) **Aim 2.** - 10 primary care practices: 2 practices per PBRN with up to 15 clinical staff participants per practice; clinician N = up to 150 (up to 30 clinician participants per PBRN). - Aim 1 patient opinion survey population; patient N = 200 (40 patients from each PBRN; adults 45-80 years old, without a prior diagnosis of COPD). - Total N = up to 350
Phase:	N/A
Description of Sites/Facilities Enrolling Participants:	**Aims 1 and 3.** Enrollment will occur in approximately 100 primary care practices affiliated with 6 primary care based practice networks (PBRN) across the United States who exhibit a broad range of gender, ethnic, racial, socioeconomic, and regional diversity. **Aim 2.** • Two primary care practices chosen by each of the same 5 PBRN co-investigator teams make up the 10 aim 2 practices from which clinician participants are enrolled. These 10 practices are separate from the 100 chosen practices in aims 1 and 3. • Patient participants are a sub-sample of those participants enrolled in aims 1 and 3.
Description of Study Intervention:	**Aims 1 and 3.** Primary care practices will be randomized to either receive basic COPD education and patient-level CAPTURE information with CAPTURE education (initially basic then later enhanced based on data collected in Aim 2) versus COPD education only. **Aim 2.** Participating primary care clinicians from 10 varied practices are surveyed at three different time points and participate in two focus groups qualitatively assessing CAPTURE implementation strategy and COPD case finding approaches in primary care. Participating patients complete one 10-minute written opinion survey about CAPTURE.
Study Duration:	**Aim 1 and 3.** 4 years **Aim 2.** 2 years
Participant Duration:	**Aims 1 and 3.** Up to 12 months

	Aim 2. • Primary care practice clinicians: questionnaires and focus groups (total 3 hours/participant) over 16 months. • Primary care patients: one 10-minute questionnaire/participant over 14 months.

1.2 SCHEMA

FIGURE 1. OVERALL STRUCTURE OF AIMS

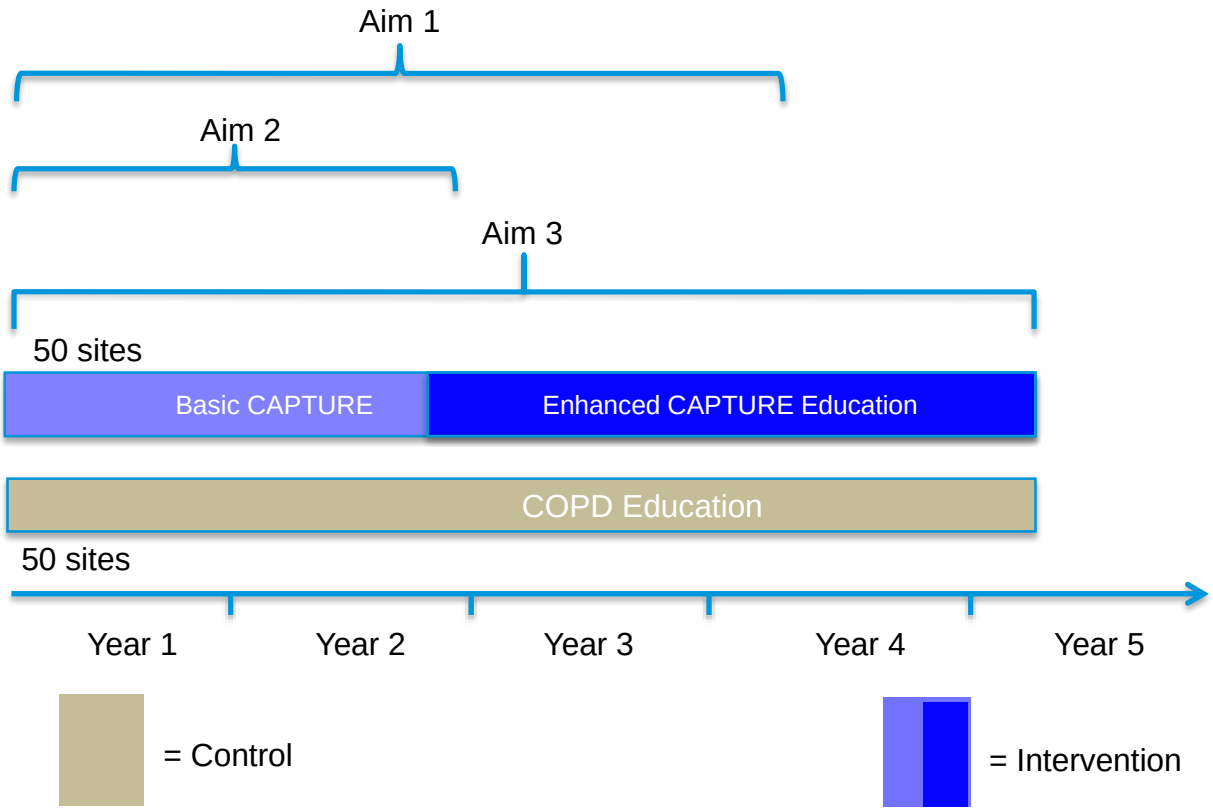

FIGURE 2. STRUCTURE OF AIM 2


CAPTURE COPD Study
Time Commitment
Introductory Phone Call
Brief phone call with CAPTURE research team to review the CAPTURE COPD: The Primary Care Practice Expert Panel aim. Discussion includes: review of the research content, timeline and scheduling of the half-day site visit for February/March 2018
Month 1
In Person Baseline Assessment/ Site Visit:
SITE VISIT INCLUDES:
• Walk through of practice and staff introduction: 2 clinical staff with CAPTURE team [60 minutes]
• Clinic flow observation and mapping [1/2 day]
• Post clinic flow observation Q&A: 2 clinical staff and CAPTURE research team [30 minutes]
• CAPTURE COPD information distribution and consent process
Online Questionnaire: 1st of three
Online/written questionnaire at baseline [20 minutes]
Month 2-3
State-of-the-Art COPD Web-based Continuing Education
Three modules encouraged; All modules optional 20 minutes/module; per Aim 3 description
Month 3-7
Practice Expert Panel Focus Group #1
Prescribers and Non-Prescribers (2 different days) 60 minute focus group
Online Questionnaire: 2nd of three
Online/written questionnaire at 6 months [20 minutes]
Month 6-10
Online Questionnaire: 3rd of three
Online/written questionnaire at 12 months [20 minutes]
Month 11-14
Practice Expert Panel Focus Group #2
Pooled prescribers and Non-Prescriber Clinical Staff [60 minutes]
Month 14-16
CAPTURE COPD: The Primary Care Practice Expert Panel Study will take place in 10 practices in 5 regions in the US. Central to the success of CAPTURE COPD is the role of clinical staff expertise in providing feedback, information and suggestions about clinical workflow for COPD diagnosis.
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1.3 SCHEDULE OF ACTIVITIES (SOA)

Table 1: Schedule of Activities (Aims 1 and 3)

	Pre-Visit Contact[1]	**Baseline**	**12 Months[3]**
Contact (C)/ Visit (V)/Medical Record Review (MRR)	**C1**	**V1**	**C2/MRR[5]**
Time point, days (Visit window)	**Prior to outpatient visit (≤-1)**	**Within 30 days of pre-visit contact**	**365 ±30 (C2)**
Contact patient re: interest in study visit[1]	X		
Informed consent		X	
Demographics		X	
Medical history (Co-morbidities)[2]		X	
Vaccination status		X	X
CAPTURE 5-item questionnaire		X	X
CAPTURE item additional questionnaire		X	
Peak Expiratory Flow (PEF)		X	
Height and weight		X	
Respiratory medications review		X	X
Spirometry[4]		X*	
Respiratory symptoms, exacerbation assessment		X	X
Smoking exposure history		X	
Smoking cessation review[6]			X
COPD Assessment Test (CAT)		X	X
Adverse Events		X	
Medical record review			X

1. Optional per site recruitment preferences
2. Comorbidities including cardiovascular, respiratory and malignant disorders
3. Recorded for a subset of participants who meet any of the following criteria: 1) CAPTURE+ subjects defined as CAPTURE Score ≥ 5 or CAPTURE score of 2, 3, or 4 with a low PEF, defined as <350 L/min for males and <250 L/min for females 2) abnormal spirometry defined as $FEV_1/FVC < 0.70$ or $FEV_1 < 80\%$ predicted at baseline; and, 3) a random sample of approximately 5% of those who do not meet criteria 1 and 2. For participants meeting criteria 1 and 2 who cannot or choose not to complete the 12-month assessment, medical record review will still be completed. For participants meeting criteria 1 and 2 who change medical practices and medical record review cannot be completed, patients will be contacted for completion of patient reported data. For

participants meeting criterion 3 where all of the protocol-specified 12-month assessments cannot be made, another participant will be selected at random to replace this participant.

4. Pre-bronchodilator spirometry will be done for all participants. Post-bronchodilator spirometry will be performed for participants with abnormal spirometry ($FEV_1/FVC < 0.70$ or $FEV_1 < 80\%$ predicted) *If the participant has taken a bronchodilator within a 2-hour window of spirometry the spirometry will be considered post-bronchodilator and a pre-bronchodilator spirometry will not be done.
5. The 12-month assessment consists of patient reported data, collected by the COPD Foundation, and medical record review completed by site coordinators.
6. This will be completed in those that are smoking at V1.

2 INTRODUCTION

2.1 STUDY RATIONALE

Undiagnosed COPD is a leading cause of morbidity and mortality. Spirometry, the 'gold standard' for diagnosis, is not recommended for screening in asymptomatic individuals or untargeted case finding and remains widely underutilized in primary care settings. Targeted case finding approaches have been strongly advocated but currently available approaches generally identify patients across the spectrum of mild to severe disease without reference to potential therapeutic benefit or exacerbation risk, thereby limiting clinical impact and acceptance in primary care. There is an urgent need to develop and implement simple case finding approaches that can identify patients with clinically significant COPD in primary care settings.

Through a multi-stage, iterative process we developed a simple case finding tool using five questions combined with selective peak expiratory flow **(PEF)** measurement that identifies individuals with 1) an $FEV_1 < 60\%$ predicted and/or 2) at risk for ECOPD. We call this tool CAPTURE (**C**OPD **A**ssessment in **P**rimary Care **T**o Identify **U**ndiagnosed **R**espiratory Disease and **E**xacerbation Risk)(1). As clinical trials have demonstrated benefit and therapeutic guidelines recommend therapy for these individuals we have labeled these patients as suffering from 'clinically significant' COPD. The long-term goal of this project is to identify these patients so that they can be treated and result in improved health status, reduced exacerbations, and decreased morbidity.

The *overall objectives* of Aims 1 and 3 of this project are to 1) validate the sensitivity, specificity, and predictive value of CAPTURE to identify undiagnosed, clinically significant COPD patients in a diverse primary care population; and explore whether identifying these patients results in improved COPD specific care and health status. Our *principal hypothesis* is that CAPTURE can effectively and efficiently identify primary care patients with undiagnosed, clinically significant COPD. We objectively test our principal hypothesis by completing to two separate and linked aims:

Aim 1 – Determine the sensitivity and specificity of CAPTURE in identifying clinically significant COPD patients in a broad range of primary care outpatient practices.

Working hypothesis - A simple case finding methodology using a five-item questionnaire with selective PEF measurement will identify undiagnosed patients with clinically significant COPD.

We will conduct a 5,000 participant cohort study in 100 primary care practices affiliated with five

primary care based research networks **(PBRN)** that provide access to previously undiagnosed patients with clinically significant COPD who exhibit gender, ethnic, racial, socioeconomic and regional diversity.

Aim 3 – Define the impact of CAPTURE screening in a broad range of primary care outpatient practices and evaluate practice and patient characteristics that are associated with care implementation and clinical outcomes for patients with respiratory symptoms (CAPTURE+).

Working hypothesis – Provision of patient specific CAPTURE data to practicing clinicians will result in improved management of patients with respiratory symptoms (CAPTURE+).

We will provide basic COPD education and patient level CAPTURE information and education to site clinicians at 50 of the sites and prospectively follow selective, pre-defined subgroups of patients to define relevant outcomes. Care at the other 50 clinical sites will follow standard of care with basic COPD education to clinicians.

Assessing the potential clinical impact of a novel COPD case finding strategy includes confirmation of validity in a diverse primary care patient population and a quantitative research evaluation of its impact on clinical decision-making and COPD patient outcomes, as found in aims 1 and 3 above. Equally important is exploration through validated implementation methods that the newly designed CAPTURE tool, even if valid and impactful, can provide real-world utility within a variety of primary care practice settings. While we find no evidence in previous COPD screening studies of such detailed appraisal, ascertaining the feasibility of clinical testing is a vital component of assuring that new approaches address potential clinical practice need, capacity, knowledge and diagnostic gaps. As much as possible, clinical respiratory innovations should align with busy workflow at all practice staff levels to more effectively identify primary care patients with undiagnosed, clinically significant COPD.

To maximize success of the CAPTURE adoption, education and implementation in this study and in future work, Aim 2 is introduced to assess practice experience, need and preference that can inform clinical COPD case finding and education in primary care settings:

Aim 2 – Explore clinical practice implementation approaches to and acceptance of CAPTURE case finding for clinically significant COPD in a range of primary care practices.

The *overall objective* of this aim is to qualitatively explore primary care clinical practice acceptance of COPD case finding implementation and define education and feasibility strategies to enhance adoption in primary care practice. This assessment includes understanding clinician and clinical staff COPD practice and perceptions in addition to the feasibility of case finding integration into existent clinical work patterns. To attain this objective, we address one *working hypothesis* – a COPD case finding methodology using a validated one-page, five-item questionnaire with selective PEF measurement (CAPTURE) can be incorporated into the clinical practice patterns, clinical workflow, communication and practice-based quality improvement paradigms in a variety of primary care clinical settings. The *rationale* for this objective reflects the importance of establishing if an innovative approach to COPD case finding (CAPTURE) is considered a pragmatic tool with potential utility for primary care clinicians within real-world clinical practice settings. With the completion of this aim we anticipate confirming that future validated approaches to COPD case finding can be adopted in a broad variety of clinical care settings thereby providing further impetus for the rigorous evaluation of a) case finding guided patient outcomes as part of routine primary care clinical practice; b) case finding use in a range of primary care health professional COPD-related education approaches, clinical quality improvement models and

diagnostic guidelines; and c) the capacity of clinical case finding with informed follow-up to enhance future COPD clinical care therapeutic paradigms used in primary care practice.

2.2 BACKGROUND

Aims 1 and 3.

COPD remains a major cause of morbidity and mortality. COPD results in substantial morbidity and mortality worldwide.(2-4) Globally, the prevalence of COPD and years lived with disability increased from 1990 to 2013.(5) This is particularly evident in older individuals.(6) These well-designed population based studies confirm the growing impact of COPD.

COPD is frequently undiagnosed. We recently documented that only 28% of participants with chronic airway obstruction **(CAO)** had physician diagnosed disease.(7) Importantly, an FEV_1 <50% predicted was noted in 10% of those with undiagnosed CAO; this is similar to other cohorts or population based surveys.(8-11) There is consistency in these well-conducted studies that confirm most COPD patients are undiagnosed.

Spirometry is underutilized. The U.S. Preventive Services Task Force **(USPSTF)** recently recommended against the use of spirometry for routine, general population or practice-based screening in asymptomatic individuals.(12) An editorial by the PI of this application highlighted the limitations of this conclusion.(13) Within primary care spirometry is often viewed as time consuming and difficult to implement and interpret.(14) As such, it is not routinely used.(15-19) Even the availability of less expensive and easily used spirometers(20) has not resulted in increased utilization.(21, 22)

Undiagnosed COPD is associated with a negative clinical impact. In a robust, population based study we confirmed that undiagnosed patients experienced impaired health status and a higher risk for all-cause mortality compared to those without CAO; this was particularly evident with more severe CAO.(7) Others have confirmed increased mortality,(23) health status impairment,(24) exacerbation-like respiratory events,(11) and increased health care costs.(25, 26) As such, there are consistent data suggesting that undiagnosed COPD patients experience negative clinical events and impaired health status.

Therapeutic interventions improve COPD clinical outcomes. Well designed, randomized controlled trials confirm that COPD therapy is effective, particularly in patients with an FEV_1 < 60% predicted who are symptomatic or at risk for ECOPD.(27, 28) Despite limited data, some have suggested that earlier detection of patients with previously undiagnosed, yet clinically significant COPD, in primary care settings could improve short- and long-term patient outcomes and may be cost-effective. (29, 30)

COPD case finding approaches to date have generally been methodologically limited. Several COPD case finding tools have been created based on existing epidemiologic literature or expert opinion.(31, 32) This includes tools created by investigators in this study.(33, 34) In general, current approaches were designed to identify COPD patients without reference to disease severity or ECOPD risk, resulting in the identification of a high proportion of patients with mild or minimally symptomatic disease.(21, 33-39) Several studies have tested the accuracy of handheld flow meters for case identification with varying sensitivity and specificity.(40) Although informative in terms of CAO, PEF meters have been unable to systematically identify patients at risk of ECOPD. We tested a three-staged approach (risk-factor questionnaire, PEF, and spirometry) for identifying moderate to severe COPD (FEV_1<60% predicted) in a convenience sample of the general population.(41) This study was limited by the nature of the population screened and the screening questionnaire used but supported the concept that PEF can facilitate COPD case finding.

A systematic analysis of existing databases provides insight into the best variables for COPD Case Identification. To identify potential items that could be useful in the identification of undiagnosed COPD we interrogated three robust datasets of populations in which the investigators on this application had major roles [COPD Foundation Peak Flow Study Cohort (n=5761); Burden of Obstructive Lung Disease Kentucky site (n=508); and COPDGene® (n=10,214)].(42) We utilized the machine learning statistical method of random forests to identify and validate variables most important in identifying patients with clinically significant COPD. COPD case finding candidate content included items reflecting exposure, personal and family history, respiratory symptoms, recent health history, activity limitation and demographics.

A comprehensive, qualitative study identified key constructs for identifying recently diagnosed patients with clinically significant COPD. We completed a two phase study that included focus groups followed by cognitive interviews to refine the key constructs for identifying patients with clinically significant COPD.(43) Fifty participants were recruited including those with mild airflow obstruction, diagnosed within the previous six months and without previous ECOPD; those diagnosed within the previous six months and with a history of at least one ECOPD within the prior year; those with 2-3 risk factors for COPD but without CAO; and those with $\geq$ 4 risk factors for COPD but without CAO. Using a content analysis approach, key themes and constructs were identified and integrated with the content of the previous literature review and data mining. We identified 44 candidate items that resonated with patients and provided important insights into a case finding instrument.

A five-item questionnaire exhibits excellent operating characteristics to identify clinically significant COPD patients. We completed a prospective, multi-site, case-control study of four groups: cases with clinically significant COPD – COPD with > 1 ECOPD in the previous year (n=97) and COPD with no ECOPD but an FEV_1 < 60% predicted (n=89); controls – no known COPD (n=87) and COPD with an FEV_1 > 60% predicted and no ECOPD in the previous year (n=74). Using random forest analyses the 44 candidate items were reduced to 34-item, 21-item, 8-item and two different five-item sets. Through-out the item reduction process, the item sets maintained good performance, consistently misclassifying fewer than 27% of cases and controls, and with sensitivity greater than 80% and specificity greater than 70%. A five-item questionnaire exhibited good operating characteristics for separating COPD cases from controls. These characteristics were even better when separating COPD from controls without COPD.

Selective PEF measurement enhances the operating characteristics of a COPD case finding strategy. In the above case control study PEF was measured using a mechanical PEF meter with disposable mouthpieces. To optimize sensitivity and specificity, the following cut-off scores were selected, based on our data, for identifying cases of clinically significant COPD using PEF alone: males: <350 L/min; females: <250 L/min. The best method for predicting cases was a combination of the questionnaire and PEF **(CAPTURE)**, where PEF is used only for mid-range scores. Under this scoring scenario, patients with scores of 0 or 1 are not considered at risk of clinically significant COPD; they would not require further evaluation. Those with a score of 5 or 6 are considered to be at high risk of clinically significant COPD and should be referred directly for further evaluation, including clinical spirometry. Patients scoring in the middle range (2 to 4) would undergo PEF testing, applying the 350/250 interpretation thresholds. In our sample, 52% of the participants required PEF to determine if spirometry was indicated. The other 48% needed only the five-item questionnaire. This approach provided 90% sensitivity, 93% specificity and an overall error rate of 9%.

CAPTURE exhibits similar operating characteristics in a Spanish speaking population. To broaden our target population, the five-item questionnaire was methodically translated to Spanish using previously validated, rigorous methods(44) to yield an instrument that is equivalent to the English questionnaire

and linguistically and culturally applicable to persons of diverse Spanish-speaking backgrounds residing in the US. In a subset of Spanish speaking participants CAPTURE exhibited excellent sensitivity (88%), specificity (92%) and overall error rate (10%) for identifying patients with clinically significant COPD.

Aim 2.

Consistent with national criteria for preventive and chronic disease care quality, feasibility science is designed to assist clinical and health education evaluators plan for assessing and evaluating specific implementation factors essential to the success of new diagnostic, therapeutic and programmatic options in real-world clinical practice. This aim's analysis of primary care clinical practice COPD case finding feasibility includes an initial evaluation of existing COPD diagnostic and case finding processes within the practices, assessment of practices' capacity to change from existing respiratory symptom assessment strategies and an understanding of practice-specific learning preferences associated with new diagnostics in chronic disease diagnosis and management. The aim addresses through the RE-AIM feasibility approach how a new tool might a) identify target populations (Reach); b) appraise optimal targeted respiratory history and symptoms consistent with clinically significant COPD (Effectiveness or Impact); c) integrate into practice workflow (Adoption); d) deliver changes and improvements to COPD care within the scope of real-world clinical practice (Implementation); and e) persist in use and quality over time (Maintenance) (45-53).

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Potential risks associated with Aims 1 and 3 of this study are outlined below.

Spirometry: Participants may become short of breath. Syncope, light-headedness and fainting may develop during this test. These are uncommon.

Albuterol: Tremulousness, feeling of a strong, rapid heartbeat, and palpitations can occur with inhaled albuterol. A targeted safety questionnaire will be administered to all participants prior to albuterol to exclude those with a previous adverse event with the medication.. Note that albuterol is only administered to those with abnormal spirometry on the baseline spirometry assessment (defined as $FEV_1/FVC < 0.70$ or $FEV_1 < 80\%$ predicted).

Peak Expiratory Flow: Participants may become short of breath. Syncope, light-headedness and fainting may develop during this test. These are uncommon.

Other non-physical risks of the study include those from economic loss from participation in the study; this will be minimized by scheduling tests and evaluations in a timely manner in the fewest number of visits possible. Patient and physician participants will be provided a modest fee to cover their time to participate in the study.

We anticipate few adverse events due to the non-invasive nature of the study procedures and the rarity of such events encountered during the initial visits and longitudinal follow-up. Medical care will be available at each Clinical Center to treat participants who develop adverse events during in-person study visits.

Potential risks associated with Aim 2 of this study include:

No more than minimal risk exists for participants within aim 2.

Confidentiality of information and identification are the risks associated with this project. Based on previous research and the protocols that have been developed, we believe that the likelihood of these risks to the participants would be minimal, i.e. "rare".

Potential risks associated with the study (all Aims) include:

Loss of confidentiality of study data: This is unlikely since data collected will be stored in locked file cabinets in locked rooms at the Clinical Centers. In addition, only participant IDs are used to identify participants in the secure server at the Data Coordinating Center.

Poor quality data: If the data collected are of poor quality such that it is not useable to achieve study aims, participants will have unnecessarily been exposed to other risks in the study.

2.3.2 KNOWN POTENTIAL BENEFITS

For Aims 1 and 3 of this study, participants could receive direct benefit as a result of their participation in this research. Current state-of-the-art COPD education is offered to all clinicians at participating PBRN sites (see aim 3 protocol) that could result in improved care for their COPD patients. At the conclusion of the study, both patients and their care providers will have received the results of the CAPTURE screening tool and research spirometry that could result in further diagnostic testing leading to a diagnosis of COPD or other respiratory disorder. Some participants, however, will not have respiratory disease and therefore may not benefit. For Aims 1, 2 and 3, physician participants may benefit in learning how better to identify COPD participants in clinic.

Known potential benefits for each participating clinical staff include critical review their clinical respiratory practice. In general, aim 2 offers the ability to assess and address CAPTURE-specific primary care practice feasibility issues which could augment or hamper clinical communication or implementation of COPD case-finding in real-world primary care clinical practice.

Potential benefits to society include improved understanding of how best to identify individuals with COPD in the primary care setting. This could ultimately lead to better treatments and lower morbidity and mortality for patients with COPD.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The demonstrated and potential future benefits to improved understanding of COPD case finding outweigh the minimal risks of the procedures performed.

Increased understanding of how best to diagnose individuals at risk for COPD in the primary care population has the potential to benefit both patients with COPD and society at large. The risk to individuals associated with this study protocol is small and the knowledge to be gained is substantial.

3 OBJECTIVES AND ENDPOINTS

Aims 1 and 3.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Aim 1: Define the sensitivity and specificity of CAPTURE for identifying previously undiagnosed patients with *clinically significant COPD* in a broad range of primary care settings	Sensitivity and specificity of CAPTURE to identify previously undiagnosed patients with clinically significant COPD at baseline.	Standard methodology for COPD diagnosis will be used (1).
Aim 3: Define the impact of CAPTURE information provided to clinicians in identifying and managing patients with respiratory symptoms (*CAPTURE+*) across a broad range of primary care settings.	Proportion of CAPTURE+ participants who meet at least one of the following within 12 months of study baseline (composite endpoint): 1) referral for or completion of clinical spirometry testing, 2) new diagnosis of COPD, 3) newly prescribed respiratory medication (long acting bronchodilator or anti-inflammatory for respiratory condition), or 4) referral to a specialist for respiratory evaluation/treatment.	The composite endpoint is clinically relevant and consistent with published data (45). This will test the impact of CAPTURE on clinician behavior.
Secondary		
Aim 1: Define the sensitivity and specificity of CAPTURE for patients with COPD across a broad range of racial and ethnic subgroups in a range of primary care settings	Sensitivity and specificity of CAPTURE to identify previously undiagnosed patients with COPD across sex, ethnic groups, urban vs rural location, and educational status.	Patient characteristics will be used to assess the robustness of CAPTURE.
Aim 1: Determine positive and negative predictive values (PPV and NPV) in different practice settings.	Positive and negative predictive values (PPV and NPV) in different practice settings.	PPV and NPV will be used to assess the robustness and usefulness of CAPTURE in various settings.
Aim 1: Verify the optimal use (cutoff threshold) of the CAPTURE tool in combination with FEV_1 measurements for identifying undiagnosed COPD.	AUC for various cutpoints of CAPTURE and PEF measurements to determine the best cutpoint for clinically significant COPD screen.	The best discrimination for CAPTURE combined with FEV_1 will indicate the optimal usage of the tool.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Aim 1: Determine patient and site characteristics that, with the CAPTURE assessment, will best identify persons with undiagnosed COPD.	AUC to identify the combination of patient/site characteristics which best discriminates those with clinically significant COPD.	The best discrimination will determine which site and patient characteristics best predicted undiagnosed COPD in combination with the CAPTURE tool.
Aim 1: Determine whether CAPTURE is useful in identifying other definitions of undiagnosed COPD: 1) spirometry-defined COPD, and 2) mild COPD	All primary and secondary endpoints as applied to 1) spirometry-defined COPD and 2) mild COPD	This will determine the robustness of the CAPTURE tool.
Aim 3: Define the impact of CAPTURE clinician education, and patient-level CAPTURE information to clinicians ("CAPTURE education") on selected additional therapeutic interventions in previously undiagnosed patients with *clinically significant COPD.*	Proportion of CAPTURE+ participants who meet the components of the composite endpoint.	Each endpoint is clinically relevant and consistent with published data. (45) This will test the impact of CAPTURE on clinician behavior.
Aim 3: Assess impact of CAPTURE education on clinician interventions specific to smokers.	In participants with clinically significant COPD who are current smokers, the incidence of physician referral to a formal smoking cessation program, prescribed smoking cessation medication, and referral to pulmonary rehabilitation program.	Certain outcomes are specific to only smokers and should be assessed.
Aim 3: Determine the impact of CAPTURE education on patient symptoms, exacerbations, hospitalizations, and mortality.	In participants with clinically significant COPD, change in CAT score, and proportion of patients who experience exacerbations, hospitalizations, or mortality.	This endpoint is important for quality of life, and long-term patient outlook.
Aim 3: Determine the impact of CAPTURE education when COPD is defined spirometrically.	All of the above endpoints for Aim 3, with the patient population defined as those who have COPD defined spirometrically.	This will determine the robustness of the CAPTURE tool

Aim 2.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Explore clinical practice implementation approaches to and acceptance of CAPTURE case finding for clinically significant COPD in a range of primary care practices.	Primary care clinician recommendations that inform CAPTURE RE-AIM strategies at both provider and clinical support levels of primary care practice. Primary clinician recommendations that inform CAPTURE-associated COPD education models for primary care clinicians. Primary care clinician recommendations that inform CAPTURE-associated COPD clinical quality improvement designs across a variety of primary care practice types.	Clinical improvement models that introduce new testing must investigate practice opinion and behavior and incorporate clinician recommendation.
Secondary		
Qualitatively assess primary care clinical staff COPD practice behavior – including COPD screening and diagnostic perceptions, beliefs and knowledge – that will inform strategies to improve CAPTURE RE-AIM (reach, impact, adoption, implementation and maintenance of use) characteristics.	Existing COPD screening and diagnostic and case-finding processes within a variety of primary care practices. Primary care practice beliefs about capacity to change from existing COPD screening and diagnostic assessment strategies. Practice-specific COPD screening and diagnostic continuing education preference.	Awareness of existing clinician knowledge and behavior can influence workflow implementation and overall effectiveness of new clinical tools.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Qualitatively assess primary care patient opinion of CAPTURE COPD case finding that will inform strategies to improve CAPTURE RE-AIM (reach, impact, adoption, implementation and maintenance of use) characteristics.	CAPTURE opinion survey ascertaining participant comprehension of CAPTURE instructions and testing and ease of completion.	Patient satisfaction, understanding and ease of test completion affects staff implementation and workflow decision. Participant opinion survey results will seed CAPTURE implementation planning practice staff focus groups.

4 STUDY DESIGN

4.1 OVERALL DESIGN

A prospective, multicenter study that includes three key aims: 1) cross-sectional validation to define sensitivity and specificity of CAPTURE; 2) *qualitative* research exploration engaging clinical staff at all levels from primary care practices serving US patient populations of differing gender, racial, ethnic, urban/rural and socio-economic blends, and 3) explore the impact of CAPTURE on clinical care and patient outcomes across a broad range of primary care settings in a cluster randomized controlled clinical trial. The CAPTURE tool consists of a 5-item self-administered questionnaire and selected use of peak expiratory flow (PEF) measurement, designed to identify clinically significant Chronic Obstructive Pulmonary Disease (COPD).

For Aim 1, approximately 5,000 patients will be recruited at the time of their regularly-scheduled appointment across 100 participating primary care clinics associated with practice-based research networks (PBRNs). Eligible participants will undergo a baseline visit during which the CAPTURE tool and spirometry will be obtained, as well as PEF and other participant characteristics.

For Aim 2, approximately 150 clinicians from 10 participating primary care practices across 5 US PBRNs will undergo detailed implementation investigation of the CAPTURE case finding model for clinically significant COPD. In addition, 200 primary care patients recruited as part of Aim 1 will complete a 10-minute written CAPTURE opinion survey.

To address Aim 3, participating primary care practices will be randomized in a 1:1 fashion to one of the following interventions:

- Arm 1: Practice clinicians will receive basic COPD education, and patient-level CAPTURE information with CAPTURE interpretation education (CAPTURE+ COPD education). As the second aim addresses the optimal format for delivering practice CAPTURE education this will be incorporated at the sites randomized to this arm (see Enhanced CAPTURE education in Figure 1).
- Arm 2: Practice clinicians will receive basic COPD education only (COPD education).

Basic COPD and CAPTURE specific education will use an interactive, web-based education program which will be provided to all practice personnel, including physicians, nurse practitioners, physician assistants, nurses, medical assistants, clerical staff and administrative staff. Practitioners at sites randomized to the CAPTURE+COPD education intervention will receive the CAPTURE score from the central study coordinators soon after the baseline assessments have been completed.

Addressing Aims 1 and 3 will include a baseline visit for all participants and for Aim 3 longitudinal follow-up over 12 months for a predefined cohort of participants. Determination of the participants included in the longitudinal follow-up cohorts will be made after the baseline visit.

Baseline Data

Practices and/or study staff will pre-screen patients according to local guidelines to identify potential participants based on the following criteria: no prior COPD diagnoses, between 45 and 80 years old, and speak and read either English or Spanish. The timing of the pre-screening and the method to approach these patients for participation in the study (e.g., at the next outpatient visit, via telephone) will be flexible, depending upon site recruitment preferences. Patients who are eligible based on the pre-screening questions and agree to participate in the study will sign informed consent. After signing the consent, they will complete the CAPTURE questionnaire, PEF testing, spirometry testing, other respiratory questionnaires, and provide past medical history and demographic information. Local/PBRN study coordinators for each of the 6 PBRNs will perform the study procedures and record baseline information into the electronic data capture (EDC) system.

The EDC system will calculate a CAPTURE score for each participant, based on his/her CAPTURE questionnaire answers and PEF measurement. A binary score (positive or negative CAPTURE) will be emailed to the central study coordinator only for participants randomized to CAPTURE+COPD education intervention practices. The coordinator will communicate this information to these practitioners. Practitioners at sites randomized to the COPD education only intervention will be blinded to CAPTURE scores. Practitioners in both intervention arms will be blinded to research spirometry results.

Analyses will include a comparison of CAPTURE scores with data from spirometry testing and participant reported data to determine sensitivity and specificity of the CAPTURE tool. *The hypothesis is that a simple case finding methodology using a five-item questionnaire with selective PEF measurement will identify undiagnosed patients with clinically significant COPD.*

Based on the data collected at baseline, participants will be classified into the following groups for analyses:

Cohort	**Definition**
CAPTURE+	Participants with • CAPTURE score $\geq$ 5, or • CAPTURE score of 2, 3, or 4 with a low PEF, defined as <350 L/min for males and <250 L/min for females
CAPTURE-	Participants with • CAPTURE score < 2 or scores 2-4 with normal PEF (defined as $\geq$350 L/min for males and $\geq$250 L/min for females)
Spirometrically defined COPD	Participants with abnormal spirometry, defined as post-bronchodilator FEV_1/FVC <0.7. If a participant is unable to complete a post-bronchodilator spirometry (refusal, technical error on the part of coordinator, etc.), and the pre-bronchodilator

	FEV1/FVC is less than 0.65, the participant will be considered to have COPD for the purpose of follow-up in this study.
Clinically significant COPD	Participants with abnormal spirometry, defined as post-bronchodilator FEV_1/FVC <0.7, plus one of the following: 1) FEV_1 < 60% predicted or > 1 exacerbation like event within the past 12 months.
Mild COPD	Participants with abnormal spirometry, defined as post-bronchodilator FEV_1/FVC<0.7 plus both of the following: • FEV_1 ≥ 60% and • No prior history of ECOPD

Longitudinal Follow-up

A pre-defined subgroup of enrolled participants, who meet any of the below criteria will undergo longitudinal follow-up at 12 months,

1. Participants with a CAPTURE Score ≥ 5 or CAPTURE score of 2, 3, or 4 with a low PEF, defined as <350 L/min for males and <250 L/min for females
2. Participants who have abnormal spirometry results, defined as post-bronchodilator FEV_1/FVC < 0.7 or FEV_1 < 80% predicted at baseline. If a participant is unable to complete a post-bronchodilator spirometry (refusal, technical error on the part of coordinator, etc.), and the pre-bronchodilator FEV1/FVC is less than 0.65, the participant will be considered to have COPD for the purpose of follow-up in this study.
3. A random sample of approximately 5% who do not meet criteria 1 - 2

Participants who meet the criteria for follow-up will be sent notification/reminder letters within the first 3 weeks of enrollment and at 3, 6, and 9 months. Patient-reported data will be collected by COPD Foundation via telephone, secure web-based server, or mail-based methodologies, based on participant preference.

Subject medical data will be collected from the medical record to assess for changes in practice-level care.

The hypothesis for Aim 3 is that sites where COPD and CAPTURE education and patient-level CAPTURE data are provided to clinicians will exhibit improved COPD diagnosis and COPD-related care compared to sites where COPD education is provided to clinicians.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Aims 1 and 3

The totality of the published data confirms the clinical and economic impact of undiagnosed COPD, continuing under-diagnosis, and incomplete application of spirometric testing in the primary care community. It suggests that there is value in COPD case-finding that targets COPD patients most likely to benefit from available therapies. These points identify a pressing health care problem that requires an innovative approach to facilitate identifying these individuals. Our preliminary studies enumerated in section 2.2 extend these concepts by demonstrating that:

- Six key domains identify patients with clinically significant COPD.

- Forty-four distinct items resonate with patients and provide important insights for COPD case-finding.
- Five items exhibit excellent sensitivity and specificity in identifying patients with clinically significant COPD.
- PEF provides incremental value in a case-finding strategy.
- The combination of a five-item questionnaire and PEF optimizes a COPD case-finding strategy in English and Spanish speaking patients.

Our proposed study will provide crucial data to address the operating characteristics and clinical translation to our COPD case-finding strategy into the primary care setting. It will also provide an important initial evaluation of the potential clinical impact of the systematic identification of previously undiagnosed COPD patients.

Aim 2

The rationale for this aim reflects the importance of establishing if an innovative approach to COPD case finding is considered a pragmatic tool with potential utility for primary care clinicians within real-world clinical practice settings. With the completion of this aim we anticipate confirming that future validated approaches to COPD case finding can be adopted in a broad variety of clinical care settings thereby providing further impetus for the rigorous evaluation of a) case finding guided patient outcomes as part of routine primary care clinical practice; b) case finding use in a range of primary care health professional COPD-related education approaches, clinical quality improvement models and diagnostic guidelines; and c) the capacity of clinical case finding and informed follow-up to enhance future COPD clinical care therapeutic paradigms used in primary care practice.

Consistent with Institute of Medicine criteria and US health quality standards for preventive and chronic disease care, the feasibility science qualitative research framework is designed to assist clinical and health education evaluators prepare, assess and evaluate specific implementation factors essential to the success of new diagnostic, therapeutic, educational and programmatic options in real-world clinical practice. This aim's analysis of primary care clinical practice COPD case finding feasibility considerations for CAPTURE includes an initial evaluation of existing COPD diagnostic and case finding processes within the practices, assessment of practices' capacity to change from existing respiratory symptom assessment strategies and an understanding of practice-specific learning preferences associated with new diagnostics and chronic disease diagnosis and management. Patient perceptions of the CAPTURE case-finding process are also obtained to provide a holistic perspective of the clinical feasibility of CAPTURE implementation in primary care practice. Borrowing from the RE-AIM implementation science approach, this aim explores how real-word primary care practices might potentially use CAPTURE to: a) identify target populations (Reach); b) refine current practice appraisal of patient respiratory history, symptoms and diagnostics used to identify clinically significant COPD (Effectiveness/Impact); c) change or integrate COPD case finding into practice workflow (Adoption); d) alter practice communication, education and/or care quality improvement planning for COPD diagnosis and management (Implementation); and e) use COPD case finding consistently over time (Maintenance).

Ten primary care practices will undergo detailed implementation investigation of the CAPTURE case finding model designed to identify patients with COPD most likely to benefit from available therapeutic options. CAPTURE, a one-page questionnaire with selective PEF measurement, is presented to the clinicians of ten practices not participating in aims 1 and 3 as a prospective COPD case finding option awaiting validation. By representing CAPTURE as a model—and not introducing it into actual practice—aim 2 gains recommendation from primary care clinical practice experience with sufficient feasibility

generality to circumvent interdependence between the operating characteristic exploration (aim 1) and qualitative feasibility understanding (aim 2) components of our study. The aim 2 results, that include the pooled CAPTURE clinical communication, education and implementation recommendations from real-world primary care practice, are analyzed and applied in concert with local and national research team expertise to enhance the potential impact of CAPTURE's introduction into clinical care in aim 3. Aim 2 results also provide previously unexplored qualitative information necessary for future long-term patient outcome studies of COPD case finding approaches in primary care.

4.3 END OF STUDY DEFINITION

Participants that do not meet the criteria for, or are not selected for, longitudinal follow-up will be considered to have completed the study after completion of the baseline visit.

Participants included in the longitudinal follow-up phase will be considered to have completed the study after completion of the Month 12 Assessment as shown in the Schedule of Activities (SoA), Section 1.3.

Clinician participants in aim 2 will have completed the study after participation on their second focus group between months 14 and 16 as shown in the Figure 2, Structure of Aim 2.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Inclusion criteria for Aims 1 and 3
In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Male or female, aged 45 – 80 years

Inclusion criteria for Aim 2

Two Aim 2 practices are selected by each of their 5 affiliated PBRNs based upon willingness to participate and variability of primary care practice type within the PBRN. Differences in practice size, staffing, ownership, prior quality improvement engagement, geography, patient population socioeconomic status (SES) or languages spoken are among the among the selection criteria the PBRNs will utilize to choose.

Clinician participants (10 practices with up to 15 clinicians per practice):
1. Provision of signed and dated informed consent form.
2. Stated willingness to comply with availability and all study procedures for the duration of aim 2 by the 10 practices (through PBRN recruitment) and their up to 15 clinicians within (through informed consent).

Patient participants [200 patients (approximately 40 from each PBRN)] for CAPTURE survey:
1. Provision of signed and dated informed consent form.

2. Stated willingness to comply with all study procedures and availability for the duration of the study.
3. Male or female, aged 45 – 80 years.

5.2 EXCLUSION CRITERIA

Exclusion criteria for Aims 1 and 3

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Previous clinician provided diagnosis of COPD
2. Treated respiratory infection (with antibiotics and/or systemic steroids) in the past 30 days of baseline
3. Participants unable to perform spirometry due to any of the following conditions within the past 30 days of baseline
    a) Chest surgery
    b) Abdominal surgery
    c) Eye surgery
    d) Heart attack
    e) Stroke

Exclusion criteria for Aim 2

1. Clinician participants: current employment at practices participating in aims 1 and/or 3
2. Clinician participants: from practices providing fewer than 2 clinician participants
3. Patient participants: meeting the exclusion criteria for aims 1 and 3 (above)

5.3 SCREEN FAILURES

PBRN coordinators, in conjunction with clinical study site personnel, will pre-screen individuals who are unlikely to be able to complete research spirometry. These individuals will be considered *pre-screen failures*.

Participants who are consented to participate but have a prior clinician diagnosis of COPD will be considered *screen failures*.

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment and retention strategies for Aims 1 and 3

Approximately 5,000 participants will be recruited from 100 primary care clinics affiliated with six PBRNs. Each PBRN has centrally-based research coordinators with a history of success working in PBRN practices, documented expertise in previous large diagnostic or therapeutic trials, and personnel experienced in recruitment and data collection.

IRB approval will be obtained at each PBRN for approval for patient contact, informed consent and participation in this study.

All patients who meet all inclusion and no exclusion criteria at the participating PBRN clinical site will be eligible for participation. Research coordinators will work with participating practices to identify and approach potential participants. Recruitment strategies may vary depending on the practice.

Enrollment of participants will depend on the gender, ethnic and racial makeup of those that are being recruited from the practices included in this trial. No exclusion criteria apply specifically to women or to minorities. The Data Coordinating Center (DCC) will track enrollment of participants throughout the course of this study. If women and minorities are under-represented in the initial phase of recruitment, a commitment exists to develop recruitment strategies that target these populations so the final study group is a well-balanced representation of the studied population.

Recruitment and retention strategies for Aim 2

Clinician participants: Approximately 150 clinic participants are recruited by: 1) introductory telephone contact with the practice leadership by PBRN research coordinators and the aim 2 research team; 2) follow up letter, time commitment infographic and informed consent forms sent to interested practices outlining aim 2 clinician participant activities and responsibilities; and 3) in-person aim 2 study explanation to clinician participants at the committed practices during the introductory baseline study site visit.

Clinician participant recruitment draws from both prescribing (or "provider") staff and non-prescribing (or "clinical support") staff. The aim 2 research team will attempt to obtain an even mix of both clinician staff types from each practice. Retention incentive of clinician participants over 2 years includes provision of on-line COPD education to all clinician participants and monetary incentive to practices as determined by each individual PBRN.

Patient participants: 200 participants (40 from each PBRN) are recruited as a sub-set of the aim 1. Each of the 200 patient participants in aim 2 are asked to complete a one-time 10-minute written opinion survey. Their aim 2 participation is concluded at the end of the opinion survey completion.

The aim 2 research team and DCC will track enrollment and retention of all aim 2 participants throughout the course of the 2-year aim 2 study.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

The study intervention is applicable to Aims 2 and 3 and consists of healthcare provider education modules.

The practitioners at the 10 sites selected for Aim 2 will receive module 1, Basic COPD education, and may elect to take modules 3-5 for supplemental information on COPD.

For Aim 3, half of the practices will receive Basic COPD education (module 1) and half will receive Basic COPD Education and CAPTURE Education (modules 1 and 2). Practitioners at practices randomized to COPD only education must take module 1 and may elect to take modules 3-5; however, they will not take module 2. Practitioners at practices randomized to COPD+CAPTURE education must take modules 1 and 2, and may elect to take modules 3-5.

1 - Basic COPD Education will be provided in order for providers to optimally manage patients with COPD. The education will incorporate evidence-based recommendations using the 2018 update of the Global Obstructive Lung Disease Strategy(45).

A 40-minute overview will be presented in the most expeditious manner at each practice site, for example by webinar for all practice personnel over the lunch hour, or audiovisual presentation available on a dedicated CAPTURE web site. The PBRNs have indicated that this module should be no longer than 40 minutes. Topics will include: CAPTURE study description and rationale, importance of COPD in the region of the local practices, COPD definition and diagnosis, patient goals, and management approach. Attendance at this mandatory training will be documented and continuing education credits will be provided for physicians and nurse practitioners by National Jewish Health, an accredited CME provider.

2 - **CAPTURE education**. An online audiovisual module will be developed to explain CAPTURE interpretation and use in patient evaluation and diagnosis of COPD. This module will only be available to practices randomized to receive the results of CAPTURE for clinical use.

With the information provided in Aim 2 about practice preferences for education, the CAPTURE education module will be revised and made available to practices enrolled in Aim 1 after the completion of Aim 2.

3 - Online advanced COPD education will be available for all practices and continuing education credits will be provided to enhance practitioner participation. Practitioner attendance at each online audiovisual module will be collected including the amount of time spent on each education module, completion of each module with a post-test and evaluation, and CME will be provided. Education will be case-based and will include role playing where appropriate. Seven basic modules of 20 minutes or less will be available both to practices randomized to receive CAPTURE results for clinician use and to control practices that will not receive CAPTURE results and will cover:

1. Diagnosis of COPD: How to diagnose COPD in primary care including medical history, physical exam and role of spirometry, severity categorization
2. Spirometry overview: Basic clinical interpretation
3. Advanced spirometry: Test performance, evaluating quality, advanced case-based interpretation
4. Management overview: Patient goals, smoking cessation, vaccination, patient education, shared decision-making
5. Pharmacotherapy: Inhaled bronchodilators, inhaled corticosteroids
6. Other therapies: Oxygen, pulmonary rehabilitation, surgical approaches
7. Inhalation devices: Patient education

4 – On-site COPD education. Additional funds will be sought to provide on-site COPD education. We have experience in successfully providing half-day on-site education to primary care practices to enhance their management of COPD.

5 – Social media and case conferences. We will use social media (Facebook and Twitter) to provide ongoing education about COPD. Facebook and Twitter posts will provide tips on managing COPD. Online conferences will be scheduled to discuss cases submitted by primary care providers.

6.2 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

For Aims 1 and 3, this study will use randomization and blinding as two of the cardinal principles of clinical trials to minimize bias.

Randomization. Practices will be randomized into one of the two interventions, COPD education or COPD education + CAPTURE education, in a 1:1 manner, stratified by PBRN. Randomization will occur at the time of site activation and each site will be assigned a unique randomization number. The DCC will prepare the randomization schedule, using computer-generated block randomization with the block size(s) known only by the DCC. A secure web-based application will be built that will be used by the central study coordinators to enter site information (e.g., site ID, stratification factor) and to obtain the randomization number. The information can be printed and sent and/or emailed directly to the study coordinator.

Blinding. This is a single-blind study with the participants blinded to whether their practitioners have received CAPTURE education and patient-level CAPTURE results. Practitioners at sites that are randomized to the control arm (COPD education alone) will be blinded to the CAPTURE questionnaire and PEF results. All practitioners and participants will be blinded to the baseline COPD status of the participants (i.e., blinded to spirometry results), except for safety reasons. In this situation, participants and their clinician will be notified if a participant's post-bronchodilator FEV_1 is less than 30% predicted. For all other participants, they and their practitioners will be blinded to research spirometry results. The coordinator should make every effort to conceal the spirometry results from the participants in these latter cases. Study coordinators should also make every effort to conceal the administration of a post-bronchodilator spirometry test from the practice staff so as not to unblind the physicians to abnormal spirometry.

6.3 STUDY INTERVENTION COMPLIANCE

In practices randomized to share the CAPTURE results with the clinician, the goal is to share results with the clinician at the time of the CAPTURE study visit. Providing results at the time of the clinical visit will allow the clinician to act on the CAPTURE results as soon as possible when the participant is in front of the clinician. Based on the workflow at each of the practices, this may not always be possible.

Sharing of the CAPTURE results with the participant's primary care clinician will be tracked by the study coordinator enrolling patients at sites randomized to receive CAPTURE results. The sharing of CAPTURE results will be recorded on the study eCRF form. The eCRF will collect the timing of when the results were provided to the practitioner - whether the results were provided to the clinician at the time of the enrollment visit prior to the clinician visit with the patient, or were provided at another time.

If results were not shared at the time of the CAPTURE study visit, then the date of sending the CAPTURE results will be recorded on the appropriate eCRF by filling in the date (day/month/year) the exact copy of the CAPTURE Toolwere sent to the clinician through a HIPPA-compliant method and placed in the medical record. The goal is to communicate the results to the clinician. The DCC will monitor review all participants' eCRFs to assure that all those enrolled from practices randomized to CAPTURE results have been shared with clinicians..

6.4 CONCOMITANT THERAPY

Practitioners will treat participants using their own clinical judgment. No medications are prohibited. This is not an interventional therapeutic trial.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

In this cluster randomized controlled trial (Aim 3), where practices are the recipients of the intervention and where the interventions are based upon education and access to CAPTURE and PEF results, it is not anticipated that study intervention will be discontinued at the practice level. However, one of the CO-PIs will review safety data, especially SAEs related to baseline spirometry and PEF procedures, to ensure there are no untoward effects of the study on participants.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in Aims 1 and 3 of the study at any time upon request.

Clinician participants in Aim 2 are free to withdraw from participation in the study at any time upon request. If a clinician is no longer working at the participating practice then their involvement in Aim 2 activities will end and no further attempt will be made to include them in the remaining questionnaires or focus groups.

7.3 LOST TO FOLLOW-UP

If a participant selected for longitudinal follow up does not respond to the 12-month questionnaires, coordinators will attempt to contact participants first by the participant's preferred method of communication, either phone or email. At least three attempts will be made. If no response is obtained, the participant's alternate contact method will be attempted three times. Phone calls will be made at different times of the day. If there is no response, a registered letter will be sent to the participant. If the participant cannot be reached, the alternate contact will be called and/or emailed. If no response is received, a registered letter will be sent to the alternate contact. If after all of these methods are employed and no contact with the participant results, the participant will be considered lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 BASELINE ASSESSMENTS AND DATA COLLECTION

Efficacy data will be collected by patient-reported outcomes and medical record review.

For Aim 1, CAPTURE, PEF results, acute respiratory event history and spirometry will be considered efficacy assessments. They are collected at the baseline visit.

CAPTURE. Participants will complete the 5-item *self-administered* questionnaire and measurement of Peak Expiratory Flow (PEF).

Peak Expiratory Flow (PEF). PEF using the Vitalograph® AsmaPlan® mechanical PEF meter with SafeTway® disposable mouthpieces (Vitalograph LTD, UK) will be measured for all participants. Ideally, PEF should be prior to the participant's physician appointment. The participant will perform three PEF tests. All three measurements will be recorded.

Spirometry. Before spirometry is performed, participants will be asked if they have taken a medicine which they breathed into their lungs from any puffer or inhaler within the past two hours. If participant answers yes, then spirometry will be performed but considered a post-bronchodilator spirometry test. No further spirometry will be needed. If participant answers no, then pre-bronchodilator spirometry will be performed for measurement of forced vital capacity (FVC), forced expiratory volume in one-second (FEV_1), and calculation of FEV_1/FVC (using EasyOne® Spirometer, ndd Medical Technologies Inc., Andover, MA). Testing will be performed in accordance with established American Thoracic Society/European Thoracic Society (ATS/ERS) standards.

A Spirometry post-bronchodilator will only be performed if pre-bronchodilator spirometry FEV_1/FVC is less than 0.70 or FEV_1 is less than 80% predicted. Post-bronchodilator spirometry will be performed within 15 to 20 minutes after inhalation of 2 puffs of albuterol 180 mcg HFA using an AeroChamber Plus* Flow-Vu® spacer with one minute between the first and the second inhalation. A separate AeroChamber will be provided for each participant's testing. A standing order for albuterol administration may be used if necessary.

Spirometry is a valid, reproducible means of documenting the presence and severity of airflow limitation. When properly performed with maximum effort and attention to the details of calibration of the instrument, spirometry maneuvers are among the most reproducible of biomedical measures. In the setting of a highly trained, experienced therapist, a coefficient of variation of 2-3% is not unusual. Spirometry will be performed in a standardized manner in accordance with the ATS guidelines, as described in the manual of procedures (MOP). Spirometry is the timed-based measurement of the amount of air that can be forcefully exhaled from the lungs after a full inspiration. In the forced expiratory vital capacity maneuver, a person inhales as big a breath as possible and then blows it out as fast and as long as possible until no more air can leave the lungs. The volume of air leaving the lungs is recorded continuously throughout the maneuver in order to allow calculation of important measures of lung function.

NHANES prediction equations, which are programmed into the Easy On PC spirometers, will be used to calculate the predicted lung function levels. These require the input of age, height, and race/ethnicity (White, Black, Hispanic). For people of mixed or unknown race the White prediction equations will be used.

PBRN Research Coordinators will be trained and certified in the performance of spirometry testing. Spirometry will be sent for central review for quality control assurance.

Adjudication of the Presence of Obstruction on Post-Bronchodilator Spirometry

The presence of obstruction is determined by the presence of an FEV_1/FVC ratio less than 0.70 after the administration of a bronchodilator. A bronchodilator will be administered to study subjects whose baseline FEV_1/FVC is less than 0.70 or whose FEV_1 is less than 80% of the predicted value.

If a subject is unable to complete a post-bronchodilator spirometry (refusal, technical error on the part of coordinator, etc.), and the pre-bronchodilator FEV_1/FVC is less than 0.65, the patient will be considered to have COPD for the purpose of follow-up in this study.

Height and weight
Height and weight will be recorded in order to determine appropriate prediction equations for spirometry and possible effect of obesity on spirometry. Height will be recorded and weight will be measured prior to spirometry testing.

Demographic Data Collection
Demographic data including date of birth, gender, ethnicity, race, educational level achieved, daily work schedule, living arrangement and health insurance will be entered into the EDC system.

Contact information including address, phone numbers and email address will be obtained. Alternate contact information will be obtained for two other people, family members not living with the participant or close contacts, who may be knowledgeable about the participant in the event that the participant cannot be contacted for subsequent longitudinal follow-up. Alternate contact information will include name, address, phone numbers and email addresses. All contact information will be stored securely at the clinical site or in a database separate from that developed for the clinical data.

Medical History
Previous medical diagnoses will include comorbidities such as cardiovascular, respiratory and malignant disorders. Influenza vaccination history will also be recorded. This questionnaire will be completed under supervision of the coordinator.

Concomitant Medication Review
Respiratory medications will be recorded at baseline for all participants. This questionnaire will be completed under supervision of the coordinator.

CAPTURE Additional Items Questionnaire
Participants will complete the 13-item *self-administered* questionnaire.

COPD Assessment Test (CAT)
Participants will complete the 8-item *self-administered* questionnaire.

Respiratory symptoms, smoke exposure and exacerbation like events
History of respiratory symptoms and exacerbation like events over the past year as well as smoke exposure (including e-cigarette or equivalent) will be recorded. This questionnaire will be completed under supervision of the coordinator.

Whenever possible, informed consent, eligibility review, CAPTURE Questionnaire and PEF will be performed prior to the participant's clinic appointment, so that CAPTURE results may be provided to the physician at the time of his/her appointment if the patient is cared for in a clinical center randomized to CAPTURE+ education.

Adverse events
Adverse events related to study procedures will be recorded by the coordinator.

8.2 LONGITUDINAL FOLLOW-UP ASSESSMENTS AND DATA COLLECTION

For Aim 3, the follow-up efficacy assessments are collected from the time of baseline to 12 months in selected cohorts (as described in section 4.1). Medical record abstractions completed by PBRN coordinators and participant questionnaires administered by study team members from the COPD Foundation are used.

Data collected from medical record include:

All participants undergoing 12-month follow-up as described in section 4.1	Current Smokers Only
Clinical spirometry ordered or administered	Smoking cessation counseling
Referral to specialist for respiratory evaluation/treatment	New prescription for smoking cessation medication
New recorded clinical diagnosis of COPD	Formal smoking cessation program referral/completion
New prescription for respiratory medication (long acting bronchodilator, inhaled steroids, oral anti-inflammatory)	
Exacerbation like event assessment (hospital, ED, minute clinic, antibiotic/steroid prescription/administration)	
Vaccination status	
Formal pulmonary rehabilitation program referral/completion*	

*only collected in relevant participants

Data from clinical visits to be collected at follow-up by telephone, secure web-based server, or mail-based methodologies directly from participants and administered by COPD Foundation study personnel include:

All participants undergoing 12-month follow-up as described in section 4.1	Current Smokers Only
Spirometry	Smoking cessation counseling
New diagnosis of COPD	Smoking cessation medications (including OTC)

Referral to pulmonologist or other respiratory specialist	
Exacerbation like event assessment	
New prescription for respiratory medication (long acting bronchodilator, inhaled steroids, oral anti-inflammatory)	
CAT score	
Attendance of pulmonary rehabilitation*	

*only collected in relevant participants

8.3 AIM 2 ASSESSMENTS AND DATA COLLECTION

Practice study introduction and participation confirmation: After PBRN practice selection, the CAPTURE study Aim 2 lead together with the local PBRN Aim 2 coordinator conduct a 15-minute participation confirmation and introduction phone call with the key PBRN contact at each of the two selected practices. The study specifics and timeline are reviewed. After practice participation is confirmed, the on-site practice assessment date is scheduled. Informed consent forms for clinical staff are mailed to each confirmed practice. To reduce practice burden, completed clinical staff informed consent forms (up to 15 clinical staff per practice) can be returned by mail to the University of Michigan School of Public Health office, addressed to Dr. Randall Brown, or saved for completion and picked up at the on-site practice assessment site visit. Following the confirmation phone call, the PBRN Aim 2 coordinator completes a short (15 minute) qualitative questionnaire detailing the selected and confirmed practice demographics and PBRN parameter of practice choice for each of the two practices. The completed PBRN Practice Selection Questionnaire is returned to the Aim 2 data team and stored securely.

On-site Practice Assessment (OSPA): The OSPA is an in-person on-site practice workflow assessment. It includes 2 practice clinicians per practice choice, the PBRN Aim 2 coordinator (if available), the CAPTURE study Aim 2 lead and the CAPTURE Aim 2 research specialist (if the PBRN Aim 2 coordinator is not present). The objective of the visit is to detail specifics of practice workflow, practice physical characteristics, staff roles, clinical information gathering patterns for respiratory patients, electronic health record communication, continuing education structure, and quality improvement structure. The assessment takes place in three parts; the pre-observation practice overview (conducted with the 2 practice clinicians – 60 minutes), the ½ day practice workflow observation (observation by one member of the Aim 2 research team of common and testing areas used for the respiratory patient). There is no patient engagement and no collection of patient-specific identification or health information), and the post-observation practice summary (conducted with the same 2 practice clinicians – 30 minutes).

The 3 OSPA assessment tools are:

i) The Pre-workflow Observation Practice Assessment Review Questionnaire
ii) Respiratory Workflow Assessment Review
iii) The Post-workflow Observation Practice Assessment Review Questionnaire

Also at the OSPA, informed consent is obtained from all remaining participating staff (up to 15 clinical staff per practice) by the CAPTURE Aim 2 team and returned to the Aim 2 data team for secure storage.

Clinical Staff Questionnaires (Baseline/6/12 months). Written or on-line questionnaires are provided to participating and consented staff personnel at two practice levels -- Non-Prescribing clinical (also known as "support") staff and Prescribing (PR) clinical (also known as "provider") staff.

Non-Prescribing (NPR) clinical staff are clinical practice personnel involved in clinical workflow (including registered nurses, licensed practical nurses, medical assistants, medical assistants and receptionists), yet not having the role to make final and official medical diagnostic and management disposition plan decisions for and with patients. Prescribing (PR) clinical staff are prescribing clinical practice personnel involved in clinical workflow (including doctors, nurse practitioners, and physician assistants) who may independently make final medical diagnostic and management disposition plan decisions for and with patients.

Questionnaire items explore clinician demographics, including past education, duration of current employment and currently held clinical position. COPD knowledge, attitudes, beliefs, practice patterns and self-efficacy regarding COPD diagnosis, management, spirometry testing and interpretation, practice workflow and communication in the clinical primary practice care of adult patients with respiratory disease. Additional questions include preferred continuing education method and clinical staff quality improvement modalities for respiratory disease management. Specific examples of past practice chronic disease diagnostic changes and the individual and practice-wide levers of success and challenge associated with those changes are explored.

Each of the 3 (baseline, 6-month and 12-month) questionnaires are completed within 30 minutes. No identifying patient data is collected. Online questionnaires are collected and secured by the CAPTURE DCC and Aim 2 research team. The participants who complete written questionnaires (per their preference) mail completed questionnaires via pre-addressed stamped envelope to the CAPTURE DCC and Aim 2 research team.

Patient Opinion Surveys:
200 patient participants, 40 from each PBRN, are recruited as a sub-sample from Aim 1 practices. Patient participants fulfill all inclusion and exclusion criteria and receive informed consent for survey participation as part of aim 1.

Eligible participants complete a written one-time 5 to 10 minute CAPTURE opinion survey. Patient survey data is collected by Aim 1 research coordinators and is processed with Aim 1 baseline patient data. Patients receive a $10 gift card for completion of the survey Aim 2 patient participation ends at the completion on the lone opinion survey.

Participants who prefer to complete the 5 to 10-minute survey online via Qualtrics will be sent a secure, Qualtrics link via email. The Qualtrics survey will include a brief, introductory screen affirming consent, describing the survey and instructions about participation. Once the survey is complete, participants will see a screen with instructions about how to obtain their $10 gift card and how to contact study staff with questions regarding the survey.

Modular online COPD education. Access to free, COPD on-line, continuing education is provided for all clinical staff at each practice. Each module will take 20 minutes or less. Modular components of and access to COPD education is described in the protocol. Aim 2 clinician participant access and completion of COPD education modules is assessed by clinician questionnaires and focus group item response over 12 months (between months 2 and 14 of Aim 2 timeline).

COPD in Primary Care/CAPTURE Introduction Focus Groups:
Two 45 to 60-minute focus group discussions occur at each Aim 2 practice. Focus groups are informed by practice demographics, practice assessment data – including respiratory workflow, baseline clinical staff questionnaire data regarding respiratory knowledge, attitudes, beliefs and practice preference for the diagnosis and care of adult patients with respiratory disease as well as patient opinion from CAPTURE surveys and past CAPTURE study (46, 47). Focus group candidate themes and prompts are developed for non-prescribing clinical staff (NPR) and prescribing clinical staff (PR) and are presented at separate on-site focus group sessions to allow more detailed discussion of role responsibility in the context of daily practice workflow, generating a more abundant qualitative data sample. Separation of and PR clinical staffing implementation themes into two focus groups also limits potential for hierarchical work-related discussion suppression described in other short duration focus group studies (48-52).

The focus group moderator introduces the CAPTURE tool utilizing CAPTURE education components described in Section 6.1.1. The focus group moderator follows RE-AIM prompts for CAPTURE implementation planning discussion throughout the focus group. Targeted COPD self-efficacy limitation themes from questionnaire data (including awareness and/or use of validated respiratory assessment questionnaires, spirometry, COPD guidelines, inhaled medication patient education, oxygen therapy, smoking cessation education, vaccination recommendation, pulmonology specialty care and pulmonary rehabilitation referral) are explored. Questions will probe clinicians to identify and explain levers that may maximize uptake of CAPTURE use in their practices as well as potential barriers to implementation. The Aim 2 research team will record each focus group using audio and written note-taking that will allow an abridged yet detailed tape-based micro-interlocutor analysis of focus group emergent themes, questions, answers and interactions. Key themes informing consensus discussion, program modifications and key elements of the CAPTURE RE-AIM implementation dimensions will be identified. Audio-recordings will be professionally transcribed and codes will be generated for the interview topics and key research questions. Reviewing the transcripts line-by-line, all substantive information will be assigned a priori codes as relevant for CAPTURE RE-AIM implementation planning, COPD diagnosis and CAPTURE intra-office clinical communication and COPD/CAPTURE education preference assessment. Additional codes will be developed for sub-themes and emergent themes.

Development of Practice-Based CAPTURE Implementation PBL Cases:
From analyses of the 2 NPR and 2 PR CAPTURE Introduction focus groups per PBRN, baseline clinical staff questionnaire data, online CAPTURE opinion surveys, and on-site practice assessments, 1 primary care practice CAPTURE implementation case per PBRN (total implementation cases = 5) is created by the Aim 2 research team. Given local knowledge of chronic disease management quality improvement history, effort, challenge and successes, each PBRN's participation in case creation will be instrumental. The Aim 2 research team will lead case creation using evidence-based problem based learning (PBL) techniques (53-57). The Center for Research on Learning and Teaching (CRLT) at the University of Michigan will serve as research reference for PBL case development qualification (58). Each local PBRN PBL case will be distributed to the Aim 2 clinical staff at the 2 participating PBRN practices 2 weeks prior to the CAPTURE Implementation focus groups, giving Aim 2 participants an opportunity to read the case introductions prior to the focus group session. Also, each practice will receive one additional non-PBRN case for focus group discussion as selected by the Aim 2 research team. Therein, each of the 5 CAPTURE implementation PBL cases will receive 2 comprehensive focus group reviews (see below).

CAPTURE Implementation PBL Case Presentation Focus Groups:

Each practice participates in a final pooled (NPRs and PRs together) on-site focus group. Two CAPTURE implementation cases (described above) are discussed at each focus group. The focus will explore, discuss, glean and create optimal 1) CAPTURE implementation, 2) CAPTURE clinical communication, 3) CAPTURE/COPD education and 4) CAPTURE primary care quality improvement recommendations pooled from all clinical practice levels for each of the 2 presented cases.

The Aim 2 research team will record each focus group using audio and written note-taking that will allow an abridged yet detailed tape-based micro-interlocutor analysis of focus group emergent themes, questions, answers and interactions. Key themes informing consensus discussion, program modifications and key elements of the CAPTURE RE-AIM implementation dimensions will be identified. Audio-recordings will be professionally transcribed and codes will be generated for the interview topics and key research questions. Reviewing the transcripts line-by-line, all substantive information will be assigned a priori codes as relevant for CAPTURE RE-AIM implementation planning, COPD diagnosis, CAPTURE intra-office clinical communication, and COPD and CAPTURE education preference, and COPD diagnosis quality improvement assessment. Additional codes will be developed for sub-themes and emergent themes.

8.4 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.4.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.4.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.4.2.1 SEVERITY OF EVENT

The following guidelines will be used to describe severity of AEs.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.4.2.2 RELATIONSHIP TO STUDY INTERVENTION

All AEs must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.
- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the study intervention). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.4.2.3 EXPECTEDNESS

The Principal Investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.4.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

Adverse events (AE)s that occur during the baseline visit will be recorded.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed.

8.4.4 ADVERSE EVENT REPORTING

All AEs that occur at baseline visit will be recorded in the case report form and reported to the DCC. We anticipate few adverse events due to the non-invasive nature of the study procedures. Participants will only be enrolled if they meet the study eligibility criteria, including assessment for contraindications for

spirometry. Targeted safety questions will be asked of all patient participants prior to albuterol to exclude those with a previous adverse event with the medication and others at high risk due to cardiac abnormalities.

8.4.5 SERIOUS ADVERSE EVENT REPORTING

SAEs will be reported to the IRB at the institution where the event occurred and the University of Michigan IRB will be notified of any serious adverse experience within 7 calendar days of occurrence. These will be reported to the DSMB.

Follow-up of serious adverse events

All SAEs will be followed up until resolution or permanent outcome of the event. All follow-up information will be included in the case report form. The DSMB will make recommendations to ensure data integrity and the safety of study participants.

8.5 UNANTICIPATED PROBLEMS

8.5.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.5.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing IRB and to the DCC. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the DCC within 7 calendar days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC within 14 calendar days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within one month of the IRB's receipt of the report of the problem from the investigator.

8.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a DSMB (physicians with the appropriate expertise, including non-involved pulmonologists, primary care physicians, and independent statisticians with clinical experience). Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the Principal Investigators.

9 STATISTICAL AND ANALYTICAL PLANS

9.1 SAMPLE SIZE AND POWER

9.1.1 PRIMARY OBJECTIVES

Define the sensitivity and specificity of CAPTURE for identifying previously undiagnosed patients with clinically significant COPD in a broad range of primary care settings. We will also explore clinical practice implementation approaches to and acceptance of CAPTURE case finding for clinically significant COPD in a range of primary care practices. Further, we will define the impact of CAPTURE information provided to clinicians in identifying and managing patients with respiratory symptoms (CAPTURE+) across a broad range of primary care settings.

9.1.1.1 SENSITIVITY AND SPECIFICITY OF THE CAPTURE TOOL

Primary Hypothesis 1. *The CAPTURE tool will exhibit excellent sensitivity and specificity in diagnosing clinically significant COPD as defined by post-bronchodilator $FEV_1/FVC < 0.70$ in addition to either >1 exacerbation-like event (ECOPD) within the past 12 months or an $FEV_1 < 60\%$ predicted.* Approximately 5000 patients will be enrolled in the study with the expectation that 300-800 of these will have previously undiagnosed clinically significant COPD, identified through research spirometry and documentation of prior respiratory events. Amongst cases, we will calculate the proportion of individuals who are at high risk for clinically significant COPD based on CAPTURE (sensitivity). Similarly, amongst non-cases, we will calculate the proportion of individuals not classified as having clinically significant COPD based on CAPTURE (specificity). Corresponding 95% confidence intervals will be calculated.

Based on our preliminary data drawn from a research setting, we noted 89.7% sensitivity and 93.1% specificity for CAPTURE. Table 9-1 shows the range of sensitivity and specificity 95% confidence interval

widths that would result if the true sensitivity or specificity is 85%, 90% or 95% across a range of sample sizes. For instance, if we find 500 individuals with confirmed clinically significant COPD and CAPTURE has 90% sensitivity, then the 95% confidence interval for sensitivity would be 90% ± 2.6%. Similarly, if 4,000 individuals are confirmed to have no evidence of clinically significant COPD and CAPTURE has 90% specificity, then the 95% confidence interval for specificity would be 90% ± 0.9%.

Table 9-1 Projected Confidence Interval Widths for Various Sensitivity/Specificity Percentages (Columns) and Sample Sizes (Rows).

	Sensitivity or Specificity		
Sample Size	**85%**	**90%**	**95%**
5000	± 1.0%	± 0.8%	± 0.6%
4000	± 1.1%	± 0.9%	± 0.7%
1000	± 2.2%	± 1.9%	± 1.4%
500	± 3.1%	± 2.6%	± 1.9%
250	± 4.4%	± 3.7%	± 2.7%
100	± 7.0%	± 5.9%	± 4.3%
50	± 9.9%	± 8.3%	± 6.0%

9.1.1.2 ADOPTION AND IMPLEMENTATION OF THE CAPTURE TOOL IN PRIMARY CARE PRACTICE

Primary Hypothesis 2: *A COPD case finding methodology using a validated one-page, five-item questionnaire with selective PEF measurement (CAPTURE) can be incorporated into the clinical practice patterns, clinical workflow, communication and practice-based quality improvement paradigms of a variety of primary care clinical settings.*

Aim 2 is a qualitative study to determine the efficacy of workflow integration of the CAPTURE tool. Statistical analysis of the clinician questionnaire will involve simple sums of each item and reviewing answers across practices and region. Standard frequencies for questions will be developed to examine patterns in responses.

The clinician focus groups will be conducted on-site at each practice at a time convenient for the participating clinicians. The number of prescribing and non-prescribing clinicians will equal 15 per practice and is based on interest with a maximum of 8 prescribing clinicians/practice. The sample size will follow a basic qualitative sampling standard of interviewing to redundancy or saturation. The number of clinicians to be interviewed (up to n=15 in each practice) is estimated based on achieving concept saturation. Reflecting regional primary care practice norms and to bolster concept saturation, PBRN Aim 2 coordinator focus group discussion participation is encouraged for very small practices where the participating prescribing and non-prescribing clinician total is less than or equal to 4. For all practice focus groups questions will explore the described Aim 2 CAPTURE RE-AIM concepts, barriers to implementation of the CAPTURE tool at other practice sites, standard processes for COPD and respiratory care diagnosis and management for each clinical role within the practice, and perception of quality improvement methods at each practice. Clinician focus groups are conducted on-site at each of the 10 practices.

Transcripts of clinician focus groups will all be digital and entered into a qualitative data analysis program, NVivo for Mac. This program allows for an investigation of the salience, patterning, and

contexts of key discourse items. Grounded theory methods will be used to identify and label recurrent themes and concepts within textual materials. Texts will be examined line-by-line, key phrases assigned tentative category labels, and coded passages grouped under the themes of feasibility, barrier and utility. The analyses will look for "traces" in dialogue, including repetitions, key words, evaluation statements, and metaphors. Change in salience, patterning, or content of key themes will provide further empirical evidence regarding the efficacy of our program's efforts to impact community norms and behaviors. An audit trail will be maintained to document the position of text material from which codes and themes are developed. We will use word/code counts of repetitive themes and concepts to indicate patterns. By allowing for open-ended responses, the narratives and notes will allow us to capture significant changes in participants' attitudes or behaviors. Codes and themes will be discussed iteratively with the research team members to hone definitions and assure consistency of interpretation. We will establish a coding dictionary and all interviews will be coded using the complete set of themes. Two independent coders will code each document to assure inter-coder reliability. Preliminary results will be shared with our Aim 2 research team and will inform the development of the case studies for the latter part of the project.

9.1.1.3 PRACTICE BEHAVIOR IN SITES WITH VERSUS WITHOUT CAPTURE EDUCATION AND PATIENT LEVEL CAPTURE DATA PROVIDED

Primary Hypothesis 3: *Sites where basic COPD and CAPTURE education are provided to clinicians, along with patient level CAPTURE data, will have a higher probability than control sites (i.e., those receiving only basic COPD education) of meeting the composite endpoint in their CAPTURE+ patients within 12 months of baseline.* From record review, the composite endpoint is met if one of the following is recorded: (1) referral for clinical spirometry testing, 2) new clinical diagnosis of COPD, 3) newly prescribed respiratory medication (long acting bronchodilator or anti-inflammatory for respiratory condition), or 4) referral to a specialist for respiratory evaluation/ treatment.

The study will enroll 50 CAPTURE practices and 50 control practices; each practice will enroll 50 patients (for a total of 5,000 patients). We project that within each practice, there will be at least 5 patients previously undiagnosed with COPD who have a CAPTURE+ screening result. The primary analysis will be to compare the average proportion of CAPTURE+ patients per practice that meet the composite endpoint in the two intervention arms. For power and sample sizes computations, this is a cluster randomized trial of n=50 clusters (practices) per intervention arm with 5 CAPTURE+ patients per cluster (practice). The primary power calculation is based on comparing the average cluster sample proportion (average proportion of CAPTURE+ patients per practice meeting composite endpoint) between intervention arms. Table 9-2 displays power for a two-sample test comparing average cluster sample proportions, accounting for possible intra-cluster correlation coefficient (ICC) values of 0.05, 0.10 and 0.15 that are typically seen in cluster randomized trials of behavioral interventions (https://www.abdn.ac.uk/hsru/research/research-tools/study-design/). These calculations assume a type I error of 5% and that the control arm meets the composite endpoint in 5% of CAPTURE+ patients and the CAPTURE arm meets the composite endpoint in higher percentages (columns of Table 9-2). There will be variability in the actual number of CAPTURE+ patients per practice. It is standard practice to inflate the number of needed clusters by 12% to account for this extra source of variability. Therefore, our power calculations are based on 44 clusters per intervention arm.

Table 9-2. Overall power to detect a difference in rate of meeting primary endpoint in CAPTURE group (50 practices/clusters) vs usual care (50 practices/clusters),

assuming 5% performance rate in usual care; 50 patients total / practice; assuming 10% prevalence gives 5 CAPTURE+/practice					
Improvement over usual care	+7.5%	+10%	+15%	+25%	+50%
ICC=0.05	0.72	0.89	0.99	>0.99	>0.99
ICC=0.10	0.65	0.84	0.98	>0.99	>0.99
ICC=0.15	0.59	0.79	0.97	>0.99	>0.99

9.1.2 SECONDARY OBJECTIVES

9.1.2.1 SENSITIVITY AND SPECIFICITY IN PREDEFINED SUBGROUPS

We will also examine several subgroups of interest that are key to addressing our overall goal of defining the value of CAPTURE across a broad range on individuals. These will include sex, ethnic groups, rural and urban location, and educational level, among individuals with clinically significant COPD, spirometrically defined COPD and individuals with "mild" COPD as defined in this protocol. We have specifically chosen clinical sites with a diverse gender, racial and ethnic mix, and rural and urban mix with the expected prevalence of clinically significant COPD cases and controls by subgroup outlined in Table 9-3, again with corresponding sensitivity and specificity confidence interval widths in Table 9-1. For example, if sensitivity of CAPTURE in Hispanic individuals is 90%, then a sample size of approximately 100 would give a confidence interval of 90% ± 5.9%. We believe that with an overall sample size of 5,000 recruited patients we will have adequately sized subgroups to assess the operating characteristics of CAPTURE in the subgroups of interest.

Table 9-3. Projected numbers of clinically significant COPD cases and non-cases we expect by subgroup of interest assuming prevalence of obstructed individuals is between 6-16%. (*Non-Hispanic) This table assumes prevalence of non-clinically significant COPD similar to clinically significant COPD (not included in this table).

	Total	**Men (50%)**	**Women (50%)**	**White* (62%)**	**Black* (15%)**	**Hispanic (18%)**	**Rural (46%)**	**Urban (54%)**	**Ever-Smokers (40%)**	**Never-smokers (60%)**
Projected # confirmed clinically significant COPD by subgroup	300-800	150-400	150-400	186-496	45-120	54-144	138-368	162-432	120-320	180-480
Projected # confirmed no COPD by subgroup	3,400-4,400	1,700-2,200	1,700-2,200	2,108-2,728	510-660	612-792	1,564-2,024	1,836-2,376	1,360-1,760	2,040-2,640

9.1.2.2 FURTHER ANALYSIS OF ASSOCIATIONS BETWEEN MEETING COMPOSITE ENDPOINT AND INDIVIDUAL AND PRACTICE LEVEL OUTCOMES

Secondary analyses for evaluating practice behavior are exploratory, and therefore not included in a formal power and sample size analysis. These analyses are described further in Section 9.3.2.

9.2 POPULATIONS FOR ANALYSES

Aim 1
Population used for sensitivity calculations are all enrolled patients with clinically significant COPD as defined by post-bronchodilator $FEV_1/FVC < 0.70$ in addition to either >1 exacerbation-like event (ECOPD) within the past 12 months or an $FEV_1 < 60\%$ predicted.

Population used for specificity calculations are all enrolled patients with no demonstrable COPD as determined by research spirometry conducted upon study entry, $FEV_1/FVC \geq 0.70$.

Aim 2
Clinician participants: enrolled clinicians are from 2 primary care practices in each of five US PBRN regions that do not engage in Aims 1 or 3 investigation. Eligible clinicians include primary care providers and primary care clinical non-provider support personnel.

Patient participants: enrolled as a sub-sample of Aim 1 participants at baseline. One CAPTURE patient opinion survey is administered at baseline.. Aim 2 participants fulfill the inclusion, exclusion and population analysis criteria of aim 1.

Aim 3
Populations used in 2-sample comparisons of the average proportion of CAPTURE+ patients per practice that meet the composite endpoint in the two intervention arms will be based on randomization group (intent-to-treat analysis).

9.3 STATISTICAL ANALYSES

9.3.1 SENSITIVITY AND SPECIFICITY (AIM 1)

SAS version 9.4 PROC LOGISTIC will be used for computations. Calculations of sensitivity and specificity along with their corresponding 95% confidence intervals assume independent Bernoulli outcomes for each patient. Clinically significant COPD+ and COPD- populations selected for these analyses are described in Section 9.2. CAPTURE+ patients are those with a baseline CAPTURE score $\geq$ 5 or with a baseline CAPTURE score of 2, 3, or 4 with a low PEF (defined as <350 L/min for males, <250 L/min for females).

In addition to the primary sensitivity/specificity calculations, sensitivity/specificity and associated 95% confidence intervals will be calculated in predefined subgroups: sex, ethnic subgroups, rural and urban location, and educational status. As part of secondary analyses, receiver operating characteristic (ROC) curve analyses will evaluate different thresholds of the CAPTURE questionnaire score in defining a positive clinically significant + COPD screen, separately and in combination with low PEF characteristics, **and the additional CAPTURE questions**. As part of this exploration, participant and practice level data as well as interactions with the CAPTURE tool results, will be considered as predictors of clinically significant COPD using multivariable logistic regression. Corresponding positive and negative predictive values will be estimated across the range of prevalence percentages seen at the enrolled practices. Model selection in secondary logistic regression analyses will be based on forward selection using maximum likelihood theory, with entry into the model dependent on statistical significance at the 0.05 level. Exploration of this nature has the potential to produce artificially high operating characteristics (area under the curve [AUC], sensitivity and specificity) based on overfitting the data. SAS 9.4 PROC

LOGISTIC includes a cross-validation approach to ROC curve analysis [ROCOPTIONS(CROSSVALIDATE)] that we will use when assessing operating characteristics for any new prediction tool that goes beyond the original CAPTURE metric considered in primary analyses. Once a final logistic regression model has been selected, classification thresholds for predicting clinically significant COPD will be described by the investigative team from the cross-validated ROC curve. Calibration plots of observed versus predicted sensitivity, and observed versus predicted specificity, will be conducted across previously specified subgroups of interest (sex, ethnic subgroups, rural and urban location, and educational status).

All of the above analyses will be applied to these additional populations: (1) patients with spirometrically defined COPD and (2) patients with mild COPD.

9.3.2 PRACTICE BEHAVIOR (AIM 3)

The primary analysis will be to compare the average cluster sample proportion (average proportion of CAPTURE+ patients per practice meeting composite endpoint) between intervention arms. Practices that do not identify any CAPTURE + subjects will not contribute to the primary analysis, although this is felt to be an unlikely occurrence. A two-sample test comparing average cluster sample proportions will be used that explicitly takes into account correlation between individuals treated within the same practice. A two-sided p-value < 0.05 will be considered statistically significant. This analysis corresponds to a generalized estimating equation (GEE) regression analysis with (1) individual-level binary composite outcome data, (2) CAPTURE intervention group as a covariate, (3) practice id used to identify correlated outcomes, (4) exchangeable correlation matrix that assumes similar correlation between all composite outcome results for patients within the same practice, and (5) a logistic link function. The primary analysis would then correspond to a test for the CAPTURE intervention group parameter. There are no planned interim analyses for the primary endpoint, the rationale being that this is not a pharmaceutical or device trial that would benefit from standard stopping rules for efficacy. A DSMB will be monitoring the study for safety and study integrity.

Secondary analyses on meeting the composite outcome for participants who are CAPTURE+ will employ the GEE analysis framework with individual and practice level predictors in addition to the CAPTURE intervention group. Interactions will be assessed. We will also use the GEE framework to study and describe each of the individual components of the composite outcome as they relate to individual and practice level outcomes. In the subset of smoking patients, we will use GEE regression analysis to study additional binary outcomes, such as incidence of physician referral to a formal smoking cessation program, prescribed smoking cessation medication in participants who are smokers, and referral to pulmonary rehabilitation program.

In participants who are CAPTURE+, change in CAT score will be analyzed using mixed models with a random effect for practice. The average cluster sample proportion of patients who experience exacerbations will be compared between intervention groups using methodology similar to that used for the primary endpoint. Survival analysis allowing for correlation of endpoints within cluster (practice) will be used to compare mortality between intervention groups and perform multivariable analysis. We will explore differences between intervention groups in the average cluster sample rate of hospitalizations again using GEE. All additional secondary analyses will also be applied to patients with clinically significant and spirometrically defined COPD. Practices that do not have any clinically significant COPD or spirometrically defined COPD will not contribute to analyses of these secondary endpoints, respectively.

Model selection in GEE secondary analyses will be based on statistical significance at the 0.05 level using robust sandwich estimation of variability within clusters. Model fit will be checked by comparing observed versus predicted values within predefined subgroups of interest (sex, ethnic subgroups, rural and urban location, and educational status).

9.3.3 CAPTURE IMPLEMENTATION RECOMMENDATIONS (AIM 2)

Site-specific practice information, clinician knowledge and behavioral questionnaires, as well as patient opinion survey responses are recorded primarily to populate focus group themes for qualitative analysis. Secondary analyses of individual clinician and patient response using frequencies, means, ranking and dispersion by clinician type, practice and PBRN is accomplished using SAS version 9.4. Correlation with implementation recommendation is determined using GEE variance models.

Audio transcripts of clinician focus groups will all be digital and entered into a qualitative data analysis program, NVivo for Mac. This program allows for an investigation of the salience, patterning, and contexts of key discourse items. Grounded theory methods will be used to identify and label recurrent themes and concepts within textual materials. Texts will be examined line-by-line, key phrases assigned tentative category labels, and coded passages grouped under the themes of feasibility, barrier and utility. The analyses will look for "traces" in dialogue, including repetitions, key words, evaluation statements, and metaphors. Micro-interlocutor analysis of focus group emergent themes, questions, answers and interactions will account for individual gaps in focus group participation. Change in salience, patterning, or content of key themes will provide further empirical evidence regarding the efficacy of our program's efforts to impact clinician community norms and behaviors. An audit trail will be maintained to document the position of text material from which codes and themes are developed. We will use word/code counts of repetitive themes and concepts to indicate patterns. By allowing for open-ended responses, the narratives and notes will allow us to capture significant changes in participants' attitudes or behaviors. Codes and themes will be discussed iteratively with the research team members to hone definitions and assure consistency of interpretation. We will establish a coding dictionary and all interviews will be coded using the complete set of themes. Reviewing the transcripts line-by-line, all substantive information will be assigned a priori codes as relevant for CAPTURE RE-AIM implementation planning, COPD diagnosis, CAPTURE intra-office clinical communication, and COPD and CAPTURE education preference, and COPD diagnosis quality improvement assessment. Two independent coders will code each document to assure inter-coder reliability. Preliminary results will be shared with the Aim 2 data team and will inform the development of the CAPTURE case studies and primary care practice implementation recommendations.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise.

A HIPPA waiver will be submitted to each IRB to prescreen clinic schedules and patient panels for recruitment purposes. The PHI reviewed by the coordinator in the electronic health record (EHR) will include age, date of birth, diagnosis of COPD, respiratory medications, and other medical conditions that are contraindicated for spirometry. A waiver of written consent will be submitted to each IRB to pre-screen potential participants for eligibility criteria prior to informed consent. The pre-screening will either be by telephone prior to an upcoming clinic visit, or in person at the time of the visit. An IRB-approved telephone/in-person screening script will be submitted to each IRB.

A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. Participants will additionally have the opportunity to review the study and informed consent prior to providing consent for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

All PBRN research coordinators, COPD Foundation study staff and other clinical investigators will be certified by their local IRB in informed consent and human studies research.

Clinicians interested in participating in the qualitative, minimal risk study for Aim 2, will be given the opportunity to review the consent form below and sign it. This can happen once their practice agrees to participate in Aim 2 activities or during the first in person site visit with Dr. Brown.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

When a study is prematurely terminated, refer to Section 7, Study Intervention Discontinuation and Participant Discontinuation/Withdrawal, for handling of enrolled study participants.

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. In addition, it may be transmitted and stored at the DCC in a database separate from the clinical database (used for statistical analysis and scientific reporting) and with COPD Foundation study team access to aid in contacting participants at the 12-month follow-up. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the DCC. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by DCC research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the DCC.

For the online Aim 2 patient opinion survey, Qualtrics is used. Qualtrics is a secure University of Michigan (U-M) contracted-for cloud service that can be used to maintain or share the university's sensitive unregulated data, as well as some kinds of sensitive regulated data.

U-M's agreement with Qualtrics includes a Business Associate Agreement. This means individuals may use this service to maintain Protected Health Information (PHI) regulated by HIPAA. Complying with HIPAA's requirements is a *shared responsibility*. Users sharing and storing PHI in Qualtrics are responsible for complying with HIPAA safeguards, including:

- Using and disclosing only the minimum necessary PHI for the intended purpose.
- Obtaining all required authorizations for using and disclosing PHI.
- Ensuring that PHI is seen only by those who are authorized to see it.
- Obtaining all necessary data-sharing agreements and Business Associate Agreements for using and disclosing PHI.

- Following any additional steps required by your unit to comply with HIPAA.

Sensitive data, including PHI, may be collected and stored in Qualtrics for non-clinical, academic purposes only (for example, research and hospital quality improvement initiatives). Qualtrics cannot be used for any clinical applications, no matter the sensitivity level of the data

11 STUDY ADMINISTRATION AND OVERSIGHT

11.1 STUDY LEADERSHIP

11.1.1 PRINCIPAL INVESTIGATORS

The principal investigators are responsible for providing direction and oversight of all study activities.

Principal Investigators	
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11.1.2 PRACTICE BASED RESEARCH NETWORKS (PBRN)

PBRNs will have the following roles and responsibilities:

CAPTURE Study Preparation

1. Review protocol to help identify operational details
2. Submit final protocol and informed consents to all IRBs necessary for the participating sites
3. Complete and maintain current human participants training for all main study personnel as required by the IRB
4. Attendance of PBRN coordinators at in person training, spirometry certification for all coordinators, update of spirometry quality assessments and training
5. Identify and recruit local practice sites to participate in the study

CAPTURE Study Implementation

1. Facilitate COPD and when appropriate CAPTURE education
2. Maintain regular contact with participating PBRN practice sites during their period of patient enrollment
3. Supervise and send PBRN Research Coordinators to enroll patients, perform study visits including completion of the CAPTURE questions, peak flow, spirometry, and collect other information on all enrolled patients
4. Complete pre bronchodilator spirometry on all participants

5. Complete post bronchodilator spirometry on participants with abnormal pre-bronchodilator spirometry as defined by study algorithm (e.g. those with pre bronchodilator results consistent with obstruction)
6. Facilitate completion of data entry to the data coordinating center
7. Follow up by research coordinator for patients failing to respond to the follow up questionnaires
8. Collect practice outcome data related to enrolled patients at close of study from either electronic medical records or if practice does not have EMR, by manual record review

Patient participants and staff participants will be recruited from the PBRNs.

PBRN	Location	Director
Atrium Health	North Carolina	Hazel Tapp, PhD
LA Net Community Health Network	Southern California	Lyndee Knox, PhD
High Plains Network	Colorado	Linda Zittleman, MD
Duke Primary Care Research Consortium	North Carolina	Rowena Dolor, MD
Oregon Rural Practice-Based Research Network	Oregon	Nancy Elder, MD
University of Illinois, Chicago	Illinois	Min Joo, MD

11.1.3 SPIROMETRY CORE

Led by Dr. David Mannino, the Spirometry Core will maintain quality of the research spirometry that is integral to the success of the study. The work will be done in conjunction with a research assistant. This includes the following functions:

1. Development of the operation manual for the sites
2. Training of the site staff in the use of the spirometry equipment (including travel to training and sites as needed)
3. Certification of staff in spirometry
4. Assessing staff adherence to protocols for the use of bronchodilators
5. Grading and adjudication of spirometry
6. Importing processed spirometry into spreadsheets
7. Uploading processed data to data coordinating center
8. Working with data coordinating center to verify and clean data

In addition, Dr. Mannino will be a critical part of the team that evaluates the data both from spirometry and the other components of this study (the CAPTURE tool, quality of life measures, etc.), in addition to being part of the writing team that analyzes data and disseminates the findings from this study.

11.1.4 IMPLEMENTATION CORE

Dr. Randall Brown will lead the qualitative Aim 2 activities which assess the implementation strategy and acceptance recommendations for CAPTURE use in primary care practice. His team includes an Aim 2 project manager and dedicated research assistant. Led by Dr. Brown the Aim 2 team coordinates with PBRNs and their selected Aim 2 practices and will conduct qualitative site visits and focus groups in addition to administering clinical practice behavioral questionnaires. Drs. Barbara Yawn, Barry Make,

Bruce Bender and Julia Houfek will contribute to the development of the web based educational modules and the qualitative efforts on this project.

11.1.5 DATA COORDINATING CENTER (DCC)

Dr. Cathie Spino directs the DCC, housed at the University of Michigan within the Statistical Analysis of Biomedical & Educational Research (SABER) Unit of the Department of Biostatistics in the School of Public Health. The DCC staff will include a Database programmer, Data manager, Senior Unblinded Statistician, Statistical Analyst, Project Manager, Clinical Monitor, Web Programmer/Designer, and a Research Administrator. In addition, the blinded senior statistician, Dr. Susan Murray, is located at the University of Michigan. The DCC plays a pivotal role in the design, implementation, execution and administration of the study. The DCC will be responsible for randomization, eCRFs and online reporting systems, preparation of the manual of operations for data entry, addressing questions regarding entry and analysis, monitoring recruitment, follow-up and adherence to protocol, and scheduling and arranging meetings of the Executive Committee, Steering Committee, and Medical Monitor. The DCC will prepare all of the routine study reports for the Executive Committee, Operations Committee, and Medical Monitor. The DCC will interact with all of the Cores and other Committees, as needed. The DCC will compile data tables and listing for DSMB reports.

11.1.6 CLINICAL COORDINATING CENTER

The Clinical Coordinating Center (CCC) will be led by Principal Investigators Fernando Martinez, MD, MS at Weill Cornell Medicine, and MeiLan Han, MD, MS at the University of Michigan. Dr. Martinez will be responsible for overall study oversight as well as fiscal management of the overall project and capitation payments to sites for work performed. He will also be responsible for communication with NIH and submission of annual reports. Dr. Han will work with the Data Coordinating Center to oversee clinical trial enrollment and, along with her statistical team, be responsible for coordinating statistical analysis. The process for making decisions on scientific direction and allocation of resources will be made by both Drs. Martinez and Han, with input from the rest of the investigative team as needed.

Additional Clinical Coordinating Center (CCC) responsibilities:

- Establish subcontracts with enrolling sites, central laboratories, imaging service providers, and others as appropriate
- Protocol development and scientific design oversight
- Statistical analysis
- Participating study site selection
- Review of serious adverse events and unanticipated problems involving risk to participants or others, reporting to participating centers and regulatory reporting
- Prepare and maintain Clinical Coordinating Center IRB submissions
- Analyze and present data to DSMB

Clinical Coordinating Center Personnel

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11.1.7 12 MONTH SURVEY COORDINATING CENTER

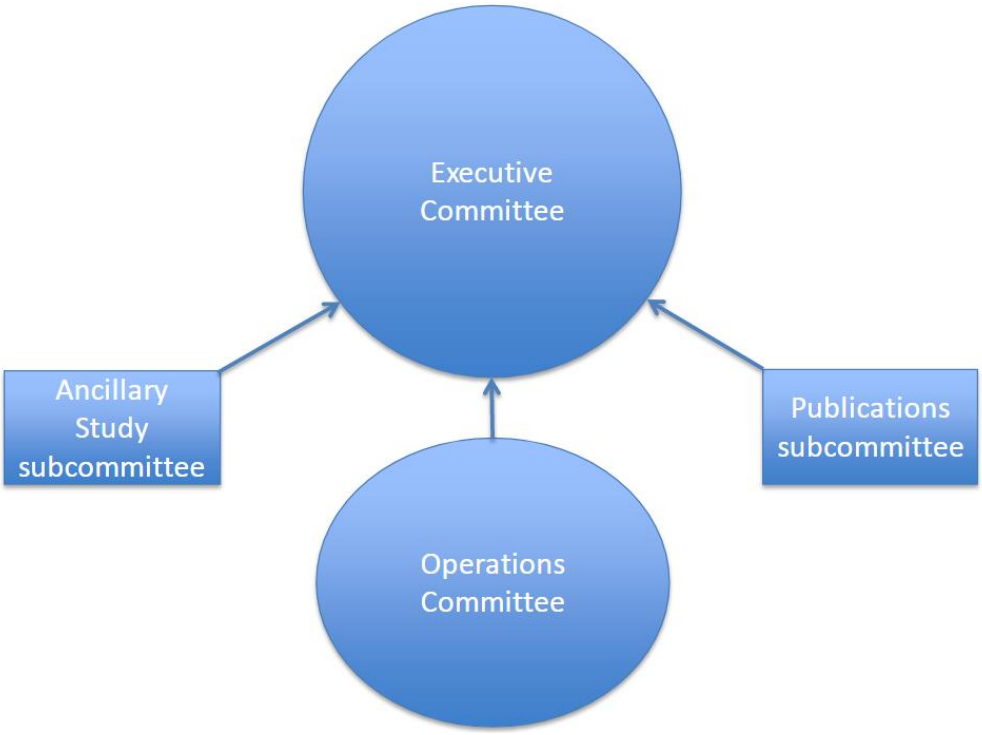
The 12 month Survey Coordinating Center will be led by Co-Investigator Barbara Yawn, MD MSc, Chief Science Officer at the COPD Foundation. Dr. Yawn will be responsible for oversight of the development and implementation of the reminder notices and 12 month survey administration by COPD Foundation study personnel for participants selected to complete the 12 month follow up survey.

11.2 ORGANIZATIONAL STRUCTURE

The Executive Committee will be led by the Principal Investigators and will consist of the 2 elected PBRN Directors, 1 representative of the COPD Foundation, Co-Investigators, Data Coordinating Center PI and Project Manager, NIH official and Clinical Coordinating Center Project Managers. The Executive Committee will meet every one-to-two weeks to administratively direct and monitor the progress of the study and to respond to any design, implementation or administrative issues that arise during the study.

The Operations Committee will consist of Overall Principal Investigators, PBRN Directors and lead coordinators, DCC Project Managers, and Co-Investigators. It will address implemental and administration faced by the PBRN practices that arise during the study.

Other subcommittees, such as the Publications and Ancillary Studies Subcommittees, will be constituted to support maximizing the utility of the CAPTURE study to the scientific community.



12 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data, documentation and completion. An individualized quality management plan will be developed.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

13 DATA HANDLING AND RECORD KEEPING

13.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Comprehensive data coordinating center (DCC) functions for this clinical trial, including clinical monitoring, database development, web-based data entry and management, as well as the creation and export of study reports for the DSMB will be provided by the University of Michigan Statistical Analysis of Biomedical and Education Research (SABER) group. Housed in the top nationally ranked Department of Biostatistics, SABER, in its 17-year existence, has served as the DCC for over 50 studies, including multiple NIH-sponsored networks.

The DCC will use OpenClinica® (OpenClinica Clinical Trial Software; OpenClinica, LLC, Waltham, MA), a clinical trial software platform for electronic remote (i.e., site-based entry) data capture and clinical data

management, as the basis for our custom-designed data entry and management system. The majority of data will be collected via electronic Case Report Forms (CRFs); however, other data sources, such as laboratory data from the central laboratory, may be used. In these circumstances, the DCC will also utilize electronic data transfer. Protocols for the transfer of data, with careful attention to data integrity, will be written by experienced programmers and stored in the OpenClinica database or data mart.

The DCC has established a set of standard operating procedures (SOPs) governing the processes used to ensure patient privacy and data confidentiality, including the use of anonymous participant IDs on CRFs and in reports. OpenClinica® enables compliance with Good Clinical Practice (GCP) and regulatory requirements by providing differentiated user roles and privileges, password and user authentication security, electronic signatures, SSL encryption, and comprehensive auditing to record and monitor access and data changes.

Data collection is the responsibility of the central study staff at the PBRN under the supervision of the PBRN Director (investigator). The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. In addition to the protocol, the DCC will prepare a Manual of Procedures which provides additional detail on data collection procedures, including source documentation, eCRF completion guidelines, data handling procedures and procedures for data monitoring and quality control that ensure these data are accurate, consistent, complete and reliable and in accordance with ICH 36.

13.2 STUDY RECORDS RETENTION

Study documents should be retained as required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

13.3 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation or scheduled protocol-required activity. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

13.4 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers after the completion of the primary endpoint by contacting Drs. Martinez and Han.

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The CAPTURE Study: Validating a unique COPD case finding tool in primary care

Protocol Number: 1R01HL136682

National Clinical Trial (NCT) Identified Number:

NCT03581227, NCT03653611, NCT03583099

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Funder:

National Heart, Lung, and Blood Institute (NHLBI)

Version Number: v. 4.0

10 July 2020

Protocol Amendment 4.0 - Summary of Changes				
Location	**Page Number**	**Type of Change**	**Description**	**Rationale**
1.2 Schema Table 1, 8.2 Longitudinal follow-up assessment	9, 32	*New*	A COVID-19 questionnaire was added to the 12-month follow-up visit, performed by the COPD Foundation.	A COVID-19 questionnaire was added to collect information about the COVID-19 prevalence in primary care, impact on symptoms, relation to comorbidities, and impact on provider outcomes.
2.1 Study Rationale, 4.1 Overall Design, 4.2 Scientific Rationale for Study Design	11, 22, 23	*New*	Rationale for collecting COVID-19 information from participants was added.	The impact of COVID-19 on COPD Case Finding and respiratory symptoms in primary care is unknown. COVID-19 information will be used to investigate this.
4.1 Overall Study Design	21	*Revision*	The following change was made: Participants who meet the criteria for follow-up will be sent notification~~/reminder letters within the first 3 weeks of~~ **shortly after** enrollment and **receive** at 3, 6, and 9 months	Language was updated for flexibility in notification of participants in order to allow time to confirm follow-up criteria.
8.1 Baseline Assessments and Data Collection	29	*Revision*	Additional guidance for sites to follow their local institutional guidelines for spirometry was added.	Institutional guidance for minimizing the risk of COVID-19 spread during spirometry varies across sites. Sites should ensure they are following local guidance.
8.2 Longitudinal follow-up assessment	31	*New*	Extraction of data related to COVID-19 confirmed and suspected cases will be added to the 12 month medical record review.	A COVID-19 questionnaire was added to collect information about the COVID-19 prevalence in primary care, impact on symptoms, relation to comorbidities, and impact on provider outcomes.
Protocol Amendment Summary of Changes Table	---	*Administrative*	Protocol Amendment 2.0 – Summary of Changes was added to the Summary of Protocol Amendments Table.	Summary of Changes for protocol versions 2.0 and 3.0 –were added to Section 14 to provide a comprehensive list of changes across all protocol amendments.

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STATEMENT OF COMPLIANCE

This study will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CAO	Chronic Airflow Obstruction
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
ECOPD	Exacerbation of Chronic Obstructive Pulmonary Disease
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FEV1	Forced Expiratory Volume in 1 second
FFR	Federal Financial Report
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practice
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act

IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PBRN	Practice-Based Research Network
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
RE-AIM	Reach, Effectiveness, Adoption, Implementation, Maintenance
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States
USPSTF	United States Preventive Services Task Force

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	The CAPTURE Study: Validating a unique Chronic Obstructive Pulmonary Disease (COPD) case finding tool in primary care
Study Description:	**Aims 1 and 3**. A prospective, multicenter study including a cross-sectional validation to define sensitivity and specificity of CAPTURE and its impact on clinical care across a broad range of primary care settings in a cluster randomized controlled clinical trial. The CAPTURE tool consists of a 5-item self-administered questionnaire and peak expiratory flow (PEF) measurement, designed to identify undiagnosed patients with Chronic Obstructive Pulmonary Disease (COPD). **Aim 2.** This study delivers a qualitative assessment of clinical practice acceptance of and implementation strategy for CAPTURE case finding within 10 varied primary care practices across 5 US PBRN regions. We evaluate primary care practice attitudes, beliefs and recommendations about CAPTURE's potential to feasibly integrate into clinical practice patterns, workflow and quality improvement paradigm planning in a variety of primary care clinical settings.
Definitions:	**CAPTURE+ =** Participants with • CAPTURE score $\geq$ 5, or • CAPTURE score of 2, 3, or 4 with a low PEF, defined as <350 L/min for males and <250 L/min for females **CAPTURE-** = Participants with CAPTURE score < 2 or scores 2-4 with normal PEF, defined as >350 L/min for males and > 250 L/min for females **Spirometrically defined COPD =** Participants with abnormal spirometry, defined as post-bronchodilator FEV_1/FVC <0.7. If a participant is unable to complete a post-bronchodilator spirometry (refusal, technical error on the part of coordinator, etc.), and the pre-bronchodilator FEV1/FVC is less than 0.65, the participant will be considered to have COPD for the purpose of follow-up in this study. **Clinically significant COPD =** Participants with abnormal spirometry, defined as post-bronchodilator FEV_1/FVC <0.7, plus one of the following: • FEV_1 < 60% predicted, or • > 1 exacerbation-like event within the past 12 months. **Mild COPD =** Participants with abnormal spirometry, defined as post-bronchodilator FEV_1/FVC<0.7 plus both of the following: • $FEV_1 \geq$ 60% and • No prior history of ECOPD
Objectives:	**Aims 1 and 3 Primary Objectives:** • **Aim 1 -** Define the sensitivity and specificity of CAPTURE for identifying previously undiagnosed patients with clinically significant COPD in a broad range of primary care settings.

	• **Aim 3 –** Define the impact of CAPTURE information provided to clinicians in identifying and managing patients with respiratory symptoms (CAPTURE+) across a broad range of primary care settings. **Aim 2 Primary Objective:** Explore clinical practice implementation approaches to and acceptance of CAPTURE case finding for clinically significant COPD in a range of primary care practices. **Aims 1 and 3 Secondary Objectives:** • **Aim 1 –** • Define the sensitivity and specificity of CAPTURE for patients with COPD across a broad range of racial and ethnic groups in a range of primary care settings. • Determine positive and negative predictive values (PPV and NPV) in different practice settings. • Verify the optimal use (cutoff threshold) of the CAPTURE tool in combination with PEF measurements for identifying undiagnosed COPD. • Determine patient and site characteristics that, with the CAPTURE assessment, will best identify persons with undiagnosed COPD. • Determine whether CAPTURE is useful in identifying other definitions of undiagnosed COPD including: 1) spirometry-defined COPD, and 2) mild COPD • Determine the potential impact of SARS CoV-2 infection on the above operating characteristics of the CAPTURE approach. • **Aim 3 -** • Define the impact of CAPTURE clinician education, and patient-level CAPTURE information to clinicians (“CAPTURE education”) on selected additional therapeutic interventions in previously undiagnosed patients with clinically significant COPD. • Assess impact of CAPTURE education on clinician interventions specific to smokers. • Determine the impact of CAPTURE education on patient symptoms, exacerbations, hospitalizations, and mortality. • Determine the impact of CAPTURE education when COPD is defined spirometrically. • Determine the potential impact of SARS CoV-2 infection on clinical actions taken in response to CAPTURE screening. **Aim 2 Secondary Objectives:** • Qualitatively assess primary care clinical staff COPD practice behavior – including COPD screening and diagnostic perceptions, beliefs and knowledge – that will inform strategies to improve

	CAPTURE RE-AIM (reach, impact, adoption, implementation and maintenance of use) characteristics. • Qualitatively assess primary care patient opinion of CAPTURE COPD case finding that will inform strategies to improve CAPTURE RE-AIM (reach, impact, adoption, implementation and maintenance of use) characteristics. • Determine the potential impact of SARS CoV-2 infection on the application of the CAPTURE approach.
Endpoints:	**Aims 1 and 3 Primary Endpoints:** • Aim 1 – o Sensitivity and specificity of CAPTURE to identify previously undiagnosed patients with clinically significant COPD at baseline. • Aim 3 – o Proportion of CAPTURE+ participants who meet at least one of the following within 12 months of study baseline (composite endpoint): 1) referral for or completion of clinical spirometry testing, 2) new diagnosis of COPD, 3) newly prescribed respiratory medication (long acting bronchodilator or anti-inflammatory for respiratory condition), or 4) referral to a specialist for respiratory evaluation/treatment **Aim 2 Primary Endpoints:** • Primary care clinician recommendations that inform CAPTURE RE-AIM strategies at both provider and clinical support levels of primary care practice. • Primary clinician recommendations that inform CAPTURE-associated COPD education models for primary care clinicians. • Primary care clinician recommendations that inform CAPTURE-associated COPD clinical quality improvement designs across a variety of primary care practice types. **Aims 1 and 3 Secondary Endpoints:** • Aim 1 – o Sensitivity and specificity of CAPTURE to identify previously undiagnosed patients with COPD across sex, ethnic groups, urban vs rural location, and educational level. o Positive and negative predictive values (PPV and NPV) in different practice settings. o Areas under the receiving operator characteristic curve (AUC) for various cutpoints of CAPTURE and PEF_1 measurements to determine the best cutpoint for COPD+ screen. o AUC to identify the combination of patient/site characteristics which best discriminates those with clinically significant COPD. o All primary and secondary endpoints as applied to 1) spirometry-defined COPD and 2) mild COPD • Aim 3 –

	o Proportion of CAPTURE+ patients who meet the components of the composite endpoint. o Proportion of patients with clinically significant COPD who meet the composite endpoint. o In participants with clinically significant COPD who are current smokers, the incidence of physician referral to a formal smoking cessation program, prescribed smoking cessation medication, and referral to pulmonary rehabilitation program. o In participants with clinically significant COPD, change in CAT score, and proportion of patients who experience exacerbations, hospitalizations, or mortality. o All of the above endpoints for Aim 3, with the patient population defined as those who have COPD defined spirometrically. **Aim 2 Secondary Endpoints:** • Existing COPD screening and diagnostic and case finding processes within a variety of primary care practices. • Primary care practice belief about capacity to change from existing COPD screening and diagnostic assessment strategies. • Practice-specific COPD screening and diagnostic continuing education preference.
Study Population:	**Aims 1 and 3.** Adults 45-80 years old without a prior diagnosis of COPD (total N = 5000) **Aim 2.** - 10 primary care practices: 2 practices per PBRN with up to 15 clinical staff participants per practice; clinician N = up to 150 (up to 30 clinician participants per PBRN). - Aim 1 patient opinion survey population; patient N = 200 (40 patients from each PBRN; adults 45-80 years old, without a prior diagnosis of COPD). - Total N = up to 350
Phase:	N/A
Description of Sites/Facilities Enrolling Participants:	**Aims 1 and 3.** Enrollment will occur in approximately 100 primary care practices affiliated with 6 primary care based practice networks (PBRN) across the United States who exhibit a broad range of gender, ethnic, racial, socioeconomic, and regional diversity. **Aim 2.** • Two primary care practices chosen by each of the same 5 PBRN co-investigator teams make up the 10 aim 2 practices from which clinician participants are enrolled. These 10 practices are separate from the 100 chosen practices in aims 1 and 3. • Patient participants are a sub-sample of those participants enrolled in aims 1 and 3.
Description of Study Intervention:	**Aims 1 and 3.** Primary care practices will be randomized to either receive basic COPD education and patient-level CAPTURE information with CAPTURE education (initially basic then later enhanced based on data collected in Aim 2) versus COPD education only.

	Aim 2. Participating primary care clinicians from 10 varied practices are surveyed at three different time points and participate in two focus groups qualitatively assessing CAPTURE implementation strategy and COPD case finding approaches in primary care. Participating patients complete one 10-minute written opinion survey about CAPTURE.
Study Duration:	**Aim 1 and 3.** 4 years **Aim 2.** 2 years
Participant Duration:	**Aims 1 and 3.** Up to 12 months **Aim 2.** • Primary care practice clinicians: questionnaires and focus groups (total 3 hours/participant) over 16 months. • Primary care patients: one 10-minute questionnaire/participant over 14 months.

1.2 SCHEMA

FIGURE 1. OVERALL STRUCTURE OF AIMS

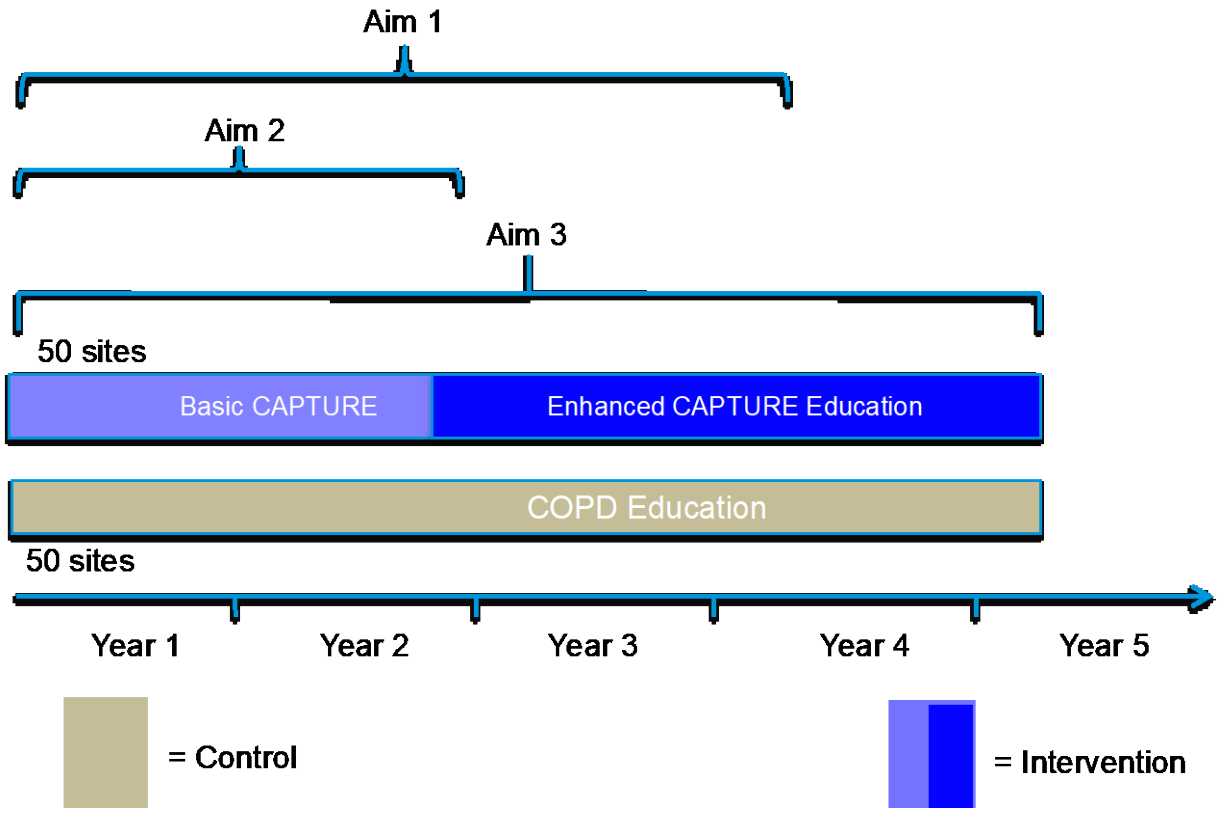

FIGURE 2. STRUCTURE OF AIM 2

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1.3 SCHEDULE OF ACTIVITIES (SOA)

Table 1: Schedule of Activities (Aims 1 and 3)

	Pre-Visit Contact[1]	**Baseline**	**12 Months[3]**
Contact (C)/ Visit (V)/Medical Record Review (MRR)	**C1**	**V1**	**C2/MRR[5]**
Time point, days (Visit window)	**Prior to outpatient visit (≤-1)**	**Within 30 days of pre-visit contact**	**365 ±30 (C2)**
Contact patient re: interest in study visit[1]	X		
Informed consent		X	
Demographics		X	
Medical history (Co-morbidities)[2]		X	
Vaccination status		X	X
CAPTURE 5-item questionnaire		X	X
CAPTURE item additional questionnaire		X	
Peak Expiratory Flow (PEF)		X	
Height and weight		X	
Respiratory medications review		X	X
Spirometry[4]		X*	
Respiratory symptoms, exacerbation assessment		X	X
Smoking exposure history		X	
Smoking cessation review[6]			X
COPD Assessment Test (CAT)		X	X
COVID-19 Questionnaire		X	X
Adverse Events		X	
Medical record review Additional COVID-19 items			X X

1. Optional per site recruitment preferences
2. Comorbidities including cardiovascular, respiratory and malignant disorders
3. Recorded for a subset of participants who meet any of the following criteria: 1) CAPTURE+ subjects defined as CAPTURE Score ≥ 5 or CAPTURE score of 2, 3, or 4 with a low PEF, defined as <350 L/min for males and <250 L/min for females 2) abnormal spirometry defined as $FEV_1/FVC < 0.70$ or $FEV_1 < 80\%$ predicted at baseline; and, 3) a random sample of approximately 5% of those who do not meet criteria 1 and 2. For participants meeting criteria 1 and 2 who cannot or choose not to complete the 12-month assessment, medical record

review will still be completed. For participants meeting criteria 1 and 2 who change medical practices and medical record review cannot be completed, patients will be contacted for completion of patient reported data. For participants meeting criterion 3 where all of the protocol-specified 12-month assessments cannot be made, another participant will be selected at random to replace this participant.

4. Pre-bronchodilator spirometry will be done for all participants. Post-bronchodilator spirometry will be performed for participants with abnormal spirometry ($FEV_1/FVC < 0.70$ or $FEV_1 < 80\%$ predicted) *If the participant has taken a bronchodilator within a 2-hour window of spirometry the spirometry will be considered post-bronchodilator and a pre-bronchodilator spirometry will not be done.
5. The 12-month assessment consists of patient reported data, collected by the COPD Foundation, and medical record review completed by site coordinators.
6. This will be completed in those that are smoking at V1.

2 INTRODUCTION

2.1 STUDY RATIONALE

Undiagnosed COPD is a leading cause of morbidity and mortality. Spirometry, the 'gold standard' for diagnosis, is not recommended for screening in asymptomatic individuals or untargeted case finding and remains widely underutilized in primary care settings. Targeted case finding approaches have been strongly advocated but currently available approaches generally identify patients across the spectrum of mild to severe disease without reference to potential therapeutic benefit or exacerbation risk, thereby limiting clinical impact and acceptance in primary care. There is an urgent need to develop and implement simple case finding approaches that can identify patients with clinically significant COPD in primary care settings.

Through a multi-stage, iterative process we developed a simple case finding tool using five questions combined with selective peak expiratory flow **(PEF)** measurement that identifies individuals with 1) an $FEV_1 < 60\%$ predicted and/or 2) at risk for ECOPD. We call this tool CAPTURE (**C**OPD **A**ssessment in **P**rimary Care **T**o Identify **U**ndiagnosed **R**espiratory Disease and **E**xacerbation Risk)(1). As clinical trials have demonstrated benefit and therapeutic guidelines recommend therapy for these individuals we have labeled these patients as suffering from 'clinically significant' COPD. The long-term goal of this project is to identify these patients so that they can be treated and result in improved health status, reduced exacerbations, and decreased morbidity.

The *overall objectives* of Aims 1 and 3 of this project are to 1) validate the sensitivity, specificity, and predictive value of CAPTURE to identify undiagnosed, clinically significant COPD patients in a diverse primary care population; and explore whether identifying these patients results in improved COPD specific care and health status. Our *principal hypothesis* is that CAPTURE can effectively and efficiently identify primary care patients with undiagnosed, clinically significant COPD. We objectively test our principal hypothesis by completing to two separate and linked aims:

Aim 1 – Determine the sensitivity and specificity of CAPTURE in identifying clinically significant COPD patients in a broad range of primary care outpatient practices.

Working hypothesis - A simple case finding methodology using a five-item questionnaire with

selective PEF measurement will identify undiagnosed patients with clinically significant COPD.

We will conduct a 5,000 participant cohort study in 100 primary care practices affiliated with five primary care based research networks **(PBRN)** that provide access to previously undiagnosed patients with clinically significant COPD who exhibit gender, ethnic, racial, socioeconomic and regional diversity.

Aim 3 – Define the impact of CAPTURE screening in a broad range of primary care outpatient practices and evaluate practice and patient characteristics that are associated with care implementation and clinical outcomes for patients with respiratory symptoms (CAPTURE+).

Working hypothesis – Provision of patient specific CAPTURE data to practicing clinicians will result in improved management of patients with respiratory symptoms (CAPTURE+).

We will provide basic COPD education and patient level CAPTURE information and education to site clinicians at 50 of the sites and prospectively follow selective, pre-defined subgroups of patients to define relevant outcomes. Care at the other 50 clinical sites will follow standard of care with basic COPD education to clinicians.

Assessing the potential clinical impact of a novel COPD case finding strategy includes confirmation of validity in a diverse primary care patient population and a quantitative research evaluation of its impact on clinical decision-making and COPD patient outcomes, as found in aims 1 and 3 above. Equally important is exploration through validated implementation methods that the newly designed CAPTURE tool, even if valid and impactful, can provide real-world utility within a variety of primary care practice settings. While we find no evidence in previous COPD screening studies of such detailed appraisal, ascertaining the feasibility of clinical testing is a vital component of assuring that new approaches address potential clinical practice need, capacity, knowledge and diagnostic gaps. As much as possible, clinical respiratory innovations should align with busy workflow at all practice staff levels to more effectively identify primary care patients with undiagnosed, clinically significant COPD. The SARS-CoV-2 pandemic may potentially alter the approach to COPD Case Finding in the primary care community; the protocol has been adapted to investigate this possibility. Similarly, the potential of SARS-CoV-2 infection and the COVID-19 clinical syndrome to impact respiratory symptoms in primary care patients will also be explored.

To maximize success of the CAPTURE adoption, education and implementation in this study and in future work, Aim 2 is introduced to assess practice experience, need and preference that can inform clinical COPD case finding and education in primary care settings:

Aim 2 – Explore clinical practice implementation approaches to and acceptance of CAPTURE case finding for clinically significant COPD in a range of primary care practices.

The *overall objective* of this aim is to qualitatively explore primary care clinical practice acceptance of COPD case finding implementation and define education and feasibility strategies to enhance adoption in primary care practice. This assessment includes understanding clinician and clinical staff COPD practice and perceptions in addition to the feasibility of case finding integration into existent clinical work patterns. To attain this objective, we address one *working hypothesis* – a COPD case finding methodology using a validated one-page, five-item questionnaire with selective PEF measurement (CAPTURE) can be incorporated into the clinical practice patterns, clinical workflow, communication and practice-based quality improvement paradigms in a variety of primary care clinical settings. The *rationale* for this objective reflects the importance of

establishing if an innovative approach to COPD case finding (CAPTURE) is considered a pragmatic tool with potential utility for primary care clinicians within real-world clinical practice settings. With the completion of this aim we anticipate confirming that future validated approaches to COPD case finding can be adopted in a broad variety of clinical care settings thereby providing further impetus for the rigorous evaluation of a) case finding guided patient outcomes as part of routine primary care clinical practice; b) case finding use in a range of primary care health professional COPD-related education approaches, clinical quality improvement models and diagnostic guidelines; and c) the capacity of clinical case finding with informed follow-up to enhance future COPD clinical care therapeutic paradigms used in primary care practice.

2.2 BACKGROUND

Aims 1 and 3.

COPD remains a major cause of morbidity and mortality. COPD results in substantial morbidity and mortality worldwide.(2-4) Globally, the prevalence of COPD and years lived with disability increased from 1990 to 2013.(5) This is particularly evident in older individuals.(6) These well-designed population based studies confirm the growing impact of COPD.

COPD is frequently undiagnosed. We recently documented that only 28% of participants with chronic airway obstruction **(CAO)** had physician diagnosed disease.(7) Importantly, an FEV_1 <50% predicted was noted in 10% of those with undiagnosed CAO; this is similar to other cohorts or population based surveys.(8-11) There is consistency in these well-conducted studies that confirm most COPD patients are undiagnosed.

Spirometry is underutilized. The U.S. Preventive Services Task Force **(USPSTF)** recently recommended against the use of spirometry for routine, general population or practice-based screening in asymptomatic individuals.(12) An editorial by the PI of this application highlighted the limitations of this conclusion.(13) Within primary care spirometry is often viewed as time consuming and difficult to implement and interpret.(14) As such, it is not routinely used.(15-19) Even the availability of less expensive and easily used spirometers(20) has not resulted in increased utilization.(21, 22)

Undiagnosed COPD is associated with a negative clinical impact. In a robust, population based study we confirmed that undiagnosed patients experienced impaired health status and a higher risk for all-cause mortality compared to those without CAO; this was particularly evident with more severe CAO.(7) Others have confirmed increased mortality,(23) health status impairment,(24) exacerbation-like respiratory events,(11) and increased health care costs.(25, 26) As such, there are consistent data suggesting that undiagnosed COPD patients experience negative clinical events and impaired health status.

Therapeutic interventions improve COPD clinical outcomes. Well designed, randomized controlled trials confirm that COPD therapy is effective, particularly in patients with an FEV_1 < 60% predicted who are symptomatic or at risk for ECOPD.(27, 28) Despite limited data, some have suggested that earlier detection of patients with previously undiagnosed, yet clinically significant COPD, in primary care settings could improve short- and long-term patient outcomes and may be cost-effective. (29, 30)

COPD case finding approaches to date have generally been methodologically limited. Several COPD case finding tools have been created based on existing epidemiologic literature or expert opinion.(31, 32) This includes tools created by investigators in this study.(33, 34) In general, current approaches were designed to identify COPD patients without reference to disease severity or ECOPD risk, resulting in the identification of a high proportion of patients with mild or minimally symptomatic disease.(21, 33-39) Several studies have tested the accuracy of handheld flow meters for case identification with varying

sensitivity and specificity.(40) Although informative in terms of CAO, PEF meters have been unable to systematically identify patients at risk of ECOPD. We tested a three-staged approach (risk-factor questionnaire, PEF, and spirometry) for identifying moderate to severe COPD (FEV_1<60% predicted) in a convenience sample of the general population.(41) This study was limited by the nature of the population screened and the screening questionnaire used but supported the concept that PEF can facilitate COPD case finding.

A systematic analysis of existing databases provides insight into the best variables for COPD Case Identification. To identify potential items that could be useful in the identification of undiagnosed COPD we interrogated three robust datasets of populations in which the investigators on this application had major roles [COPD Foundation Peak Flow Study Cohort (n=5761); Burden of Obstructive Lung Disease Kentucky site (n=508); and COPDGene® (n=10,214)].(42) We utilized the machine learning statistical method of random forests to identify and validate variables most important in identifying patients with clinically significant COPD. COPD case finding candidate content included items reflecting exposure, personal and family history, respiratory symptoms, recent health history, activity limitation and demographics.

A comprehensive, qualitative study identified key constructs for identifying recently diagnosed patients with clinically significant COPD. We completed a two phase study that included focus groups followed by cognitive interviews to refine the key constructs for identifying patients with clinically significant COPD.(43) Fifty participants were recruited including those with mild airflow obstruction, diagnosed within the previous six months and without previous ECOPD; those diagnosed within the previous six months and with a history of at least one ECOPD within the prior year; those with 2-3 risk factors for COPD but without CAO; and those with $\geq$ 4 risk factors for COPD but without CAO. Using a content analysis approach, key themes and constructs were identified and integrated with the content of the previous literature review and data mining. We identified 44 candidate items that resonated with patients and provided important insights into a case finding instrument.

A five-item questionnaire exhibits excellent operating characteristics to identify clinically significant COPD patients. We completed a prospective, multi-site, case-control study of four groups: cases with clinically significant COPD – COPD with > 1 ECOPD in the previous year (n=97) and COPD with no ECOPD but an FEV_1 < 60% predicted (n=89); controls – no known COPD (n=87) and COPD with an FEV_1 > 60% predicted and no ECOPD in the previous year (n=74). Using random forest analyses the 44 candidate items were reduced to 34-item, 21-item, 8-item and two different five-item sets. Through-out the item reduction process, the item sets maintained good performance, consistently misclassifying fewer than 27% of cases and controls, and with sensitivity greater than 80% and specificity greater than 70%. A five-item questionnaire exhibited good operating characteristics for separating COPD cases from controls. These characteristics were even better when separating COPD from controls without COPD.

Selective PEF measurement enhances the operating characteristics of a COPD case finding strategy. In the above case control study PEF was measured using a mechanical PEF meter with disposable mouthpieces. To optimize sensitivity and specificity, the following cut-off scores were selected, based on our data, for identifying cases of clinically significant COPD using PEF alone: males: <350 L/min; females: <250 L/min. The best method for predicting cases was a combination of the questionnaire and PEF **(CAPTURE)**, where PEF is used only for mid-range scores. Under this scoring scenario, patients with scores of 0 or 1 are not considered at risk of clinically significant COPD; they would not require further evaluation. Those with a score of 5 or 6 are considered to be at high risk of clinically significant COPD and should be referred directly for further evaluation, including clinical spirometry. Patients scoring in the middle range (2 to 4) would undergo PEF testing, applying the 350/250 interpretation thresholds. In our sample, 52% of the participants required PEF to determine if spirometry was indicated. The other

48% needed only the five-item questionnaire. This approach provided 90% sensitivity, 93% specificity and an overall error rate of 9%.

CAPTURE exhibits similar operating characteristics in a Spanish speaking population. To broaden our target population, the five-item questionnaire was methodically translated to Spanish using previously validated, rigorous methods(44) to yield an instrument that is equivalent to the English questionnaire and linguistically and culturally applicable to persons of diverse Spanish-speaking backgrounds residing in the US. In a subset of Spanish speaking participants CAPTURE exhibited excellent sensitivity (88%), specificity (92%) and overall error rate (10%) for identifying patients with clinically significant COPD.

Aim 2.

Consistent with national criteria for preventive and chronic disease care quality, feasibility science is designed to assist clinical and health education evaluators plan for assessing and evaluating specific implementation factors essential to the success of new diagnostic, therapeutic and programmatic options in real-world clinical practice. This aim's analysis of primary care clinical practice COPD case finding feasibility includes an initial evaluation of existing COPD diagnostic and case finding processes within the practices, assessment of practices' capacity to change from existing respiratory symptom assessment strategies and an understanding of practice-specific learning preferences associated with new diagnostics in chronic disease diagnosis and management. The aim addresses through the RE-AIM feasibility approach how a new tool might a) identify target populations (Reach); b) appraise optimal targeted respiratory history and symptoms consistent with clinically significant COPD (Effectiveness or Impact); c) integrate into practice workflow (Adoption); d) deliver changes and improvements to COPD care within the scope of real-world clinical practice (Implementation); and e) persist in use and quality over time (Maintenance) (45-53).

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Potential risks associated with Aims 1 and 3 of this study are outlined below.

Spirometry: Participants may become short of breath. Syncope, light-headedness and fainting may develop during this test. These are uncommon.

Albuterol: Tremulousness, feeling of a strong, rapid heartbeat, and palpitations can occur with inhaled albuterol. A targeted safety questionnaire will be administered to all participants prior to albuterol to exclude those with a previous adverse event with the medication. Note that albuterol is only administered to those with abnormal spirometry on the baseline spirometry assessment (defined as $FEV_1/FVC < 0.70$ or $FEV_1 < 80\%$ predicted).

Peak Expiratory Flow: Participants may become short of breath. Syncope, light-headedness and fainting may develop during this test. These are uncommon.

Other non-physical risks of the study include those from economic loss from participation in the study; this will be minimized by scheduling tests and evaluations in a timely manner in the fewest number of visits possible. Patient and physician participants will be provided a modest fee to cover their time to participate in the study.

We anticipate few adverse events due to the non-invasive nature of the study procedures and the rarity of such events encountered during the initial visits and longitudinal follow-up. Medical care will be

available at each Clinical Center to treat participants who develop adverse events during in-person study visits.

Potential risks associated with Aim 2 of this study include:

No more than minimal risk exists for participants within aim 2.

Confidentiality of information and identification are the risks associated with this project. Based on previous research and the protocols that have been developed, we believe that the likelihood of these risks to the participants would be minimal, i.e. "rare".

Potential risks associated with the study (all Aims) include:

Loss of confidentiality of study data: This is unlikely since data collected will be stored in locked file cabinets in locked rooms at the Clinical Centers. In addition, only participant IDs are used to identify participants in the secure server at the Data Coordinating Center.

Poor quality data: If the data collected are of poor quality such that it is not useable to achieve study aims, participants will have unnecessarily been exposed to other risks in the study.

2.3.2 KNOWN POTENTIAL BENEFITS

For Aims 1 and 3 of this study, participants could receive direct benefit as a result of their participation in this research. Current state-of-the-art COPD education is offered to all clinicians at participating PBRN sites (see aim 3 protocol) that could result in improved care for their COPD patients. At the conclusion of the study, both patients and their care providers will have received the results of the CAPTURE screening tool and research spirometry that could result in further diagnostic testing leading to a diagnosis of COPD or other respiratory disorder. Some participants, however, will not have respiratory disease and therefore may not benefit. For Aims 1, 2 and 3, physician participants may benefit in learning how better to identify COPD participants in clinic.

Known potential benefits for each participating clinical staff include critical review their clinical respiratory practice. In general, aim 2 offers the ability to assess and address CAPTURE-specific primary care practice feasibility issues which could augment or hamper clinical communication or implementation of COPD case-finding in real-world primary care clinical practice.

Potential benefits to society include improved understanding of how best to identify individuals with COPD in the primary care setting. This could ultimately lead to better treatments and lower morbidity and mortality for patients with COPD.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The demonstrated and potential future benefits to improved understanding of COPD case finding outweigh the minimal risks of the procedures performed.

Increased understanding of how best to diagnose individuals at risk for COPD in the primary care population has the potential to benefit both patients with COPD and society at large. The risk to individuals associated with this study protocol is small and the knowledge to be gained is substantial.

3 OBJECTIVES AND ENDPOINTS

Aims 1 and 3.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Aim 1: Define the sensitivity and specificity of CAPTURE for identifying previously undiagnosed patients with *clinically significant COPD* in a broad range of primary care settings	Sensitivity and specificity of CAPTURE to identify previously undiagnosed patients with clinically significant COPD at baseline.	Standard methodology for COPD diagnosis will be used (1).
Aim 3: Define the impact of CAPTURE information provided to clinicians in identifying and managing patients with respiratory symptoms (*CAPTURE+*) across a broad range of primary care settings.	Proportion of CAPTURE+ participants who meet at least one of the following within 12 months of study baseline (composite endpoint): 1) referral for or completion of clinical spirometry testing, 2) new diagnosis of COPD, 3) newly prescribed respiratory medication (long acting bronchodilator or anti-inflammatory for respiratory condition), or 4) referral to a specialist for respiratory evaluation/treatment.	The composite endpoint is clinically relevant and consistent with published data (45). This will test the impact of CAPTURE on clinician behavior.
Secondary		
Aim 1: Define the sensitivity and specificity of CAPTURE for patients with COPD across a broad range of racial and ethnic subgroups in a range of primary care settings	Sensitivity and specificity of CAPTURE to identify previously undiagnosed patients with COPD across sex, ethnic groups, urban vs rural location, and educational status.	Patient characteristics will be used to assess the robustness of CAPTURE.
Aim 1: Determine positive and negative predictive values (PPV and NPV) in different practice settings.	Positive and negative predictive values (PPV and NPV) in different practice settings.	PPV and NPV will be used to assess the robustness and usefulness of CAPTURE in various settings.
Aim 1: Verify the optimal use (cutoff threshold) of the CAPTURE tool in combination with FEV_1 measurements for identifying undiagnosed COPD.	AUC for various cutpoints of CAPTURE and PEF measurements to determine the best cutpoint for clinically significant COPD screen.	The best discrimination for CAPTURE combined with FEV_1 will indicate the optimal usage of the tool.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Aim 1: Determine patient and site characteristics that, with the CAPTURE assessment, will best identify persons with undiagnosed COPD.	AUC to identify the combination of patient/site characteristics which best discriminates those with clinically significant COPD.	The best discrimination will determine which site and patient characteristics best predicted undiagnosed COPD in combination with the CAPTURE tool.
Aim 1: Determine whether CAPTURE is useful in identifying other definitions of undiagnosed COPD: 1) spirometry-defined COPD, and 2) mild COPD	All primary and secondary endpoints as applied to 1) spirometry-defined COPD and 2) mild COPD	This will determine the robustness of the CAPTURE tool.
Aim 3: Define the impact of CAPTURE clinician education, and patient-level CAPTURE information to clinicians ("CAPTURE education") on selected additional therapeutic interventions in previously undiagnosed patients with *clinically significant COPD.*	Proportion of CAPTURE+ participants who meet the components of the composite endpoint.	Each endpoint is clinically relevant and consistent with published data. (45) This will test the impact of CAPTURE on clinician behavior.
Aim 3: Assess impact of CAPTURE education on clinician interventions specific to smokers.	In participants with clinically significant COPD who are current smokers, the incidence of physician referral to a formal smoking cessation program, prescribed smoking cessation medication, and referral to pulmonary rehabilitation program.	Certain outcomes are specific to only smokers and should be assessed.
Aim 3: Determine the impact of CAPTURE education on patient symptoms, exacerbations, hospitalizations, and mortality.	In participants with clinically significant COPD, change in CAT score, and proportion of patients who experience exacerbations, hospitalizations, or mortality.	This endpoint is important for quality of life, and long-term patient outlook.
Aim 3: Determine the impact of CAPTURE education when COPD is defined spirometrically.	All of the above endpoints for Aim 3, with the patient population defined as those who have COPD defined spirometrically.	This will determine the robustness of the CAPTURE tool

Aim 2.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Explore clinical practice implementation approaches to and acceptance of CAPTURE case finding for clinically significant COPD in a range of primary care practices.	Primary care clinician recommendations that inform CAPTURE RE-AIM strategies at both provider and clinical support levels of primary care practice. Primary clinician recommendations that inform CAPTURE-associated COPD education models for primary care clinicians. Primary care clinician recommendations that inform CAPTURE-associated COPD clinical quality improvement designs across a variety of primary care practice types.	Clinical improvement models that introduce new testing must investigate practice opinion and behavior and incorporate clinician recommendation.
Secondary		
Qualitatively assess primary care clinical staff COPD practice behavior – including COPD screening and diagnostic perceptions, beliefs and knowledge – that will inform strategies to improve CAPTURE RE-AIM (reach, impact, adoption, implementation and maintenance of use) characteristics.	Existing COPD screening and diagnostic and case-finding processes within a variety of primary care practices. Primary care practice beliefs about capacity to change from existing COPD screening and diagnostic assessment strategies. Practice-specific COPD screening and diagnostic continuing education preference.	Awareness of existing clinician knowledge and behavior can influence workflow implementation and overall effectiveness of new clinical tools.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Qualitatively assess primary care patient opinion of CAPTURE COPD case finding that will inform strategies to improve CAPTURE RE-AIM (reach, impact, adoption, implementation and maintenance of use) characteristics.	CAPTURE opinion survey ascertaining participant comprehension of CAPTURE instructions and testing and ease of completion.	Patient satisfaction, understanding and ease of test completion affects staff implementation and workflow decision. Participant opinion survey results will seed CAPTURE implementation planning practice staff focus groups.

4 STUDY DESIGN

4.1 OVERALL DESIGN

A prospective, multicenter study that includes three key aims: 1) cross-sectional validation to define sensitivity and specificity of CAPTURE; 2) *qualitative* research exploration engaging clinical staff at all levels from primary care practices serving US patient populations of differing gender, racial, ethnic, urban/rural and socio-economic blends, and 3) explore the impact of CAPTURE on clinical care and patient outcomes across a broad range of primary care settings in a cluster randomized controlled clinical trial. The CAPTURE tool consists of a 5-item self-administered questionnaire and selected use of peak expiratory flow (PEF) measurement, designed to identify clinically significant Chronic Obstructive Pulmonary Disease (COPD).

For Aim 1, approximately 5,000 patients will be recruited at the time of their regularly-scheduled appointment across 100 participating primary care clinics associated with practice-based research networks (PBRNs). Eligible participants will undergo a baseline visit during which the CAPTURE tool and spirometry will be obtained, as well as PEF and other participant characteristics.

For Aim 2, approximately 150 clinicians from 10 participating primary care practices across 5 US PBRNs will undergo detailed implementation investigation of the CAPTURE case finding model for clinically significant COPD. In addition, 200 primary care patients recruited as part of Aim 1 will complete a 10-minute written CAPTURE opinion survey.

To address Aim 3, participating primary care practices will be randomized in a 1:1 fashion to one of the following interventions:

- Arm 1: Practice clinicians will receive basic COPD education, and patient-level CAPTURE information with CAPTURE interpretation education (CAPTURE+ COPD education). As the second aim addresses the optimal format for delivering practice CAPTURE education this will be incorporated at the sites randomized to this arm (see Enhanced CAPTURE education in Figure 1).
- Arm 2: Practice clinicians will receive basic COPD education only (COPD education).

Basic COPD and CAPTURE specific education will use an interactive, web-based education program which will be provided to all practice personnel, including physicians, nurse practitioners, physician assistants, nurses, medical assistants, clerical staff and administrative staff. Practitioners at sites

randomized to the CAPTURE+COPD education intervention will receive the CAPTURE score from the central study coordinators soon after the baseline assessments have been completed.

Addressing Aims 1 and 3 will include a baseline visit for all participants and for Aim 3 longitudinal follow-up over 12 months for a predefined cohort of participants. Determination of the participants included in the longitudinal follow-up cohorts will be made after the baseline visit.

Baseline Data

Practices and/or study staff will pre-screen patients according to local guidelines to identify potential participants based on the following criteria: no prior COPD diagnoses, between 45 and 80 years old, and speak and read either English or Spanish. The timing of the pre-screening and the method to approach these patients for participation in the study (e.g., at the next outpatient visit, via telephone) will be flexible, depending upon site recruitment preferences. Patients who are eligible based on the pre-screening questions and agree to participate in the study will sign informed consent. After signing the consent, they will complete the CAPTURE questionnaire, PEF testing, spirometry testing, other respiratory questionnaires, and provide past medical history and demographic information. Local/PBRN study coordinators for each of the 6 PBRNs will perform the study procedures and record baseline information into the electronic data capture (EDC) system.

The EDC system will calculate a CAPTURE score for each participant, based on his/her CAPTURE questionnaire answers and PEF measurement. A binary score (positive or negative CAPTURE) will be emailed to the central study coordinator only for participants randomized to CAPTURE+COPD education intervention practices. The coordinator will communicate this information to these practitioners. Practitioners at sites randomized to the COPD education only intervention will be blinded to CAPTURE scores. Practitioners in both intervention arms will be blinded to research spirometry results.

Analyses will include a comparison of CAPTURE scores with data from spirometry testing and participant reported data to determine sensitivity and specificity of the CAPTURE tool. *The hypothesis is that a simple case finding methodology using a five-item questionnaire with selective PEF measurement will identify undiagnosed patients with clinically significant COPD.*

Based on the data collected at baseline, participants will be classified into the following groups for analyses:

Cohort	**Definition**
CAPTURE+	Participants with • CAPTURE score $\geq$ 5, or • CAPTURE score of 2, 3, or 4 with a low PEF, defined as <350 L/min for males and <250 L/min for females
CAPTURE-	Participants with • CAPTURE score < 2 or scores 2-4 with normal PEF (defined as $\geq$350 L/min for males and $\geq$250 L/min for females)
Spirometrically defined COPD	Participants with abnormal spirometry, defined as post-bronchodilator FEV_1/FVC <0.7. If a participant is unable to complete a post-bronchodilator spirometry (refusal, technical error on the part of coordinator, etc.), and the pre-bronchodilator FEV1/FVC is less than 0.65, the participant will be considered to have COPD for the purpose of follow-up in this study.

Clinically significant COPD	Participants with abnormal spirometry, defined as post-bronchodilator FEV_1/FVC <0.7, plus one of the following: 1) FEV_1 < 60% predicted or > 1 exacerbation like event within the past 12 months.
Mild COPD	Participants with abnormal spirometry, defined as post-bronchodilator FEV_1/FVC<0.7 plus both of the following: • FEV_1 ≥ 60% and • No prior history of ECOPD

Exploratory analyses to examine the potential impact of SARS CoV-2 infection on the above operating characteristics of the CAPTURE approach will include information in the pandemic and post pandemic period collected from a simple COVID-19 questionnaire that is based on similar questionnaires from other ongoing NHLBI cohort studies.

Longitudinal Follow-up
A pre-defined subgroup of enrolled participants, who meet any of the below criteria will undergo longitudinal follow-up at 12 months,

1. Participants with a CAPTURE Score ≥ 5 or CAPTURE score of 2, 3, or 4 with a low PEF, defined as <350 L/min for males and <250 L/min for females
2. Participants who have abnormal spirometry results, defined as post-bronchodilator FEV_1/FVC < 0.7 or FEV_1 < 80% predicted at baseline. If a participant is unable to complete a post-bronchodilator spirometry (refusal, technical error on the part of coordinator, etc.), and the pre-bronchodilator FEV1/FVC is less than 0.65, the participant will be considered to have COPD for the purpose of follow-up in this study.
3. A random sample of approximately 5% who do not meet criteria 1 - 2

Participants who meet the criteria for follow-up will be sent notification shortly after enrollment, and receive reminders at 3, 6, and 9 months. Patient-reported data will be collected by COPD Foundation via telephone, secure web-based server, or mail-based methodologies, based on participant preference.

Subject medical data will be collected from the medical record to assess for changes in practice-level care.

The hypothesis for Aim 3 is that sites where COPD and CAPTURE education and patient-level CAPTURE data are provided to clinicians will exhibit improved COPD diagnosis and COPD-related care compared to sites where COPD education is provided to clinicians.

In exploratory analyses to examine the potential impact of SARS CoV-2 infection on the patient symptoms and health care utilization a simple COVID-19 questionnaire, based on other ongoing NHLBI cohort studies, has been introduced.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Aims 1 and 3

The totality of the published data confirms the clinical and economic impact of undiagnosed COPD, continuing under-diagnosis, and incomplete application of spirometric testing in the primary care community. It suggests that there is value in COPD case-finding that targets COPD patients most likely to benefit from available therapies. These points identify a pressing health care problem that requires

an innovative approach to facilitate identifying these individuals. Our preliminary studies enumerated in section 2.2 extend these concepts by demonstrating that:

- Six key domains identify patients with clinically significant COPD.
- Forty-four distinct items resonate with patients and provide important insights for COPD case-finding.
- Five items exhibit excellent sensitivity and specificity in identifying patients with clinically significant COPD.
- PEF provides incremental value in a case-finding strategy.
- The combination of a five-item questionnaire and PEF optimizes a COPD case-finding strategy in English and Spanish speaking patients.

Our proposed study will provide crucial data to address the operating characteristics and clinical translation to our COPD case-finding strategy into the primary care setting. It will also provide an important initial evaluation of the potential clinical impact of the systematic identification of previously undiagnosed COPD patients.

The impact of SARS-CoV-2 infection and its clinical illness, COVID-19, on COPD Case Finding and respiratory symptoms in primary care is unknown. In exploratory analyses a simple COVID-19 patient questionnaires and additional data elements from medical record review, based on other ongoing NHLBI cohort studies, have been introduced.

Aim 2

The rationale for this aim reflects the importance of establishing if an innovative approach to COPD case finding is considered a pragmatic tool with potential utility for primary care clinicians within real-world clinical practice settings. With the completion of this aim we anticipate confirming that future validated approaches to COPD case finding can be adopted in a broad variety of clinical care settings thereby providing further impetus for the rigorous evaluation of a) case finding guided patient outcomes as part of routine primary care clinical practice; b) case finding use in a range of primary care health professional COPD-related education approaches, clinical quality improvement models and diagnostic guidelines; and c) the capacity of clinical case finding and informed follow-up to enhance future COPD clinical care therapeutic paradigms used in primary care practice.

Consistent with Institute of Medicine criteria and US health quality standards for preventive and chronic disease care, the feasibility science qualitative research framework is designed to assist clinical and health education evaluators prepare, assess and evaluate specific implementation factors essential to the success of new diagnostic, therapeutic, educational and programmatic options in real-world clinical practice. This aim's analysis of primary care clinical practice COPD case finding feasibility considerations for CAPTURE includes an initial evaluation of existing COPD diagnostic and case finding processes within the practices, assessment of practices' capacity to change from existing respiratory symptom assessment strategies and an understanding of practice-specific learning preferences associated with new diagnostics and chronic disease diagnosis and management. Patient perceptions of the CAPTURE case-finding process are also obtained to provide a holistic perspective of the clinical feasibility of CAPTURE implementation in primary care practice. Borrowing from the RE-AIM implementation science approach, this aim explores how real-word primary care practices might potentially use CAPTURE to: a) identify target populations (Reach); b) refine current practice appraisal of patient respiratory history,

symptoms and diagnostics used to identify clinically significant COPD (Effectiveness/Impact); c) change or integrate COPD case finding into practice workflow (Adoption); d) alter practice communication, education and/or care quality improvement planning for COPD diagnosis and management (Implementation); and e) use COPD case finding consistently over time (Maintenance).

Ten primary care practices will undergo detailed implementation investigation of the CAPTURE case finding model designed to identify patients with COPD most likely to benefit from available therapeutic options. CAPTURE, a one-page questionnaire with selective PEF measurement, is presented to the clinicians of ten practices not participating in aims 1 and 3 as a prospective COPD case finding option awaiting validation. By representing CAPTURE as a model—and not introducing it into actual practice—aim 2 gains recommendation from primary care clinical practice experience with sufficient feasibility generality to circumvent interdependence between the operating characteristic exploration (aim 1) and qualitative feasibility understanding (aim 2) components of our study. The aim 2 results, that include the pooled CAPTURE clinical communication, education and implementation recommendations from real-world primary care practice, are analyzed and applied in concert with local and national research team expertise to enhance the potential impact of CAPTURE's introduction into clinical care in aim 3. Aim 2 results also provide previously unexplored qualitative information necessary for future long-term patient outcome studies of COPD case finding approaches in primary care.

The impact of SARS-CoV-2 infection and its clinical illness, COVID-19, on COPD Case Finding application in primary care is unknown. In a systematic fashion these concepts will be explored during the previously planned follow-up interviews and focus groups with clinical practice and regional PBRN personnel.

4.3 END OF STUDY DEFINITION

Participants that do not meet the criteria for, or are not selected for, longitudinal follow-up will be considered to have completed the study after completion of the baseline visit.

Participants included in the longitudinal follow-up phase will be considered to have completed the study after completion of the Month 12 Assessment as shown in the Schedule of Activities (SoA), Section 1.3.

Clinician participants in aim 2 will have completed the study after participation on their second focus group between months 14 and 16 as shown in the Figure 2, Structure of Aim 2.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Inclusion criteria for Aims 1 and 3
In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Male or female, aged 45 – 80 years

Inclusion criteria for Aim 2

Two Aim 2 practices are selected by each of their 5 affiliated PBRNs based upon willingness to participate and variability of primary care practice type within the PBRN. Differences in practice size, staffing, ownership, prior quality improvement engagement, geography, patient population socioeconomic status (SES) or languages spoken are among the among the selection criteria the PBRNs will utilize to choose.

Clinician participants (10 practices with up to 15 clinicians per practice):
1. Provision of signed and dated informed consent form.
2. Stated willingness to comply with availability and all study procedures for the duration of aim 2 by the 10 practices (through PBRN recruitment) and their up to 15 clinicians within (through informed consent).

Patient participants [200 patients (approximately 40 from each PBRN)] for CAPTURE survey:
1. Provision of signed and dated informed consent form.
2. Stated willingness to comply with all study procedures and availability for the duration of the study.
3. Male or female, aged 45 – 80 years.

5.2 EXCLUSION CRITERIA

Exclusion criteria for Aims 1 and 3
An individual who meets any of the following criteria will be excluded from participation in this study:

1. Previous clinician provided diagnosis of COPD
2. Treated respiratory infection (with antibiotics and/or systemic steroids) in the past 30 days of baseline
3. Participants unable to perform spirometry due to any of the following conditions within the past 30 days of baseline
    a) Chest surgery
    b) Abdominal surgery
    c) Eye surgery
    d) Heart attack
    e) Stroke

Exclusion criteria for Aim 2

1. Clinician participants: current employment at practices participating in aims 1 and/or 3
2. Clinician participants: from practices providing fewer than 2 clinician participants
3. Patient participants: meeting the exclusion criteria for aims 1 and 3 (above)

5.3 SCREEN FAILURES

PBRN coordinators, in conjunction with clinical study site personnel, will pre-screen individuals who are unlikely to be able to complete research spirometry. These individuals will be considered *pre-screen failures*.

Participants who are consented to participate but have a prior clinician diagnosis of COPD will be considered *screen failures*.

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment and retention strategies for Aims 1 and 3

Approximately 5,000 participants will be recruited from 100 primary care clinics affiliated with six PBRNs. Each PBRN has centrally-based research coordinators with a history of success working in PBRN practices, documented expertise in previous large diagnostic or therapeutic trials, and personnel experienced in recruitment and data collection.

IRB approval will be obtained at each PBRN for approval for patient contact, informed consent and participation in this study.

All patients who meet all inclusion and no exclusion criteria at the participating PBRN clinical site will be eligible for participation. Research coordinators will work with participating practices to identify and approach potential participants. Recruitment strategies may vary depending on the practice.

Enrollment of participants will depend on the gender, ethnic and racial makeup of those that are being recruited from the practices included in this trial. No exclusion criteria apply specifically to women or to minorities. The Data Coordinating Center (DCC) will track enrollment of participants throughout the course of this study. If women and minorities are under-represented in the initial phase of recruitment, a commitment exists to develop recruitment strategies that target these populations so the final study group is a well-balanced representation of the studied population.

Recruitment and retention strategies for Aim 2

Clinician participants: Approximately 150 clinic participants are recruited by: 1) introductory telephone contact with the practice leadership by PBRN research coordinators and the aim 2 research team; 2) follow up letter, time commitment infographic and informed consent forms sent to interested practices outlining aim 2 clinician participant activities and responsibilities; and 3) in-person aim 2 study explanation to clinician participants at the committed practices during the introductory baseline study site visit.

Clinician participant recruitment draws from both prescribing (or “provider”) staff and non-prescribing (or “clinical support”) staff. The aim 2 research team will attempt to obtain an even mix of both clinician staff types from each practice. Retention incentive of clinician participants over 2 years includes provision of on-line COPD education to all clinician participants and monetary incentive to practices as determined by each individual PBRN.

Patient participants: 200 participants (40 from each PBRN) are recruited as a sub-set of the aim 1. Each of the 200 patient participants in aim 2 are asked to complete a one-time 10-minute written opinion survey. Their aim 2 participation is concluded at the end of the opinion survey completion.

The aim 2 research team and DCC will track enrollment and retention of all aim 2 participants throughout the course of the 2-year aim 2 study.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

The study intervention is applicable to Aims 2 and 3 and consists of healthcare provider education modules.

The practitioners at the 10 sites selected for Aim 2 will receive module 1, Basic COPD education, and may elect to take modules 3-5 for supplemental information on COPD.

For Aim 3, half of the practices will receive Basic COPD education (module 1) and half will receive Basic COPD Education and CAPTURE Education (modules 1 and 2). Practitioners at practices randomized to COPD only education must take module 1 and may elect to take modules 3-5; however, they will not take module 2. Practitioners at practices randomized to COPD+CAPTURE education must take modules 1 and 2, and may elect to take modules 3-5.

1 - Basic COPD Education will be provided in order for providers to optimally manage patients with COPD. The education will incorporate evidence-based recommendations using the 2018 update of the Global Obstructive Lung Disease Strategy(45). For practices enrolled in the pandemic and post pandemic periods, additional information will be provided regarding COPD management in the pandemic era as well as information on steps to maintain patient and staff safety in the clinical sites where CAPTURE patients will be enrolled and assessed.

A 40-minute overview will be presented in the most expeditious manner at each practice site, for example by webinar for all practice personnel over the lunch hour, or audiovisual presentation available on a dedicated CAPTURE web site. The PBRNs have indicated that this module should be no longer than 40 minutes. Topics will include: CAPTURE study description and rationale, importance of COPD in the region of the local practices, COPD definition and diagnosis, patient goals, and management approach. Attendance at this mandatory training will be documented and continuing education credits will be provided for physicians and nurse practitioners by National Jewish Health, an accredited CME provider.

2 - **CAPTURE education**. An online audiovisual module will be developed to explain CAPTURE interpretation and use in patient evaluation and diagnosis of COPD. This module will only be available to practices randomized to receive the results of CAPTURE for clinical use.

With the information provided in Aim 2 about practice preferences for education, the CAPTURE education module will be revised and made available to practices enrolled in Aim 1 after the completion of Aim 2.

3 - Online advanced COPD education will be available for all practices and continuing education credits will be provided to enhance practitioner participation. Practitioner attendance at each online audiovisual module will be collected including the amount of time spent on each education module, completion of each module with a post-test and evaluation, and CME will be provided. Education will be case-based and will include role playing where appropriate. Seven basic modules of 20 minutes or less will be available both to practices randomized to receive CAPTURE results for clinician use and to control practices that will not receive CAPTURE results and will cover:

1. Diagnosis of COPD: How to diagnose COPD in primary care including medical history, physical exam and role of spirometry, severity categorization
2. Spirometry overview: Basic clinical interpretation
3. Advanced spirometry: Test performance, evaluating quality, advanced case-based interpretation
4. Management overview: Patient goals, smoking cessation, vaccination, patient education, shared decision-making

5. Pharmacotherapy: Inhaled bronchodilators, inhaled corticosteroids
6. Other therapies: Oxygen, pulmonary rehabilitation, surgical approaches
7. Inhalation devices: Patient education

4 – On-site COPD education. Additional funds will be sought to provide on-site COPD education. We have experience in successfully providing half-day on-site education to primary care practices to enhance their management of COPD.

5 – Social media and case conferences. We will use social media (Facebook and Twitter) to provide ongoing education about COPD. Facebook and Twitter posts will provide tips on managing COPD. Online conferences will be scheduled to discuss cases submitted by primary care providers.

6.2 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

For Aims 1 and 3, this study will use randomization and blinding as two of the cardinal principles of clinical trials to minimize bias.

Randomization. Practices will be randomized into one of the two interventions, COPD education or COPD education + CAPTURE education, in a 1:1 manner, stratified by PBRN. Randomization will occur at the time of site activation and each site will be assigned a unique randomization number. The DCC will prepare the randomization schedule, using computer-generated block randomization with the block size(s) known only by the DCC. A secure web-based application will be built that will be used by the central study coordinators to enter site information (e.g., site ID, stratification factor) and to obtain the randomization number. The information can be printed and sent and/or emailed directly to the study coordinator.

Blinding. This is a single-blind study with the participants blinded to whether their practitioners have received CAPTURE education and patient-level CAPTURE results. Practitioners at sites that are randomized to the control arm (COPD education alone) will be blinded to the CAPTURE questionnaire and PEF results. All practitioners and participants will be blinded to the baseline COPD status of the participants (i.e., blinded to spirometry results), except for safety reasons. In this situation, participants and their clinician will be notified if a participant's post-bronchodilator FEV_1 is less than 30% predicted. For all other participants, they and their practitioners will be blinded to research spirometry results. The coordinator should make every effort to conceal the spirometry results from the participants in these latter cases. Study coordinators should also make every effort to conceal the administration of a post-bronchodilator spirometry test from the practice staff so as not to unblind the physicians to abnormal spirometry.

6.3 STUDY INTERVENTION COMPLIANCE

In practices randomized to share the CAPTURE results with the clinician, the goal is to share results with the clinician at the time of the CAPTURE study visit. Providing results at the time of the clinical visit will allow the clinician to act on the CAPTURE results as soon as possible when the participant is in front of the clinician. Based on the workflow at each of the practices, this may not always be possible.

Sharing of the CAPTURE results with the participant's primary care clinician will be tracked by the study coordinator enrolling patients at sites randomized to receive CAPTURE results. The sharing of CAPTURE

results will be recorded on the study eCRF form. The eCRF will collect the timing of when the results were provided to the practitioner - whether the results were provided to the clinician at the time of the enrollment visit prior to the clinician visit with the patient, or were provided at another time.

If results were not shared at the time of the CAPTURE study visit, then the date of sending the CAPTURE results will be recorded on the appropriate eCRF by filling in the date (day/month/year) the exact copy of the CAPTURE Toolwere sent to the clinician through a HIPPA-compliant method and placed in the medical record. The goal is to communicate the results to the clinician. The DCC will monitor review all participants' eCRFs to assure that all those enrolled from practices randomized to CAPTURE results have been shared with clinicians..

6.4 CONCOMITANT THERAPY

Practitioners will treat participants using their own clinical judgment. No medications are prohibited. This is not an interventional therapeutic trial.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

In this cluster randomized controlled trial (Aim 3), where practices are the recipients of the intervention and where the interventions are based upon education and access to CAPTURE and PEF results, it is not anticipated that study intervention will be discontinued at the practice level. However, one of the CO-PIs will review safety data, especially SAEs related to baseline spirometry and PEF procedures, to ensure there are no untoward effects of the study on participants.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in Aims 1 and 3 of the study at any time upon request.

Clinician participants in Aim 2 are free to withdraw from participation in the study at any time upon request. If a clinician is no longer working at the participating practice then their involvement in Aim 2 activities will end and no further attempt will be made to include them in the remaining questionnaires or focus groups.

7.3 LOST TO FOLLOW-UP

If a participant selected for longitudinal follow up does not respond to the 12-month questionnaires, coordinators will attempt to contact participants first by the participant's preferred method of communication, either phone or email. At least three attempts will be made. If no response is obtained, the participant's alternate contact method will be attempted three times. Phone calls will be made at different times of the day. If there is no response, a letter will be sent to the participant. If the participant cannot be reached, the alternate contact will be called and/or emailed. If no response is

received, a letter will be sent to the alternate contact. If after all of these methods are employed and no contact with the participant results, the participant will be considered lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 BASELINE ASSESSMENTS AND DATA COLLECTION

Efficacy data will be collected by patient-reported outcomes and medical record review.

For Aim 1, CAPTURE, PEF results, acute respiratory event history and spirometry will be considered efficacy assessments. They are collected at the baseline visit.

CAPTURE. Participants will complete the 5-item *self-administered* questionnaire and measurement of Peak Expiratory Flow (PEF).

Peak Expiratory Flow (PEF). PEF using the Vitalograph® AsmaPlan® mechanical PEF meter with SafeTway® disposable mouthpieces (Vitalograph LTD, UK) will be measured for all participants. Ideally, PEF should be prior to the participant's physician appointment. The participant will perform three PEF tests. All three measurements will be recorded.

Spirometry. Before spirometry is performed, participants will be asked if they have taken a medicine which they breathed into their lungs from any puffer or inhaler within the past two hours. If participant answers yes, then spirometry will be performed but considered a post-bronchodilator spirometry test. No further spirometry will be needed. If participant answers no, then pre-bronchodilator spirometry will be performed for measurement of forced vital capacity (FVC), forced expiratory volume in one-second (FEV_1), and calculation of FEV_1/FVC (using EasyOne® Spirometer, ndd Medical Technologies Inc., Andover, MA). Testing will be performed in accordance with established American Thoracic Society/European Thoracic Society (ATS/ERS) standards. Local guidelines to minimize risk of SARS-CoV-2 infection will be adhered to, including a minimum of appropriate PPE and infection control techniques.

A Spirometry post-bronchodilator will only be performed if pre-bronchodilator spirometry FEV_1/FVC is less than 0.70 or FEV_1 is less than 80% predicted. Post-bronchodilator spirometry will be performed within 15 to 20 minutes after inhalation of 2 puffs of albuterol 180 mcg HFA using an AeroChamber Plus* Flow-Vu® spacer with one minute between the first and the second inhalation. A separate AeroChamber or comparable spacer, using a one way valve to minimize infectious risk, will be provided for each participant's testing. A standing order for albuterol administration may be used if necessary.

Spirometry is a valid, reproducible means of documenting the presence and severity of airflow limitation. When properly performed with maximum effort and attention to the details of calibration of the instrument, spirometry maneuvers are among the most reproducible of biomedical measures. In the setting of a highly trained, experienced therapist, a coefficient of variation of 2-3% is not unusual. Spirometry will be performed in a standardized manner in accordance with the ATS guidelines, as described in the manual of procedures (MOP). Spirometry is the timed-based measurement of the amount of air that can be forcefully exhaled from the lungs after a full inspiration. In the forced expiratory vital capacity maneuver, a person inhales as big a breath as possible and then blows it out as fast and as long as possible until no more air can leave the lungs. The volume of air leaving the lungs is

recorded continuously throughout the maneuver in order to allow calculation of important measures of lung function.

NHANES prediction equations, which are programmed into the Easy On PC spirometers, will be used to calculate the predicted lung function levels. These require the input of age, height, and race/ethnicity (White, Black, Hispanic). For people of mixed or unknown race the White prediction equations will be used.

PBRN Research Coordinators will be trained and certified in the performance of spirometry testing. Spirometry will be sent for central review for quality control assurance.

Adjudication of the Presence of Obstruction on Post-Bronchodilator Spirometry

The presence of obstruction is determined by the presence of an FEV_1/FVC ratio less than 0.70 after the administration of a bronchodilator. A bronchodilator will be administered to study subjects whose baseline FEV_1/FVC is less than 0.70 or whose FEV_1 is less than 80% of the predicted value.

If a subject is unable to complete a post-bronchodilator spirometry (refusal, technical error on the part of coordinator, etc.), and the pre-bronchodilator FEV_1/FVC is less than 0.65, the patient will be considered to have COPD for the purpose of follow-up in this study.

Height and weight
Height and weight will be recorded in order to determine appropriate prediction equations for spirometry and possible effect of obesity on spirometry. Height will be recorded and weight will be measured prior to spirometry testing.

Demographic Data Collection
Demographic data including date of birth, gender, ethnicity, race, educational level achieved, daily work schedule, living arrangement and health insurance will be entered into the EDC system.

Contact information including address, phone numbers and email address will be obtained. Alternate contact information will be obtained for two other people, family members not living with the participant or close contacts, who may be knowledgeable about the participant in the event that the participant cannot be contacted for subsequent longitudinal follow-up. Alternate contact information will include name, address, phone numbers and email addresses. All contact information will be stored securely at the clinical site or in a database separate from that developed for the clinical data.

Medical History
Previous medical diagnoses will include comorbidities such as cardiovascular, respiratory and malignant disorders. Influenza vaccination history will also be recorded. This questionnaire will be completed under supervision of the coordinator.

Concomitant Medication Review
Respiratory medications will be recorded at baseline for all participants. This questionnaire will be completed under supervision of the coordinator.

CAPTURE Additional Items Questionnaire
Participants will complete the 13-item *self-administered* questionnaire.

COPD Assessment Test (CAT)
Participants will complete the 8-item *self-administered* questionnaire.

Respiratory symptoms, smoke exposure and exacerbation like events
History of respiratory symptoms and exacerbation like events over the past year as well as smoke exposure (including e-cigarette or equivalent) will be recorded. This questionnaire will be completed under supervision of the coordinator.

Whenever possible, informed consent, eligibility review, CAPTURE Questionnaire and PEF will be performed prior to the participant's clinic appointment, so that CAPTURE results may be provided to the physician at the time of his/her appointment if the patient is cared for in a clinical center randomized to CAPTURE+ education.

COVID-19 Additional Items Questionnaire
Participants will complete the 18-item *self-administered* questionnaire.

Adverse events
Adverse events related to study procedures will be recorded by the coordinator.

8.2 LONGITUDINAL FOLLOW-UP ASSESSMENTS AND DATA COLLECTION

For Aim 3, the follow-up efficacy assessments are collected from the time of baseline to 12 months in selected cohorts (as described in section 4.1). Medical record abstractions completed by PBRN coordinators and participant questionnaires administered by study team members from the COPD Foundation are used.

Data collected from medical record include:

All participants undergoing 12-month follow-up as described in section 4.1	Current Smokers Only
Clinical spirometry ordered or administered	Smoking cessation counseling
Referral to specialist for respiratory evaluation/treatment	New prescription for smoking cessation medication
New recorded clinical diagnosis of COPD	Formal smoking cessation program referral/completion
New prescription for respiratory medication (long acting bronchodilator, inhaled steroids, oral anti-inflammatory)	
Exacerbation like event assessment (hospital, ED, minute clinic, antibiotic/steroid prescription/administration)	

Vaccination status	
Formal pulmonary rehabilitation program referral/completion*	
Data related to COVID-19 confirmed and suspected cases	

*only collected in relevant participants

Data from clinical visits to be collected at follow-up by telephone, secure web-based server, or mail-based methodologies directly from participants and administered by COPD Foundation study personnel include:

All participants undergoing 12-month follow-up as described in section 4.1	Current Smokers Only
Spirometry	Smoking cessation counseling
New diagnosis of COPD	Smoking cessation medications (including OTC)
Referral to pulmonologist or other respiratory specialist	
Exacerbation like event assessment	
New prescription for respiratory medication (long acting bronchodilator, inhaled steroids, oral anti-inflammatory)	
CAT score	
Attendance of pulmonary rehabilitation*	
COVID-19 related questions	

*only collected in relevant participants

8.3 AIM 2 ASSESSMENTS AND DATA COLLECTION

Practice study introduction and participation confirmation: After PBRN practice selection, the CAPTURE study Aim 2 lead together with the local PBRN Aim 2 coordinator conduct a 15-minute participation confirmation and introduction phone call with the key PBRN contact at each of the two selected practices. The study specifics and timeline are reviewed. After practice participation is confirmed, the on-site practice assessment date is scheduled. Informed consent forms for clinical staff are mailed to each confirmed practice. To reduce practice burden, completed clinical staff informed consent forms (up to 15 clinical staff per practice) can be returned by mail to the University of Michigan School of Public Health office, addressed to Dr. Randall Brown, or saved for completion and picked up at the on-site practice assessment site visit. Following the confirmation phone call, the PBRN Aim 2 coordinator completes a short (15 minute) qualitative questionnaire detailing the selected and confirmed practice demographics and PBRN parameter of practice choice for each of the two practices. The completed PBRN Practice Selection Questionnaire is returned to the Aim 2 data team and stored securely.

On-site Practice Assessment (OSPA): The OSPA is an in-person on-site practice workflow assessment. It includes 2 practice clinicians per practice choice, the PBRN Aim 2 coordinator (if available), the CAPTURE study Aim 2 lead and the CAPTURE Aim 2 research specialist (if the PBRN Aim 2 coordinator is not present). The objective of the visit is to detail specifics of practice workflow, practice physical characteristics, staff roles, clinical information gathering patterns for respiratory patients, electronic health record communication, continuing education structure, and quality improvement structure. The assessment takes place in three parts; the pre-observation practice overview (conducted with the 2 practice clinicians – 60 minutes), the ½ day practice workflow observation (observation by one member of the Aim 2 research team of common and testing areas used for the respiratory patient). There is no patient engagement and no collection of patient-specific identification or health information), and the post-observation practice summary (conducted with the same 2 practice clinicians – 30 minutes).

The 3 OSPA assessment tools are:

i) The Pre-workflow Observation Practice Assessment Review Questionnaire
ii) Respiratory Workflow Assessment Review
iii) The Post-workflow Observation Practice Assessment Review Questionnaire

Also at the OSPA, informed consent is obtained from all remaining participating staff (up to 15 clinical staff per practice) by the CAPTURE Aim 2 team and returned to the Aim 2 data team for secure storage.

Clinical Staff Questionnaires (Baseline/6/12 months). Written or on-line questionnaires are provided to participating and consented staff personnel at two practice levels -- Non-Prescribing clinical (also known as “support”) staff and Prescribing (PR) clinical (also known as “provider”) staff.

Non-Prescribing (NPR) clinical staff are clinical practice personnel involved in clinical workflow (including registered nurses, licensed practical nurses, medical assistants, medical assistants and receptionists), yet not having the role to make final and official medical diagnostic and management disposition plan decisions for and with patients. Prescribing (PR) clinical staff are prescribing clinical practice personnel involved in clinical workflow (including doctors, nurse practitioners, and physician assistants) who may independently make final medical diagnostic and management disposition plan decisions for and with patients.

Questionnaire items explore clinician demographics, including past education, duration of current employment and currently held clinical position. COPD knowledge, attitudes, beliefs, practice patterns and self-efficacy regarding COPD diagnosis, management, spirometry testing and interpretation, practice workflow and communication in the clinical primary practice care of adult patients with respiratory disease. Additional questions include preferred continuing education method and clinical staff quality improvement modalities for respiratory disease management. Specific examples of past practice chronic disease diagnostic changes and the individual and practice-wide levers of success and challenge associated with those changes are explored.

Each of the 3 (baseline, 6-month and 12-month) questionnaires are completed within 30 minutes. No identifying patient data is collected. Online questionnaires are collected and secured by the CAPTURE DCC and Aim 2 research team. The participants who complete written questionnaires (per their preference) mail completed questionnaires via pre-addressed stamped envelope to the CAPTURE DCC and Aim 2 research team.

Patient Opinion Surveys:

200 patient participants, 40 from each PBRN, are recruited as a sub-sample from Aim 1 practices. Patient participants fulfill all inclusion and exclusion criteria and receive informed consent for survey participation as part of aim 1.

Eligible participants complete a written one-time 5 to 10 minute CAPTURE opinion survey. Patient survey data is collected by Aim 1 research coordinators and is processed with Aim 1 baseline patient data. Patients receive a $10 gift card for completion of the survey Aim 2 patient participation ends at the completion on the lone opinion survey.

Participants who prefer to complete the 5 to 10-minute survey online via Qualtrics will be sent a secure, Qualtrics link via email. The Qualtrics survey will include a brief, introductory screen affirming consent, describing the survey and instructions about participation. Once the survey is complete, participants will see a screen with instructions about how to obtain their $10 gift card and how to contact study staff with questions regarding the survey.

Modular online COPD education. Access to free, COPD on-line, continuing education is provided for all clinical staff at each practice. Each module will take 20 minutes or less. Modular components of and access to COPD education is described in the protocol. Aim 2 clinician participant access and completion of COPD education modules is assessed by clinician questionnaires and focus group item response over 12 months (between months 2 and 14 of Aim 2 timeline).

COPD in Primary Care/CAPTURE Introduction Focus Groups:
Two 45 to 60-minute focus group discussions occur at each Aim 2 practice. Focus groups are informed by practice demographics, practice assessment data – including respiratory workflow, baseline clinical staff questionnaire data regarding respiratory knowledge, attitudes, beliefs and practice preference for the diagnosis and care of adult patients with respiratory disease as well as patient opinion from CAPTURE surveys and past CAPTURE study (46, 47). Focus group candidate themes and prompts are developed for non-prescribing clinical staff (NPR) and prescribing clinical staff (PR) and are presented at separate on-site focus group sessions to allow more detailed discussion of role responsibility in the context of daily practice workflow, generating a more abundant qualitative data sample. Separation of and PR clinical staffing implementation themes into two focus groups also limits potential for hierarchical work-related discussion suppression described in other short duration focus group studies (48-52).

The focus group moderator introduces the CAPTURE tool utilizing CAPTURE education components described in Section 6.1.1. The focus group moderator follows RE-AIM prompts for CAPTURE implementation planning discussion throughout the focus group. Targeted COPD self-efficacy limitation themes from questionnaire data (including awareness and/or use of validated respiratory assessment questionnaires, spirometry, COPD guidelines, inhaled medication patient education, oxygen therapy, smoking cessation education, vaccination recommendation, pulmonology specialty care and pulmonary rehabilitation referral) are explored. Questions will probe clinicians to identify and explain levers that may maximize uptake of CAPTURE use in their practices as well as potential barriers to implementation. The Aim 2 research team will record each focus group using audio and written note-taking that will allow an abridged yet detailed tape-based micro-interlocutor analysis of focus group emergent themes, questions, answers and interactions. Key themes informing consensus discussion, program modifications and key elements of the CAPTURE RE-AIM implementation dimensions will be identified. Audio-recordings will be professionally transcribed and codes will be generated for the interview topics and key research questions. Reviewing the transcripts line-by-line, all substantive information will be

assigned a priori codes as relevant for CAPTURE RE-AIM implementation planning, COPD diagnosis and CAPTURE intra-office clinical communication and COPD/CAPTURE education preference assessment. Additional codes will be developed for sub-themes and emergent themes.

Development of Practice-Based CAPTURE Implementation PBL Cases:
From analyses of the 2 NPR and 2 PR CAPTURE Introduction focus groups per PBRN, baseline clinical staff questionnaire data, online CAPTURE opinion surveys, and on-site practice assessments, 1 primary care practice CAPTURE implementation case per PBRN (total implementation cases = 5) is created by the Aim 2 research team. Given local knowledge of chronic disease management quality improvement history, effort, challenge and successes, each PBRN's participation in case creation will be instrumental. The Aim 2 research team will lead case creation using evidence-based problem based learning (PBL) techniques (53-57). The Center for Research on Learning and Teaching (CRLT) at the University of Michigan will serve as research reference for PBL case development qualification (58). Each local PBRN PBL case will be distributed to the Aim 2 clinical staff at the 2 participating PBRN practices 2 weeks prior to the CAPTURE Implementation focus groups, giving Aim 2 participants an opportunity to read the case introductions prior to the focus group session. Also, each practice will receive one additional non-PBRN case for focus group discussion as selected by the Aim 2 research team. Therein, each of the 5 CAPTURE implementation PBL cases will receive 2 comprehensive focus group reviews (see below).

CAPTURE Implementation PBL Case Presentation Focus Groups:
Each practice participates in a final pooled (NPRs and PRs together) on-site focus group. Two CAPTURE implementation cases (described above) are discussed at each focus group. The focus will explore, discuss, glean and create optimal 1) CAPTURE implementation, 2) CAPTURE clinical communication, 3) CAPTURE/COPD education and 4) CAPTURE primary care quality improvement recommendations pooled from all clinical practice levels for each of the 2 presented cases.

The Aim 2 research team will record each focus group using audio and written note-taking that will allow an abridged yet detailed tape-based micro-interlocutor analysis of focus group emergent themes, questions, answers and interactions. Key themes informing consensus discussion, program modifications and key elements of the CAPTURE RE-AIM implementation dimensions will be identified. Audio-recordings will be professionally transcribed and codes will be generated for the interview topics and key research questions. Reviewing the transcripts line-by-line, all substantive information will be assigned a priori codes as relevant for CAPTURE RE-AIM implementation planning, COPD diagnosis, CAPTURE intra-office clinical communication, and COPD and CAPTURE education preference, and COPD diagnosis quality improvement assessment. Additional codes will be developed for sub-themes and emergent themes.

8.4 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.4.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.4.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.4.2.1 SEVERITY OF EVENT

The following guidelines will be used to describe severity of AEs.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.4.2.2 RELATIONSHIP TO STUDY INTERVENTION

All AEs must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.
- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the study intervention). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.4.2.3 EXPECTEDNESS

The Principal Investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.4.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

Adverse events (AE)s that occur during the baseline visit will be recorded.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed.

8.4.4 ADVERSE EVENT REPORTING

All AEs that occur at baseline visit will be recorded in the case report form and reported to the DCC. We anticipate few adverse events due to the non-invasive nature of the study procedures. Participants will only be enrolled if they meet the study eligibility criteria, including assessment for contraindications for spirometry. Targeted safety questions will be asked of all patient participants prior to albuterol to exclude those with a previous adverse event with the medication and others at high risk due to cardiac abnormalities.

8.4.5 SERIOUS ADVERSE EVENT REPORTING

SAEs will be reported to the IRB at the institution where the event occurred and the University of Michigan IRB will be notified of any serious adverse experience within 7 calendar days of occurrence. These will be reported to the DSMB.

Follow-up of serious adverse events

All SAEs will be followed up until resolution or permanent outcome of the event. All follow-up information will be included in the case report form. The DSMB will make recommendations to ensure data integrity and the safety of study participants.

8.5 UNANTICIPATED PROBLEMS

8.5.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;

- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.5.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing IRB and to the DCC. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the DCC within 7 calendar days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC within 14 calendar days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within one month of the IRB's receipt of the report of the problem from the investigator.

8.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a DSMB (physicians with the appropriate expertise, including non-involved pulmonologists, primary care physicians, and independent statisticians with clinical experience). Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the Principal Investigators.

9 STATISTICAL AND ANALYTICAL PLANS

9.1 SAMPLE SIZE AND POWER

9.1.1 PRIMARY OBJECTIVES

Define the sensitivity and specificity of CAPTURE for identifying previously undiagnosed patients with clinically significant COPD in a broad range of primary care settings. We will also explore clinical practice implementation approaches to and acceptance of CAPTURE case finding for clinically significant COPD in a range of primary care practices. Further, we will define the impact of CAPTURE information provided to clinicians in identifying and managing patients with respiratory symptoms (CAPTURE+) across a broad range of primary care settings.

9.1.1.1 SENSITIVITY AND SPECIFICITY OF THE CAPTURE TOOL

Primary Hypothesis 1. *The CAPTURE tool will exhibit excellent sensitivity and specificity in diagnosing clinically significant COPD as defined by post-bronchodilator $FEV_1/FVC < 0.70$ in addition to either >1 exacerbation-like event (ECOPD) within the past 12 months or an $FEV_1 < 60\%$ predicted.* Approximately 5000 patients will be enrolled in the study with the expectation that 300-800 of these will have previously undiagnosed clinically significant COPD, identified through research spirometry and documentation of prior respiratory events. Amongst cases, we will calculate the proportion of individuals who are at high risk for clinically significant COPD based on CAPTURE (sensitivity). Similarly, amongst non-cases, we will calculate the proportion of individuals not classified as having clinically significant COPD based on CAPTURE (specificity). Corresponding 95% confidence intervals will be calculated.

Based on our preliminary data drawn from a research setting, we noted 89.7% sensitivity and 93.1% specificity for CAPTURE. Table 9-1 shows the range of sensitivity and specificity 95% confidence interval widths that would result if the true sensitivity or specificity is 85%, 90% or 95% across a range of sample sizes. For instance, if we find 500 individuals with confirmed clinically significant COPD and CAPTURE has 90% sensitivity, then the 95% confidence interval for sensitivity would be 90% ± 2.6%. Similarly, if 4,000 individuals are confirmed to have no evidence of clinically significant COPD and CAPTURE has 90% specificity, then the 95% confidence interval for specificity would be 90% ± 0.9%.

Table 9-1 Projected Confidence Interval Widths for Various Sensitivity/Specificity Percentages (Columns) and Sample Sizes (Rows).

	Sensitivity or Specificity		
Sample Size	**85%**	**90%**	**95%**
5000	± 1.0%	± 0.8%	± 0.6%
4000	± 1.1%	± 0.9%	± 0.7%
1000	± 2.2%	± 1.9%	± 1.4%
500	± 3.1%	± 2.6%	± 1.9%
250	± 4.4%	± 3.7%	± 2.7%
100	± 7.0%	± 5.9%	± 4.3%
50	± 9.9%	± 8.3%	± 6.0%

9.1.1.2 ADOPTION AND IMPLEMENTATION OF THE CAPTURE TOOL IN PRIMARY CARE PRACTICE

Primary Hypothesis 2: *A COPD case finding methodology using a validated one-page, five-item questionnaire with selective PEF measurement (CAPTURE) can be incorporated into the clinical practice patterns, clinical workflow, communication and practice-based quality improvement paradigms of a variety of primary care clinical settings.*

Aim 2 is a qualitative study to determine the efficacy of workflow integration of the CAPTURE tool. Statistical analysis of the clinician questionnaire will involve simple sums of each item and reviewing answers across practices and region. Standard frequencies for questions will be developed to examine patterns in responses.

The clinician focus groups will be conducted on-site at each practice at a time convenient for the participating clinicians. The number of prescribing and non-prescribing clinicians will equal 15 per practice and is based on interest with a maximum of 8 prescribing clinicians/practice. The sample size will follow a basic qualitative sampling standard of interviewing to redundancy or saturation. The number of clinicians to be interviewed (up to n=15 in each practice) is estimated based on achieving concept saturation. Reflecting regional primary care practice norms and to bolster concept saturation, PBRN Aim 2 coordinator focus group discussion participation is encouraged for very small practices where the participating prescribing and non-prescribing clinician total is less than or equal to 4. For all practice focus groups questions will explore the described Aim 2 CAPTURE RE-AIM concepts, barriers to implementation of the CAPTURE tool at other practice sites, standard processes for COPD and respiratory care diagnosis and management for each clinical role within the practice, and perception of quality improvement methods at each practice. Clinician focus groups are conducted on-site at each of the 10 practices.

Transcripts of clinician focus groups will all be digital and entered into a qualitative data analysis program, NVivo for Mac. This program allows for an investigation of the salience, patterning, and contexts of key discourse items. Grounded theory methods will be used to identify and label recurrent themes and concepts within textual materials. Texts will be examined line-by-line, key phrases assigned tentative category labels, and coded passages grouped under the themes of feasibility, barrier and utility. The analyses will look for “traces” in dialogue, including repetitions, key words, evaluation statements, and metaphors. Change in salience, patterning, or content of key themes will provide further empirical evidence regarding the efficacy of our program’s efforts to impact community norms and behaviors. An audit trail will be maintained to document the position of text material from which codes and themes are developed. We will use word/code counts of repetitive themes and concepts to indicate patterns. By allowing for open-ended responses, the narratives and notes will allow us to capture significant changes in participants’ attitudes or behaviors. Codes and themes will be discussed iteratively with the research team members to hone definitions and assure consistency of interpretation. We will establish a coding dictionary and all interviews will be coded using the complete set of themes. Two independent coders will code each document to assure inter-coder reliability. Preliminary results will be shared with our Aim 2 research team and will inform the development of the case studies for the latter part of the project.

9.1.1.3 PRACTICE BEHAVIOR IN SITES WITH VERSUS WITHOUT CAPTURE EDUCATION AND PATIENT LEVEL CAPTURE DATA PROVIDED

Primary Hypothesis 3: *Sites where basic COPD and CAPTURE education are provided to clinicians, along with patient level CAPTURE data, will have a higher probability than control sites (i.e., those receiving only basic COPD education) of meeting the composite endpoint in their CAPTURE+ patients within 12 months of baseline.* From record review, the composite endpoint is met if one of the following is recorded: (1) referral for clinical spirometry testing, 2) new clinical diagnosis of COPD, 3) newly prescribed respiratory medication (long acting bronchodilator or anti-inflammatory for respiratory condition), or 4) referral to a specialist for respiratory evaluation/ treatment.

The study will enroll 50 CAPTURE practices and 50 control practices; each practice will enroll 50 patients (for a total of 5,000 patients). We project that within each practice, there will be at least 5 patients previously undiagnosed with COPD who have a CAPTURE+ screening result. The primary analysis will be to compare the average proportion of CAPTURE+ patients per practice that meet the composite endpoint in the two intervention arms. For power and sample sizes computations, this is a cluster randomized trial of n=50 clusters (practices) per intervention arm with 5 CAPTURE+ patients per cluster (practice). The primary power calculation is based on comparing the average cluster sample proportion (average proportion of CAPTURE+ patients per practice meeting composite endpoint) between intervention arms. Table 9-2 displays power for a two-sample test comparing average cluster sample proportions, accounting for possible intra-cluster correlation coefficient (ICC) values of 0.05, 0.10 and 0.15 that are typically seen in cluster randomized trials of behavioral interventions (https://www.abdn.ac.uk/hsru/research/research-tools/study-design/). These calculations assume a type I error of 5% and that the control arm meets the composite endpoint in 5% of CAPTURE+ patients and the CAPTURE arm meets the composite endpoint in higher percentages (columns of Table 9-2). There will be variability in the actual number of CAPTURE+ patients per practice. It is standard practice to inflate the number of needed clusters by 12% to account for this extra source of variability. Therefore, our power calculations are based on 44 clusters per intervention arm.

Table 9-2. Overall power to detect a difference in rate of meeting primary endpoint in CAPTURE group (50 practices/clusters) vs usual care (50 practices/clusters), assuming 5% performance rate in usual care; 50 patients total / practice; assuming 10% prevalence gives 5 CAPTURE+/practice

Improvement over usual care	+7.5%	+10%	+15%	+25%	+50%
ICC=0.05	0.72	0.89	0.99	>0.99	>0.99
ICC=0.10	0.65	0.84	0.98	>0.99	>0.99
ICC=0.15	0.59	0.79	0.97	>0.99	>0.99

9.1.2 SECONDARY OBJECTIVES

9.1.2.1 SENSITIVITY AND SPECIFICITY IN PREDEFINED SUBGROUPS

Table 9-3. Projected numbers of clinically significant COPD cases and non-cases we expect by subgroup of interest assuming prevalence of obstructed individuals is between 6-16%. (*Non-Hispanic) This table assumes prevalence of non-clinically significant COPD similar to clinically significant COPD (not included in this table).

	Total	**Men (50%)**	**Women (50%)**	**White* (62%)**	**Black* (15%)**	**Hispanic (18%)**	**Rural (46%)**	**Urban (54%)**	**Ever-Smokers (40%)**	**Never-smokers (60%)**
Projected # confirmed clinically significant	300-800	150-400	150-400	186-496	45-120	54-144	138-368	162-432	120-320	180-480

COPD by subgroup										
Projected # confirmed no COPD by subgroup	3,400-4,400	1,700-2,200	1,700-2,200	2,108-2,728	510-660	612-792	1,564-2,024	1,836-2,376	1,360-1,760	2,040-2,640

We will also examine several subgroups of interest that are key to addressing our overall goal of defining the value of CAPTURE across a broad range on individuals. These will include sex, ethnic groups, rural and urban location, and educational level, among individuals with clinically significant COPD, spirometrically defined COPD and individuals with "mild" COPD as defined in this protocol. We have specifically chosen clinical sites with a diverse gender, racial and ethnic mix, and rural and urban mix with the expected prevalence of clinically significant COPD cases and controls by subgroup outlined in Table 9-3, again with corresponding sensitivity and specificity confidence interval widths in Table 9-1. For example, if sensitivity of CAPTURE in Hispanic individuals is 90%, then a sample size of approximately 100 would give a confidence interval of 90% ± 5.9%. We believe that with an overall sample size of 5,000 recruited patients we will have adequately sized subgroups to assess the operating characteristics of CAPTURE in the subgroups of interest.

9.1.2.2 FURTHER ANALYSIS OF ASSOCIATIONS BETWEEN MEETING COMPOSITE ENDPOINT AND INDIVIDUAL AND PRACTICE LEVEL OUTCOMES

Secondary analyses for evaluating practice behavior are exploratory, and therefore not included in a formal power and sample size analysis. These analyses are described further in Section 9.3.2.

9.2 POPULATIONS FOR ANALYSES

Aim 1
Population used for sensitivity calculations are all enrolled patients with clinically significant COPD as defined by post-bronchodilator $FEV_1/FVC < 0.70$ in addition to either >1 exacerbation-like event (ECOPD) within the past 12 months or an $FEV_1 < 60\%$ predicted.

Population used for specificity calculations are all enrolled patients with no demonstrable COPD as determined by research spirometry conducted upon study entry, $FEV_1/FVC \geq 0.70$.

Aim 2
Clinician participants: enrolled clinicians are from 2 primary care practices in each of five US PBRN regions that do not engage in Aims 1 or 3 investigation. Eligible clinicians include primary care providers and primary care clinical non-provider support personnel.

Patient participants: enrolled as a sub-sample of Aim 1 participants at baseline. One CAPTURE patient opinion survey is administered at baseline.. Aim 2 participants fulfill the inclusion, exclusion and population analysis criteria of aim 1.

Aim 3
Populations used in 2-sample comparisons of the average proportion of CAPTURE+ patients per practice that meet the composite endpoint in the two intervention arms will be based on randomization group (intent-to-treat analysis).

9.3 STATISTICAL ANALYSES

9.3.1 SENSITIVITY AND SPECIFICITY (AIM 1)

SAS version 9.4 PROC LOGISTIC will be used for computations. Calculations of sensitivity and specificity along with their corresponding 95% confidence intervals assume independent Bernoulli outcomes for each patient. Clinically significant COPD+ and COPD- populations selected for these analyses are described in Section 9.2. CAPTURE+ patients are those with a baseline CAPTURE score $\geq$ 5 or with a baseline CAPTURE score of 2, 3, or 4 with a low PEF (defined as <350 L/min for males, <250 L/min for females).

In addition to the primary sensitivity/specificity calculations, sensitivity/specificity and associated 95% confidence intervals will be calculated in predefined subgroups: sex, ethnic subgroups, rural and urban location, and educational status. As part of secondary analyses, receiver operating characteristic (ROC) curve analyses will evaluate different thresholds of the CAPTURE questionnaire score in defining a positive clinically significant + COPD screen, separately and in combination with low PEF characteristics, **and the additional CAPTURE questions**. As part of this exploration, participant and practice level data as well as interactions with the CAPTURE tool results, will be considered as predictors of clinically significant COPD using multivariable logistic regression. Corresponding positive and negative predictive values will be estimated across the range of prevalence percentages seen at the enrolled practices. Model selection in secondary logistic regression analyses will be based on forward selection using maximum likelihood theory, with entry into the model dependent on statistical significance at the 0.05 level. Exploration of this nature has the potential to produce artificially high operating characteristics (area under the curve [AUC], sensitivity and specificity) based on overfitting the data. SAS 9.4 PROC LOGISTIC includes a cross-validation approach to ROC curve analysis [ROCOPTIONS(CROSSVALIDATE)] that we will use when assessing operating characteristics for any new prediction tool that goes beyond the original CAPTURE metric considered in primary analyses. Once a final logistic regression model has been selected, classification thresholds for predicting clinically significant COPD will be described by the investigative team from the cross-validated ROC curve. Calibration plots of observed versus predicted sensitivity, and observed versus predicted specificity, will be conducted across previously specified subgroups of interest (sex, ethnic subgroups, rural and urban location, and educational status).

All of the above analyses will be applied to these additional populations: (1) patients with spirometrically defined COPD and (2) patients with mild COPD.

9.3.2 PRACTICE BEHAVIOR (AIM 3)

The primary analysis will be to compare the average cluster sample proportion (average proportion of CAPTURE+ patients per practice meeting composite endpoint) between intervention arms. Practices that do not identify any CAPTURE + subjects will not contribute to the primary analysis, although this is felt to be an unlikely occurrence. A two-sample test comparing average cluster sample proportions will be used that explicitly takes into account correlation between individuals treated within the same practice. A two-sided p-value < 0.05 will be considered statistically significant. This analysis corresponds to a generalized estimating equation (GEE) regression analysis with (1) individual-level binary composite outcome data, (2) CAPTURE intervention group as a covariate, (3) practice id used to identify correlated outcomes, (4) exchangeable correlation matrix that assumes similar correlation between all composite

outcome results for patients within the same practice, and (5) a logistic link function. The primary analysis would then correspond to a test for the CAPTURE intervention group parameter. There are no planned interim analyses for the primary endpoint, the rationale being that this is not a pharmaceutical or device trial that would benefit from standard stopping rules for efficacy. A DSMB will be monitoring the study for safety and study integrity.

Secondary analyses on meeting the composite outcome for participants who are CAPTURE+ will employ the GEE analysis framework with individual and practice level predictors in addition to the CAPTURE intervention group. Interactions will be assessed. We will also use the GEE framework to study and describe each of the individual components of the composite outcome as they relate to individual and practice level outcomes. In the subset of smoking patients, we will use GEE regression analysis to study additional binary outcomes, such as incidence of physician referral to a formal smoking cessation program, prescribed smoking cessation medication in participants who are smokers, and referral to pulmonary rehabilitation program.

In participants who are CAPTURE+, change in CAT score will be analyzed using mixed models with a random effect for practice. The average cluster sample proportion of patients who experience exacerbations will be compared between intervention groups using methodology similar to that used for the primary endpoint. Survival analysis allowing for correlation of endpoints within cluster (practice) will be used to compare mortality between intervention groups and perform multivariable analysis. We will explore differences between intervention groups in the average cluster sample rate of hospitalizations again using GEE. All additional secondary analyses will also be applied to patients with clinically significant and spirometrically defined COPD. Practices that do not have any clinically significant COPD or spirometrically defined COPD will not contribute to analyses of these secondary endpoints, respectively.

Model selection in GEE secondary analyses will be based on statistical significance at the 0.05 level using robust sandwich estimation of variability within clusters. Model fit will be checked by comparing observed versus predicted values within predefined subgroups of interest (sex, ethnic subgroups, rural and urban location, and educational status).

9.3.3 CAPTURE IMPLEMENTATION RECOMMENDATIONS (AIM 2)

Site-specific practice information, clinician knowledge and behavioral questionnaires, as well as patient opinion survey responses are recorded primarily to populate focus group themes for qualitative analysis. Secondary analyses of individual clinician and patient response using frequencies, means, ranking and dispersion by clinician type, practice and PBRN is accomplished using SAS version 9.4. Correlation with implementation recommendation is determined using GEE variance models.

Audio transcripts of clinician focus groups will all be digital and entered into a qualitative data analysis program, NVivo for Mac. This program allows for an investigation of the salience, patterning, and contexts of key discourse items. Grounded theory methods will be used to identify and label recurrent themes and concepts within textual materials. Texts will be examined line-by-line, key phrases assigned tentative category labels, and coded passages grouped under the themes of feasibility, barrier and utility. The analyses will look for “traces” in dialogue, including repetitions, key words, evaluation statements, and metaphors. Micro-interlocutor analysis of focus group emergent themes, questions,

answers and interactions will account for individual gaps in focus group participation. Change in salience, patterning, or content of key themes will provide further empirical evidence regarding the efficacy of our program's efforts to impact clinician community norms and behaviors. An audit trail will be maintained to document the position of text material from which codes and themes are developed. We will use word/code counts of repetitive themes and concepts to indicate patterns. By allowing for open-ended responses, the narratives and notes will allow us to capture significant changes in participants' attitudes or behaviors. Codes and themes will be discussed iteratively with the research team members to hone definitions and assure consistency of interpretation. We will establish a coding dictionary and all interviews will be coded using the complete set of themes. Reviewing the transcripts line-by-line, all substantive information will be assigned a priori codes as relevant for CAPTURE RE-AIM implementation planning, COPD diagnosis, CAPTURE intra-office clinical communication, and COPD and CAPTURE education preference, and COPD diagnosis quality improvement assessment. Two independent coders will code each document to assure inter-coder reliability. Preliminary results will be shared with the Aim 2 data team and will inform the development of the CAPTURE case studies and primary care practice implementation recommendations.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise.

A HIPPA waiver will be submitted to each IRB to prescreen clinic schedules and patient panels for recruitment purposes. The PHI reviewed by the coordinator in the electronic health record (EHR) will include age, date of birth, diagnosis of COPD, respiratory medications, and other medical conditions that are contraindicated for spirometry. A waiver of written consent will be submitted to each IRB to pre-screen potential participants for eligibility criteria prior to informed consent. The pre-screening will either be by telephone prior to an upcoming clinic visit, or in person at the time of the visit. An IRB-approved telephone/in-person screening script will be submitted to each IRB.

A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. Participants will additionally have the opportunity to review the study and informed consent prior to providing consent for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

All PBRN research coordinators, COPD Foundation study staff and other clinical investigators will be certified by their local IRB in informed consent and human studies research.

Clinicians interested in participating in the qualitative, minimal risk study for Aim 2, will be given the opportunity to review the consent form below and sign it. This can happen once their practice agrees to participate in Aim 2 activities or during the first in person site visit with Dr. Brown.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

When a study is prematurely terminated, refer to Section 7, Study Intervention Discontinuation and Participant Discontinuation/Withdrawal, for handling of enrolled study participants.

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. In addition, it may be transmitted and stored at the DCC in a database separate from the clinical database (used for statistical analysis and scientific reporting) and with COPD Foundation study team access to aid in contacting participants at the 12-month follow-up. At the end of the study,

all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the DCC. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by DCC research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the DCC.

For the online Aim 2 patient opinion survey, Qualtrics is used. Qualtrics is a secure University of Michigan (U-M) contracted-for cloud service that can be used to maintain or share the university's sensitive unregulated data, as well as some kinds of sensitive regulated data.

U-M's agreement with Qualtrics includes a Business Associate Agreement. This means individuals may use this service to maintain Protected Health Information (PHI) regulated by HIPAA. Complying with HIPAA's requirements is a *shared responsibility*. Users sharing and storing PHI in Qualtrics are responsible for complying with HIPAA safeguards, including:

- Using and disclosing only the minimum necessary PHI for the intended purpose.
- Obtaining all required authorizations for using and disclosing PHI.
- Ensuring that PHI is seen only by those who are authorized to see it.
- Obtaining all necessary data-sharing agreements and Business Associate Agreements for using and disclosing PHI.
- Following any additional steps required by your unit to comply with HIPAA.

Sensitive data, including PHI, may be collected and stored in Qualtrics for non-clinical, academic purposes only (for example, research and hospital quality improvement initiatives). Qualtrics cannot be used for any clinical applications, no matter the sensitivity level of the data

11 STUDY ADMINISTRATION AND OVERSIGHT

11.1 STUDY LEADERSHIP

11.1.1 PRINCIPAL INVESTIGATORS

The principal investigators are responsible for providing direction and oversight of all study activities.

Principal Investigators	
Fernando Martinez, MD, MS	MeiLan Han, MD, MS
Weill Cornell Medicine	University of Michigan
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Fjm2003@med.cornell.edu	mrking@med.umich.edu

11.1.2 PRACTICE BASED RESEARCH NETWORKS (PBRN)

PBRNs will have the following roles and responsibilities:

CAPTURE Study Preparation

1. Review protocol to help identify operational details
2. Submit final protocol and informed consents to all IRBs necessary for the participating sites
3. Complete and maintain current human participants training for all main study personnel as required by the IRB
4. Attendance of PBRN coordinators at in person training, spirometry certification for all coordinators, update of spirometry quality assessments and training
5. Identify and recruit local practice sites to participate in the study

CAPTURE Study Implementation

1. Facilitate COPD and when appropriate CAPTURE education
2. Maintain regular contact with participating PBRN practice sites during their period of patient enrollment
3. Supervise and send PBRN Research Coordinators to enroll patients, perform study visits including completion of the CAPTURE questions, peak flow, spirometry, and collect other information on all enrolled patients
4. Complete pre bronchodilator spirometry on all participants
5. Complete post bronchodilator spirometry on participants with abnormal pre-bronchodilator spirometry as defined by study algorithm (e.g. those with pre bronchodilator results consistent with obstruction)
6. Facilitate completion of data entry to the data coordinating center
7. Follow up by research coordinator for patients failing to respond to the follow up questionnaires
8. Collect practice outcome data related to enrolled patients at close of study from either electronic medical records or if practice does not have EMR, by manual record review

Patient participants and staff participants will be recruited from the PBRNs.

PBRN	Location	Director
Atrium Health	North Carolina	Hazel Tapp, PhD
LA Net Community Health Network	Southern California	Lyndee Knox, PhD
High Plains Network	Colorado	Linda Zittleman, MD
Duke Primary Care Research Consortium	North Carolina	Rowena Dolor, MD
Oregon Rural Practice-Based Research Network	Oregon	Nancy Elder, MD
University of Illinois, Chicago	Illinois	Min Joo, MD

11.1.3 SPIROMETRY CORE

Led by Dr. David Mannino, the Spirometry Core will maintain quality of the research spirometry that is integral to the success of the study. The work will be done in conjunction with a research assistant. This includes the following functions:

1. Development of the operation manual for the sites
2. Training of the site staff in the use of the spirometry equipment (including travel to training and sites as needed)
3. Certification of staff in spirometry
4. Assessing staff adherence to protocols for the use of bronchodilators
5. Grading and adjudication of spirometry
6. Importing processed spirometry into spreadsheets
7. Uploading processed data to data coordinating center
8. Working with data coordinating center to verify and clean data

In addition, Dr. Mannino will be a critical part of the team that evaluates the data both from spirometry and the other components of this study (the CAPTURE tool, quality of life measures, etc.), in addition to being part of the writing team that analyzes data and disseminates the findings from this study.

11.1.4 IMPLEMENTATION CORE

Dr. Randall Brown will lead the qualitative Aim 2 activities which assess the implementation strategy and acceptance recommendations for CAPTURE use in primary care practice. His team includes an Aim 2 project manager and dedicated research assistant. Led by Dr. Brown the Aim 2 team coordinates with PBRNs and their selected Aim 2 practices and will conduct qualitative site visits and focus groups in addition to administering clinical practice behavioral questionnaires. Drs. Barbara Yawn, Barry Make, Bruce Bender and Julia Houfek will contribute to the development of the web based educational modules and the qualitative efforts on this project.

11.1.5 DATA COORDINATING CENTER (DCC)

Dr. Cathie Spino directs the DCC, housed at the University of Michigan within the Statistical Analysis of Biomedical & Educational Research (SABER) Unit of the Department of Biostatistics in the School of Public Health. The DCC staff will include a Database programmer, Data manager, Senior Unblinded Statistician, Statistical Analyst, Project Manager, Clinical Monitor, Web Programmer/Designer, and a Research Administrator. In addition, the blinded senior statistician, Dr. Susan Murray, is located at the University of Michigan. The DCC plays a pivotal role in the design, implementation, execution and administration of the study. The DCC will be responsible for randomization, eCRFs and online reporting systems, preparation of the manual of operations for data entry, addressing questions regarding entry and analysis, monitoring recruitment, follow-up and adherence to protocol, and scheduling and arranging meetings of the Executive Committee, Steering Committee, and Medical Monitor. The DCC will prepare all of the routine study reports for the Executive Committee, Operations Committee, and Medical Monitor. The DCC will interact with all of the Cores and other Committees, as needed. The DCC will compile data tables and listing for DSMB reports.

11.1.6 CLINICAL COORDINATING CENTER

The Clinical Coordinating Center (CCC) will be led by Principal Investigators Fernando Martinez, MD, MS at Weill Cornell Medicine, and MeiLan Han, MD, MS at the University of Michigan. Dr. Martinez will be responsible for overall study oversight as well as fiscal management of the overall project and capitation payments to sites for work performed. He will also be responsible for communication with NIH and submission of annual reports. Dr. Han will work with the Data Coordinating Center to oversee clinical

trial enrollment and, along with her statistical team, be responsible for coordinating statistical analysis. The process for making decisions on scientific direction and allocation of resources will be made by both Drs. Martinez and Han, with input from the rest of the investigative team as needed.

Additional Clinical Coordinating Center (CCC) responsibilities:

- Establish subcontracts with enrolling sites, central laboratories, imaging service providers, and others as appropriate
- Protocol development and scientific design oversight
- Statistical analysis
- Participating study site selection
- Review of serious adverse events and unanticipated problems involving risk to participants or others, reporting to participating centers and regulatory reporting
- Prepare and maintain Clinical Coordinating Center IRB submissions
- Analyze and present data to DSMB

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11.1.7 12 MONTH SURVEY COORDINATING CENTER

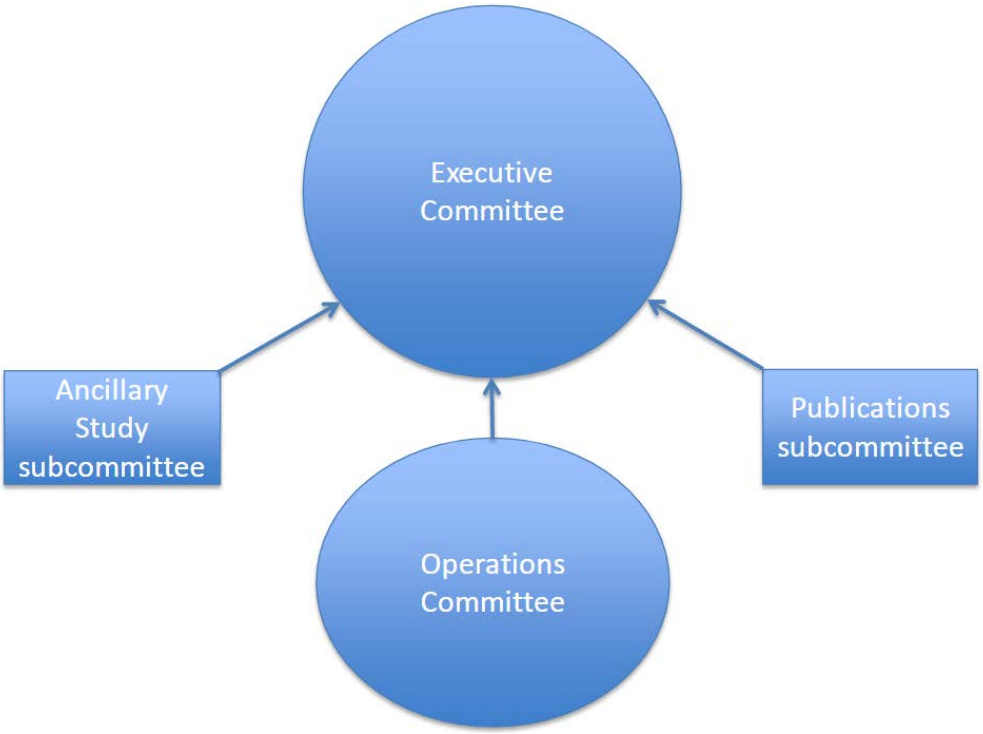
The 12 month Survey Coordinating Center will be led by Co-Investigator Barbara Yawn, MD MSc, Chief Science Officer at the COPD Foundation. Dr. Yawn will be responsible for oversight of the development and implementation of the reminder notices and 12 month survey administration by COPD Foundation study personnel for participants selected to complete the 12 month follow up survey.

11.2 ORGANIZATIONAL STRUCTURE

The Executive Committee will be led by the Principal Investigators and will consist of the 2 elected PBRN Directors, 1 representative of the COPD Foundation, Co-Investigators, Data Coordinating Center PI and Project Manager, NIH official and Clinical Coordinating Center Project Managers. The Executive Committee will meet every one-to-two weeks to administratively direct and monitor the progress of the study and to respond to any design, implementation or administrative issues that arise during the study.

The Operations Committee will consist of Overall Principal Investigators, PBRN Directors and lead coordinators, DCC Project Managers, and Co-Investigators. It will address implemental and administration faced by the PBRN practices that arise during the study.

Other subcommittees, such as the Publications and Ancillary Studies Subcommittees, will be constituted to support maximizing the utility of the CAPTURE study to the scientific community.



12 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data, documentation and completion. An individualized quality management plan will be developed.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

13 DATA HANDLING AND RECORD KEEPING

13.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Comprehensive data coordinating center (DCC) functions for this clinical trial, including clinical monitoring, database development, web-based data entry and management, as well as the creation and export of study reports for the DSMB will be provided by the University of Michigan Statistical Analysis of Biomedical and Education Research (SABER) group. Housed in the top nationally ranked Department of Biostatistics, SABER, in its 17-year existence, has served as the DCC for over 50 studies, including multiple NIH-sponsored networks.

The DCC will use OpenClinica® (OpenClinica Clinical Trial Software; OpenClinica, LLC, Waltham, MA), a clinical trial software platform for electronic remote (i.e., site-based entry) data capture and clinical data management, as the basis for our custom-designed data entry and management system. The majority of data will be collected via electronic Case Report Forms (CRFs); however, other data sources, such as laboratory data from the central laboratory, may be used. In these circumstances, the DCC will also utilize electronic data transfer. Protocols for the transfer of data, with careful attention to data integrity, will be written by experienced programmers and stored in the OpenClinica database or data mart.

The DCC has established a set of standard operating procedures (SOPs) governing the processes used to ensure patient privacy and data confidentiality, including the use of anonymous participant IDs on CRFs and in reports. OpenClinica® enables compliance with Good Clinical Practice (GCP) and regulatory requirements by providing differentiated user roles and privileges, password and user authentication security, electronic signatures, SSL encryption, and comprehensive auditing to record and monitor access and data changes.

Data collection is the responsibility of the central study staff at the PBRN under the supervision of the PBRN Director (investigator). The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. In addition to the protocol, the DCC will prepare a Manual of Procedures which provides additional detail on data collection procedures, including source documentation, eCRF completion guidelines, data handling procedures and procedures for data monitoring and quality control that ensure these data are accurate, consistent, complete and reliable and in accordance with ICH 36.

13.2 STUDY RECORDS RETENTION

Study documents should be retained as required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

13.3 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation or scheduled protocol-required activity. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

13.4 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers after the completion of the primary endpoint by contacting Drs. Martinez and Han.

14 PROTOCOL AMENDMENT HISTORY

Protocol Amendment 2.0 - Summary of Changes				
Location	**Page Number**	**Type of Change**	**Description**	**Rationale**
Cover Page	---	*Administrative*	Update Protocol Version to 2.0 and update version date to	Amendment version and date
Cover Page	---	*Administrative*	Add NCT # for each AIM	Add all 3 numbers to protocol since each AIM is registered in clinicaltrials.gov
Table of Contents	---	*Administrative*	Corrected page numbers for new version	Updating Table of Contents to reflect any page number shifts due to reformat

Multiple Sections	Multiple	*Administrative*	Changed Medical Chart Review to Medical Record Review throughout the protocol	Changed Medical Chart Review to Medical Record Review throughout the protocol
1.2 Schema Table 1	9	*Clarification*	Concomitant medications revised to read Respiratory Medications	Further clarification since these are limited to respiratory medication not all medications
1.2 Schema Table 1	9	*Clarification*	Foot note 3 moved to 12 month to reflect the data that will be collected for subjects who qualify for 12 month follow-up w	Clarification that 12 month column is for indicating what data will be collected for subjects who meet 12 month follow-up criteria
1.2 Schema Table 1	9	*Clarification*	X in last column for 12 month spirometry was deleted. This was originally meant to be footnote that post bronchodilator spirometry would be performed at baseline for those subjects that qualified	Further clarification that spirometry will not be done at 12 month follow-up, the footnote was meant to reflect post bronchodilator spirometry at baseline for those subjects who qualify
Section 2.3.1 Known Potential Risks	14	*Revision*	For Albuterol: A targeted safety questionnaire will be administered to all participants prior to albuterol to exclude those with a previous adverse event with the medication and others at high risk due to cardiac abnormalities.	Subjects are excluded who have had MI and therefore not necessary
Section 4.1 Overall Study Design	21	*Clarification*	Patient-reported data will be collected by telephone, secure web-based server, and mail-based methodologies based on participant preference and completed by the COPD Foundation., as well as medical record abstraction, depending upon practice site preferences and feasibility.	The COPD Foundation will be collecting participant 12 month follow-up subject questionnaires
Section 4.1 Overall Study Design	21	*Clarification*	Clinic site data will also be collected from the Subject medical record data will be collected from the medical record to assess for changes in practice-level care.	Further clarification that this data will be collected from medical record

Section 6.3 Study Intervention Compliance	27	*New*	If results were not shared at the time of the CAPTURE study visit, then the date of sending the CAPTURE results will be recorded on the appropriate eCRF by filling in the date (day/month/year) the exact copy of the CAPTURE Toolresults were sent to the clinician through a inter–clinic email or other HIPPA-compliant method and placed in the medical record. The goal is to communicate the results to the clinician in a timely manner within 3 business days. The DCC will monitor review all participants' eCRFs to assure that all those enrolled from practices randomized to CAPTURE results have been shared with clinicians. in the specified timeframe.	The study team wanted to clarify that the exact copy of the CAPTURE tool should be shared with clinician. Also wanted to make timing of sharing less restrictive and the team recognized that restrictive parameters cannot always be realized in clinical practice setting
Section 8.2 Longitudinal Follow-up Assessment and Data Collection	30	*Clarification*	Medical chart abstractions completed by PBRN coordinators and participant questionnaires administered by study team members from the COPD Foundation are used.	Clarification that medical chart reviews will be done by PBRN coordinators and COPD Foundation will administer participant questionnaires at 12 months
Section 8.2 Longitudinal Follow-up Assessment and Data Collection	30	*Clarification*	Data from clinical visits to be collected at follow-up by telephone, secure web-based server, or mail-based methodologies directly from participants and administered by COPD Foundation study personnel	Clarification that COPD Foundation will administer participant questionnaires at 12 months
Section 10.1.1 Informed Consent Process	45	*New*	All PBRN research coordinators, COPD Foundation study staff and other clinical investigators will be certified by their local IRB in informed consent and human studies research.	The COPD Foundation has attained IRB approval as their team will be interacting with participants
Section 10.1.3 Confidentiality and Privacy	46	*Clarification*	In addition, it may be transmitted and stored at the DCC in a database separate from the clinical database (used for statistical analysis and scientific reporting) and with COPD Foundation study team study coordinator access to aid in contacting participants at the 12-month follow-up.	COPD Foundation will have access to participant contact information from a separate database in order to contact participants for follow-up questionnaire completion
Section 11.1.2 Practice Based Research Networks (PBRN)	47	*Administrative*	Moved Roles and Responsibilities to section 11.1.2	Moved Roles and Responsibilities to section 11.1.2
Section 11.1.2 Practice Based Research Networks (PBRN)	47	*Revision*	Change Carolinas HealthCare System to Atrium Health and add new PI for Oregon Rural Practice-Based Research Network	Carolinas HealthCare System is now Atrium Health and the new PI at Oregon, Dr. Lyle Fagnan is retiring and Dr. Nancy Elder will take his place as director and site PI for CAPTURE

Section 11.1.7 Clinical Coordinating Center	49	*Clarification*	Update titles for COPD Foundation study members	Administrative change to include titles for Dr. Yawn
Section 11.1.8 12 Month Survey Coordinating Center	50	*New*	Add 12 Month Survey Coordinating Center to Study Leadership, Section 11.	The COPD Foundation study team will be coordinating outreach to 12 month follow-up subjects and administering surveys
Section 11.2 Organizational Structure	51	*Clarification*	Includes 1 representative of the COPD Foundation in the Executive Committee Organization description.	COPD Foundation representatives are part of the Executive Committee currently
Section 4.1 Overall Study Design	9, 10, 21	*New*	Deletion of CAT Score ≥ 10 and CAPTURE Score ≥ 2 and return to CAPTURE+ and abnormal spirometry as longitudinal follow-up criteria	The study team proposes to defer longitudinal follow-up based solely on an isolated, baseline CAT or CAPTURE scores as it is outside the scope of the current CAPTURE program. The study team is also proposing to return to the original scientific approach to follow CAPTURE+ (as defined in the protocol) subjects along with abnormal post-BD spirometry and 5% random sample of those subjects that meet neither of these criteria. Those subjects already selected under the current algorithm would still be followed longitudinally (and noted as selected under the initial follow-up selection criteria) and would use data as appropriate. Importantly, the primary care clinician colleagues within the CAPTURE program do not feel there is a safety issue in not following this population as there are no data defining a negative impact of an isolated, elevated CAT score in primary care patients.
Section 1.1 Synopsis, Section 4.1 Overall Study Design, Section 8.1 Baseline Assessments and Data Collection	3, 20, 29	*New*	Addition of adjudication of the presence of obstruction on post-bronchodilator spirometry	As the study commenced, several instances of the faulty spirometry software reading incomplete or participant refusal of post-bronchodilator occurred and led to the need for spirometry core to determine review process in these instances and validity of pre-bronchodilator spirometry. The rationale for this is that in other databases where all patients had both pre and post-bronchodilator spirometry, those who had a pre-bronchodilator FEV1/FVC less than 0.65 had a post-bronchodilator FEV1/FVC less than 0.70 more than 95% of the time.

8.1 Baseline Assessments and Data Collection	28	*New*	Addition of spirometry instructions if participant has taken a medicine they breathed into lungs from puffer or inhaler within two hours of spirometry test	Since study start, one participant reported taking albuterol shortly before the visit. The study clinicians confirmed this scenario would constitute the participant being in a post-bronchodilator state already with no further need to proceed after initial spirometry. The data collection process has been updated to assure these values would be placed in post-bronchodilator data. Coordinators are instructed to ask this question before spirometry should this scenario occur again during the study.
Protocol Amendment 3.0 - Summary of Changes				
Location	**Page Number**	**Type of Change**	**Description**	**Rationale**
Cover Page	---	*Administrative*	Update Protocol Version to 3.0 and update version date to 24 September 2019	Amendment version and date updated
Cover Page	---	*Administrative*	Add NCT # for each AIM	Add all 3 numbers to protocol since each AIM is registered in clinicaltrials.gov
Multiple Sections	Multiple	*Revision*	Number of PBRNs participating in aims 1 and 2 revised to 6 PBRNs throughout protocol.	Additional PBRN added
1.2 Schema Table 1	9	*Revision*	CAPTURE 12 additional items questionnaire	The CAPTURE 12 item additional questionnaire was renamed.
Section 8.1 Baseline Assessments and Data Collection	30	*Clarification*	CAPTURE Additional Items Questionnaire administration instruction added to Study Assessments.	Further instruction for administration of CAPTURE Additional Items Questionnaire, as described in Section 1.2 Schema table, was added.
Section 11.1.2 Practice Based Research Networks (PBRN)	48	*Revision*	University of Illinois, Chicago added as a participating PBRN.	University of Illinois, Chicago added as an enrolling site in aims 1 and 3.
Protocol Amendment 4.0 - Summary of Changes				
Location	**Page Number**	**Type of Change**	**Description**	**Rationale**
Protocol Amendment Summary of Changes Table	---	*Administrative*	Protocol Amendment 2.0 – Summary of Changes was added to the Summary of Protocol Amendments Table.	Amendment 2.0 – Summary of Changes was added to provide a comprehensive list of changes across all protocol amendments.

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The CAPTURE Study: Validating a unique COPD case finding tool in primary care

Protocol Number: 1R01HL136682

National Clinical Trial (NCT) Identified Number:

NCT03581227, NCT03653611, NCT03583099

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Version Number: v. 5.0

18 JUN 2021

Protocol Amendment 5.0 - Summary of Changes				
Location	**Page Number**	**Type of Change**	**Description**	**Rationale**
Cover page	---	*Administrative*	Update Protocol Version to 5.0 and update version date to 18 JUN 2021	Amendment version and date
2.3.2 Known Potential Benefits	15	*Revision*	Language related to all heath care providers and their patients receiving their CAPTURE Tool scores and spirometry results at the conclusion of the study has been removed.	Only health care providers randomized to the CAPTURE education arm (arm 1), will receive their patient participant's CAPTURE Tool scores and peak flow results. Return of the spirometry research testing results was not covered in the patient participant's informed consent
11.1.2 Practice Based Research Networks (PBRNs)	48	*Revision*	Circuit Clinical in Buffalo, New York was added as a 7th participating PBRN.	An additional PBRN was added to help increase recruitment after the lengthy COVID-19 related enrollment delay
Multiple Sections	---	*Revision*	Reference to number of PBRNs has been updated from 6 to 7 throughout the protocol.	An additional PBRN was added to help increase recruitment after the lengthy COVID-19 related enrollment delay

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STATEMENT OF COMPLIANCE

This study will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CAO	Chronic Airflow Obstruction
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
ECOPD	Exacerbation of Chronic Obstructive Pulmonary Disease
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FEV1	Forced Expiratory Volume in 1 second
FFR	Federal Financial Report
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practice
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act

IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PBRN	Practice-Based Research Network
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
RE-AIM	Reach, Effectiveness, Adoption, Implementation, Maintenance
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States
USPSTF	United States Preventive Services Task Force

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	The CAPTURE Study: Validating a unique Chronic Obstructive Pulmonary Disease (COPD) case finding tool in primary care
Study Description:	**Aims 1 and 3**. A prospective, multicenter study including a cross-sectional validation to define sensitivity and specificity of CAPTURE and its impact on clinical care across a broad range of primary care settings in a cluster randomized controlled clinical trial. The CAPTURE tool consists of a 5-item self-administered questionnaire and peak expiratory flow (PEF) measurement, designed to identify undiagnosed patients with Chronic Obstructive Pulmonary Disease (COPD). **Aim 2.** This study delivers a qualitative assessment of clinical practice acceptance of and implementation strategy for CAPTURE case finding within 10 varied primary care practices across 5 US PBRN regions. We evaluate primary care practice attitudes, beliefs and recommendations about CAPTURE's potential to feasibly integrate into clinical practice patterns, workflow and quality improvement paradigm planning in a variety of primary care clinical settings.
Definitions:	**CAPTURE+ =** Participants with • CAPTURE score $\geq$ 5, or • CAPTURE score of 2, 3, or 4 with a low PEF, defined as <350 L/min for males and <250 L/min for females **CAPTURE-** = Participants with CAPTURE score < 2 or scores 2-4 with normal PEF, defined as >350 L/min for males and > 250 L/min for females **Spirometrically defined COPD =** Participants with abnormal spirometry, defined as post-bronchodilator FEV_1/FVC <0.7. If a participant is unable to complete a post-bronchodilator spirometry (refusal, technical error on the part of coordinator, etc.), and the pre-bronchodilator FEV1/FVC is less than 0.65, the participant will be considered to have COPD for the purpose of follow-up in this study. **Clinically significant COPD =** Participants with abnormal spirometry, defined as post-bronchodilator FEV_1/FVC <0.7, plus one of the following: • FEV_1 < 60% predicted, or • > 1 exacerbation-like event within the past 12 months. **Mild COPD =** Participants with abnormal spirometry, defined as post-bronchodilator FEV_1/FVC<0.7 plus both of the following: • $FEV_1 \geq$ 60% and • No prior history of ECOPD
Objectives:	**Aims 1 and 3 Primary Objectives:** • **Aim 1 -** Define the sensitivity and specificity of CAPTURE for identifying previously undiagnosed patients with clinically significant COPD in a broad range of primary care settings.

	• **Aim 3 –** Define the impact of CAPTURE information provided to clinicians in identifying and managing patients with respiratory symptoms (CAPTURE+) across a broad range of primary care settings. **Aim 2 Primary Objective:** Explore clinical practice implementation approaches to and acceptance of CAPTURE case finding for clinically significant COPD in a range of primary care practices. **Aims 1 and 3 Secondary Objectives:** • **Aim 1 –** • Define the sensitivity and specificity of CAPTURE for patients with COPD across a broad range of racial and ethnic groups in a range of primary care settings. • Determine positive and negative predictive values (PPV and NPV) in different practice settings. • Verify the optimal use (cutoff threshold) of the CAPTURE tool in combination with PEF measurements for identifying undiagnosed COPD. • Determine patient and site characteristics that, with the CAPTURE assessment, will best identify persons with undiagnosed COPD. • Determine whether CAPTURE is useful in identifying other definitions of undiagnosed COPD including: 1) spirometry-defined COPD, and 2) mild COPD • Determine the potential impact of SARS CoV-2 infection on the above operating characteristics of the CAPTURE approach. • **Aim 3 -** • Define the impact of CAPTURE clinician education, and patient-level CAPTURE information to clinicians (“CAPTURE education”) on selected additional therapeutic interventions in previously undiagnosed patients with clinically significant COPD. • Assess impact of CAPTURE education on clinician interventions specific to smokers. • Determine the impact of CAPTURE education on patient symptoms, exacerbations, hospitalizations, and mortality. • Determine the impact of CAPTURE education when COPD is defined spirometrically. • Determine the potential impact of SARS CoV-2 infection on clinical actions taken in response to CAPTURE screening. **Aim 2 Secondary Objectives:** • Qualitatively assess primary care clinical staff COPD practice behavior – including COPD screening and diagnostic perceptions, beliefs and knowledge – that will inform strategies to improve CAPTURE RE-AIM (reach, impact, adoption, implementation and maintenance of use) characteristics.

	• Qualitatively assess primary care patient opinion of CAPTURE COPD case finding that will inform strategies to improve CAPTURE RE-AIM (reach, impact, adoption, implementation and maintenance of use) characteristics. • Determine the potential impact of SARS CoV-2 infection on the application of the CAPTURE approach.
Endpoints:	**Aims 1 and 3 Primary Endpoints:** • Aim 1 – o Sensitivity and specificity of CAPTURE to identify previously undiagnosed patients with clinically significant COPD at baseline. • Aim 3 – o Proportion of CAPTURE+ participants who meet at least one of the following within 12 months of study baseline (composite endpoint): 1) referral for or completion of clinical spirometry testing, 2) new diagnosis of COPD, 3) newly prescribed respiratory medication (long acting bronchodilator or anti-inflammatory for respiratory condition), or 4) referral to a specialist for respiratory evaluation/treatment **Aim 2 Primary Endpoints:** • Primary care clinician recommendations that inform CAPTURE RE-AIM strategies at both provider and clinical support levels of primary care practice. • Primary clinician recommendations that inform CAPTURE-associated COPD education models for primary care clinicians. • Primary care clinician recommendations that inform CAPTURE-associated COPD clinical quality improvement designs across a variety of primary care practice types. **Aims 1 and 3 Secondary Endpoints:** • Aim 1 – o Sensitivity and specificity of CAPTURE to identify previously undiagnosed patients with COPD across sex, ethnic groups, urban vs rural location, and educational level. o Positive and negative predictive values (PPV and NPV) in different practice settings. o Areas under the receiving operator characteristic curve (AUC) for various cutpoints of CAPTURE and PEF_1 measurements to determine the best cutpoint for COPD+ screen. o AUC to identify the combination of patient/site characteristics which best discriminates those with clinically significant COPD. o All primary and secondary endpoints as applied to 1) spirometry-defined COPD and 2) mild COPD • Aim 3 – o Proportion of CAPTURE+ patients who meet the components of the composite endpoint. o Proportion of patients with clinically significant COPD who meet the composite endpoint.

	○ In participants with clinically significant COPD who are current smokers, the incidence of physician referral to a formal smoking cessation program, prescribed smoking cessation medication, and referral to pulmonary rehabilitation program. ○ In participants with clinically significant COPD, change in CAT score, and proportion of patients who experience exacerbations, hospitalizations, or mortality. ○ All of the above endpoints for Aim 3, with the patient population defined as those who have COPD defined spirometrically. **Aim 2 Secondary Endpoints:** • Existing COPD screening and diagnostic and case finding processes within a variety of primary care practices. • Primary care practice belief about capacity to change from existing COPD screening and diagnostic assessment strategies. • Practice-specific COPD screening and diagnostic continuing education preference.
Study Population:	**Aims 1 and 3.** Adults 45-80 years old without a prior diagnosis of COPD (total N = 5000) **Aim 2.** - 10 primary care practices: 2 practices per PBRN with up to 15 clinical staff participants per practice; clinician N = up to 150 (up to 30 clinician participants per PBRN). - Aim 1 patient opinion survey population; patient N = 200 (40 patients from each PBRN; adults 45-80 years old, without a prior diagnosis of COPD). - Total N = up to 350
Phase:	N/A
Description of Sites/Facilities Enrolling Participants:	**Aims 1 and 3.** Enrollment will occur in approximately 100 primary care practices affiliated with 7 primary care based practice networks (PBRN) across the United States who exhibit a broad range of gender, ethnic, racial, socioeconomic, and regional diversity. **Aim 2.** • Two primary care practices chosen by each of the same 5 PBRN co-investigator teams make up the 10 aim 2 practices from which clinician participants are enrolled. These 10 practices are separate from the 100 chosen practices in aims 1 and 3. • Patient participants are a sub-sample of those participants enrolled in aims 1 and 3.
Description of Study Intervention:	**Aims 1 and 3.** Primary care practices will be randomized to either receive basic COPD education and patient-level CAPTURE information with CAPTURE education (initially basic then later enhanced based on data collected in Aim 2) versus COPD education only. **Aim 2.** Participating primary care clinicians from 10 varied practices are surveyed at three different time points and participate in two focus groups qualitatively assessing CAPTURE implementation strategy and COPD case

	finding approaches in primary care. Participating patients complete one 10-minute written opinion survey about CAPTURE.
Study Duration:	**Aim 1 and 3.** 4 years **Aim 2.** 2 years
Participant Duration:	**Aims 1 and 3.** Up to 12 months **Aim 2.** • Primary care practice clinicians: questionnaires and focus groups (total 3 hours/participant) over 16 months. • Primary care patients: one 10-minute questionnaire/participant over 14 months.

1.2 SCHEMA

FIGURE 1. OVERALL STRUCTURE OF AIMS

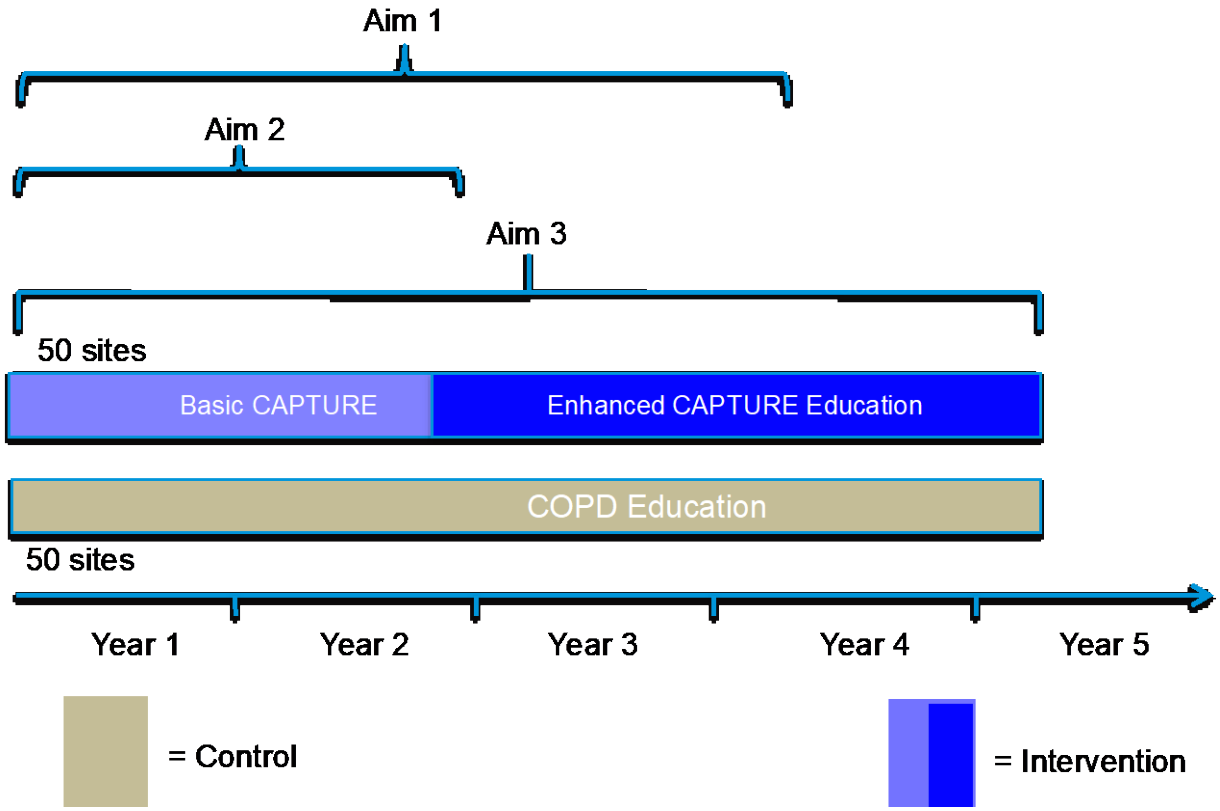

FIGURE 2. STRUCTURE OF AIM 2

CAPTURE COPD Study Time Commitment

CAPTURE COPD: The Primary Care Practice Expert Panel Study will take place in 10 practices in 5 regions in the US. Central to the success of CAPTURE COPD is the role of clinical staff expertise in providing feedback, information and suggestions about clinical workflow for COPD diagnosis.

Introductory Phone Call	Brief phone call with CAPTURE research team to review the CAPTURE COPD: The Primary Care Practice Expert Panel aim. Discussion includes: review of the research content, timeline and scheduling of the half-day site visit for February/March 2018	Month 1
In Person Baseline Assessment/ Site Visit:	SITE VISIT INCLUDES: • Walk through of practice and staff introduction: 2 clinical staff with CAPTURE team [60 minutes] • Clinic flow observation and mapping [1/2 day] • Post clinic flow observation Q&A: 2 clinical staff and CAPTURE research team [30 minutes] • CAPTURE COPD information distribution and consent process	Month 2-3
Online Questionnaire: 1st of three	Online/written questionnaire at baseline [20 minutes]	
State-of-the-Art COPD Web-based Continuing Education	Three modules encouraged; All modules optional 20 minutes/module; per Aim 3 description	Month 3-7
Practice Expert Panel Focus Group #1	Prescribers and Non-Prescribers (2 different days) 60 minute focus group	Month 6-10
Online Questionnaire: 2nd of three	Online/written questionnaire at 6 months [20 minutes]	
Online Questionnaire: 3rd of three	Online/written questionnaire at 12 months [20 minutes]	Month 11-14
Practice Expert Panel Focus Group #2	Pooled prescribers and Non-Prescriber Clinical Staff [60 minutes]	Month 14-16

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1.3 SCHEDULE OF ACTIVITIES (SOA)

Table 1: Schedule of Activities (Aims 1 and 3)

	Pre-Visit Contact[1]	Baseline	12 Months[3]
Contact (C)/ Visit (V)/Medical Record Review (MRR)	**C1**	**V1**	**C2/MRR[5]**
Time point, days (Visit window)	**Prior to outpatient visit (≤-1)**	**Within 30 days of pre-visit contact**	**365 ±30 (C2)**
Contact patient re: interest in study visit[1]	X		
Informed consent		X	
Demographics		X	
Medical history (Co-morbidities)[2]		X	
Vaccination status		X	X
CAPTURE 5-item questionnaire		X	X
CAPTURE item additional questionnaire		X	
Peak Expiratory Flow (PEF)		X	
Height and weight		X	
Respiratory medications review		X	X
Spirometry[4]		X*	
Respiratory symptoms, exacerbation assessment		X	X
Smoking exposure history		X	
Smoking cessation review[6]			X
COPD Assessment Test (CAT)		X	X
COVID-19 Questionnaire		X	X
Adverse Events		X	
Medical record review Additional COVID-19 items			X X

1. Optional per site recruitment preferences
2. Comorbidities including cardiovascular, respiratory and malignant disorders
3. Recorded for a subset of participants who meet any of the following criteria: 1) CAPTURE+ subjects defined as CAPTURE Score ≥ 5 or CAPTURE score of 2, 3, or 4 with a low PEF, defined as <350 L/min for males and <250 L/min for females 2) abnormal spirometry defined as $FEV_1/FVC < 0.70$ or $FEV_1 < 80\%$ predicted at baseline; and, 3) a random sample of approximately 5% of those who do not meet criteria 1 and 2. For participants meeting criteria 1 and 2 who cannot or choose not to complete the 12-month assessment, medical record review will still be completed. For participants meeting criteria 1 and 2 who

change medical practices and medical record review cannot be completed, patients will be contacted for completion of patient reported data. For participants meeting criterion 3 where all of the protocol-specified 12-month assessments cannot be made, another participant will be selected at random to replace this participant.

4. Pre-bronchodilator spirometry will be done for all participants. Post-bronchodilator spirometry will be performed for participants with abnormal spirometry ($FEV_1/FVC < 0.70$ or $FEV_1 < 80\%$ predicted) *If the participant has taken a bronchodilator within a 2-hour window of spirometry the spirometry will be considered post-bronchodilator and a pre-bronchodilator spirometry will not be done.
5. The 12-month assessment consists of patient reported data, collected by the COPD Foundation, and medical record review completed by site coordinators.
6. This will be completed in those that are smoking at V1.

2 INTRODUCTION

2.1 STUDY RATIONALE

Undiagnosed COPD is a leading cause of morbidity and mortality. Spirometry, the 'gold standard' for diagnosis, is not recommended for screening in asymptomatic individuals or untargeted case finding and remains widely underutilized in primary care settings. Targeted case finding approaches have been strongly advocated but currently available approaches generally identify patients across the spectrum of mild to severe disease without reference to potential therapeutic benefit or exacerbation risk, thereby limiting clinical impact and acceptance in primary care. There is an urgent need to develop and implement simple case finding approaches that can identify patients with clinically significant COPD in primary care settings.

Through a multi-stage, iterative process we developed a simple case finding tool using five questions combined with selective peak expiratory flow **(PEF)** measurement that identifies individuals with 1) an $FEV_1 < 60\%$ predicted and/or 2) at risk for ECOPD. We call this tool CAPTURE (**C**OPD **A**ssessment in **P**rimary Care **T**o Identify **U**ndiagnosed **R**espiratory Disease and **E**xacerbation Risk)(1). As clinical trials have demonstrated benefit and therapeutic guidelines recommend therapy for these individuals we have labeled these patients as suffering from 'clinically significant' COPD. The long-term goal of this project is to identify these patients so that they can be treated and result in improved health status, reduced exacerbations, and decreased morbidity.

The *overall objectives* of Aims 1 and 3 of this project are to 1) validate the sensitivity, specificity, and predictive value of CAPTURE to identify undiagnosed, clinically significant COPD patients in a diverse primary care population; and explore whether identifying these patients results in improved COPD specific care and health status. Our *principal hypothesis* is that CAPTURE can effectively and efficiently identify primary care patients with undiagnosed, clinically significant COPD. We objectively test our principal hypothesis by completing to two separate and linked aims:

Aim 1 – Determine the sensitivity and specificity of CAPTURE in identifying clinically significant COPD patients in a broad range of primary care outpatient practices.

Working hypothesis - A simple case finding methodology using a five-item questionnaire with selective PEF measurement will identify undiagnosed patients with clinically significant COPD.

We will conduct a 5,000 participant cohort study in 100 primary care practices affiliated with five primary care based research networks **(PBRN)** that provide access to previously undiagnosed patients with clinically significant COPD who exhibit gender, ethnic, racial, socioeconomic and regional diversity.

Aim 3 – Define the impact of CAPTURE screening in a broad range of primary care outpatient practices and evaluate practice and patient characteristics that are associated with care implementation and clinical outcomes for patients with respiratory symptoms (CAPTURE+).

Working hypothesis – Provision of patient specific CAPTURE data to practicing clinicians will result in improved management of patients with respiratory symptoms (CAPTURE+).

We will provide basic COPD education and patient level CAPTURE information and education to site clinicians at 50 of the sites and prospectively follow selective, pre-defined subgroups of patients to define relevant outcomes. Care at the other 50 clinical sites will follow standard of care with basic COPD education to clinicians.

Assessing the potential clinical impact of a novel COPD case finding strategy includes confirmation of validity in a diverse primary care patient population and a quantitative research evaluation of its impact on clinical decision-making and COPD patient outcomes, as found in aims 1 and 3 above. Equally important is exploration through validated implementation methods that the newly designed CAPTURE tool, even if valid and impactful, can provide real-world utility within a variety of primary care practice settings. While we find no evidence in previous COPD screening studies of such detailed appraisal, ascertaining the feasibility of clinical testing is a vital component of assuring that new approaches address potential clinical practice need, capacity, knowledge and diagnostic gaps. As much as possible, clinical respiratory innovations should align with busy workflow at all practice staff levels to more effectively identify primary care patients with undiagnosed, clinically significant COPD. The SARS-CoV-2 pandemic may potentially alter the approach to COPD Case Finding in the primary care community; the protocol has been adapted to investigate this possibility. Similarly, the potential of SARS-CoV-2 infection and the COVID-19 clinical syndrome to impact respiratory symptoms in primary care patients will also be explored.

To maximize success of the CAPTURE adoption, education and implementation in this study and in future work, Aim 2 is introduced to assess practice experience, need and preference that can inform clinical COPD case finding and education in primary care settings:

Aim 2 – Explore clinical practice implementation approaches to and acceptance of CAPTURE case finding for clinically significant COPD in a range of primary care practices.

The *overall objective* of this aim is to qualitatively explore primary care clinical practice acceptance of COPD case finding implementation and define education and feasibility strategies to enhance adoption in primary care practice. This assessment includes understanding clinician and clinical staff COPD practice and perceptions in addition to the feasibility of case finding integration into existent clinical work patterns. To attain this objective, we address one *working hypothesis* – a COPD case finding methodology using a validated one-page, five-item questionnaire with selective PEF measurement (CAPTURE) can be incorporated into the clinical practice patterns, clinical workflow, communication and practice-based quality improvement paradigms in a variety of primary care clinical settings. The *rationale* for this objective reflects the importance of establishing if an innovative approach to COPD case finding (CAPTURE) is considered a pragmatic tool with potential utility for primary care clinicians within real-world clinical practice settings.

With the completion of this aim we anticipate confirming that future validated approaches to COPD case finding can be adopted in a broad variety of clinical care settings thereby providing further impetus for the rigorous evaluation of a) case finding guided patient outcomes as part of routine primary care clinical practice; b) case finding use in a range of primary care health professional COPD-related education approaches, clinical quality improvement models and diagnostic guidelines; and c) the capacity of clinical case finding with informed follow-up to enhance future COPD clinical care therapeutic paradigms used in primary care practice.

2.2 BACKGROUND

Aims 1 and 3.

COPD remains a major cause of morbidity and mortality. COPD results in substantial morbidity and mortality worldwide.(2-4) Globally, the prevalence of COPD and years lived with disability increased from 1990 to 2013.(5) This is particularly evident in older individuals.(6) These well-designed population based studies confirm the growing impact of COPD.

COPD is frequently undiagnosed. We recently documented that only 28% of participants with chronic airway obstruction **(CAO)** had physician diagnosed disease.(7) Importantly, an FEV_1 <50% predicted was noted in 10% of those with undiagnosed CAO; this is similar to other cohorts or population based surveys.(8-11) There is consistency in these well-conducted studies that confirm most COPD patients are undiagnosed.

Spirometry is underutilized. The U.S. Preventive Services Task Force **(USPSTF)** recently recommended against the use of spirometry for routine, general population or practice-based screening in asymptomatic individuals.(12) An editorial by the PI of this application highlighted the limitations of this conclusion.(13) Within primary care spirometry is often viewed as time consuming and difficult to implement and interpret.(14) As such, it is not routinely used.(15-19) Even the availability of less expensive and easily used spirometers(20) has not resulted in increased utilization.(21, 22)

Undiagnosed COPD is associated with a negative clinical impact. In a robust, population based study we confirmed that undiagnosed patients experienced impaired health status and a higher risk for all-cause mortality compared to those without CAO; this was particularly evident with more severe CAO.(7) Others have confirmed increased mortality,(23) health status impairment,(24) exacerbation-like respiratory events,(11) and increased health care costs.(25, 26) As such, there are consistent data suggesting that undiagnosed COPD patients experience negative clinical events and impaired health status.

Therapeutic interventions improve COPD clinical outcomes. Well designed, randomized controlled trials confirm that COPD therapy is effective, particularly in patients with an FEV_1 < 60% predicted who are symptomatic or at risk for ECOPD.(27, 28) Despite limited data, some have suggested that earlier detection of patients with previously undiagnosed, yet clinically significant COPD, in primary care settings could improve short- and long-term patient outcomes and may be cost-effective. (29, 30)

COPD case finding approaches to date have generally been methodologically limited. Several COPD case finding tools have been created based on existing epidemiologic literature or expert opinion.(31, 32) This includes tools created by investigators in this study.(33, 34) In general, current approaches were designed to identify COPD patients without reference to disease severity or ECOPD risk, resulting in the identification of a high proportion of patients with mild or minimally symptomatic disease.(21, 33-39) Several studies have tested the accuracy of handheld flow meters for case identification with varying sensitivity and specificity.(40) Although informative in terms of CAO, PEF meters have been unable to systematically identify patients at risk of ECOPD. We tested a three-staged approach (risk-factor

questionnaire, PEF, and spirometry) for identifying moderate to severe COPD (FEV_1<60% predicted) in a convenience sample of the general population.(41) This study was limited by the nature of the population screened and the screening questionnaire used but supported the concept that PEF can facilitate COPD case finding.

A systematic analysis of existing databases provides insight into the best variables for COPD Case Identification. To identify potential items that could be useful in the identification of undiagnosed COPD we interrogated three robust datasets of populations in which the investigators on this application had major roles [COPD Foundation Peak Flow Study Cohort (n=5761); Burden of Obstructive Lung Disease Kentucky site (n=508); and COPDGene® (n=10,214)].(42) We utilized the machine learning statistical method of random forests to identify and validate variables most important in identifying patients with clinically significant COPD. COPD case finding candidate content included items reflecting exposure, personal and family history, respiratory symptoms, recent health history, activity limitation and demographics.

A comprehensive, qualitative study identified key constructs for identifying recently diagnosed patients with clinically significant COPD. We completed a two phase study that included focus groups followed by cognitive interviews to refine the key constructs for identifying patients with clinically significant COPD.(43) Fifty participants were recruited including those with mild airflow obstruction, diagnosed within the previous six months and without previous ECOPD; those diagnosed within the previous six months and with a history of at least one ECOPD within the prior year; those with 2-3 risk factors for COPD but without CAO; and those with $\geq$ 4 risk factors for COPD but without CAO. Using a content analysis approach, key themes and constructs were identified and integrated with the content of the previous literature review and data mining. We identified 44 candidate items that resonated with patients and provided important insights into a case finding instrument.

A five-item questionnaire exhibits excellent operating characteristics to identify clinically significant COPD patients. We completed a prospective, multi-site, case-control study of four groups: cases with clinically significant COPD – COPD with > 1 ECOPD in the previous year (n=97) and COPD with no ECOPD but an FEV_1 < 60% predicted (n=89); controls – no known COPD (n=87) and COPD with an FEV_1 > 60% predicted and no ECOPD in the previous year (n=74). Using random forest analyses the 44 candidate items were reduced to 34-item, 21-item, 8-item and two different five-item sets. Through-out the item reduction process, the item sets maintained good performance, consistently misclassifying fewer than 27% of cases and controls, and with sensitivity greater than 80% and specificity greater than 70%. A five-item questionnaire exhibited good operating characteristics for separating COPD cases from controls. These characteristics were even better when separating COPD from controls without COPD.

Selective PEF measurement enhances the operating characteristics of a COPD case finding strategy. In the above case control study PEF was measured using a mechanical PEF meter with disposable mouthpieces. To optimize sensitivity and specificity, the following cut-off scores were selected, based on our data, for identifying cases of clinically significant COPD using PEF alone: males: <350 L/min; females: <250 L/min. The best method for predicting cases was a combination of the questionnaire and PEF **(CAPTURE)**, where PEF is used only for mid-range scores. Under this scoring scenario, patients with scores of 0 or 1 are not considered at risk of clinically significant COPD; they would not require further evaluation. Those with a score of 5 or 6 are considered to be at high risk of clinically significant COPD and should be referred directly for further evaluation, including clinical spirometry. Patients scoring in the middle range (2 to 4) would undergo PEF testing, applying the 350/250 interpretation thresholds. In our sample, 52% of the participants required PEF to determine if spirometry was indicated. The other 48% needed only the five-item questionnaire. This approach provided 90% sensitivity, 93% specificity and an overall error rate of 9%.

CAPTURE exhibits similar operating characteristics in a Spanish speaking population. To broaden our target population, the five-item questionnaire was methodically translated to Spanish using previously validated, rigorous methods(44) to yield an instrument that is equivalent to the English questionnaire and linguistically and culturally applicable to persons of diverse Spanish-speaking backgrounds residing in the US. In a subset of Spanish speaking participants CAPTURE exhibited excellent sensitivity (88%), specificity (92%) and overall error rate (10%) for identifying patients with clinically significant COPD.

Aim 2.

Consistent with national criteria for preventive and chronic disease care quality, feasibility science is designed to assist clinical and health education evaluators plan for assessing and evaluating specific implementation factors essential to the success of new diagnostic, therapeutic and programmatic options in real-world clinical practice. This aim's analysis of primary care clinical practice COPD case finding feasibility includes an initial evaluation of existing COPD diagnostic and case finding processes within the practices, assessment of practices' capacity to change from existing respiratory symptom assessment strategies and an understanding of practice-specific learning preferences associated with new diagnostics in chronic disease diagnosis and management. The aim addresses through the RE-AIM feasibility approach how a new tool might a) identify target populations (Reach); b) appraise optimal targeted respiratory history and symptoms consistent with clinically significant COPD (Effectiveness or Impact); c) integrate into practice workflow (Adoption); d) deliver changes and improvements to COPD care within the scope of real-world clinical practice (Implementation); and e) persist in use and quality over time (Maintenance) (45-53).

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Potential risks associated with Aims 1 and 3 of this study are outlined below.

Spirometry: Participants may become short of breath. Syncope, light-headedness and fainting may develop during this test. These are uncommon.

Albuterol: Tremulousness, feeling of a strong, rapid heartbeat, and palpitations can occur with inhaled albuterol. A targeted safety questionnaire will be administered to all participants prior to albuterol to exclude those with a previous adverse event with the medication. Note that albuterol is only administered to those with abnormal spirometry on the baseline spirometry assessment (defined as $FEV_1/FVC < 0.70$ or $FEV_1 < 80\%$ predicted).

Peak Expiratory Flow: Participants may become short of breath. Syncope, light-headedness and fainting may develop during this test. These are uncommon.

Other non-physical risks of the study include those from economic loss from participation in the study; this will be minimized by scheduling tests and evaluations in a timely manner in the fewest number of visits possible. Patient and physician participants will be provided a modest fee to cover their time to participate in the study.

We anticipate few adverse events due to the non-invasive nature of the study procedures and the rarity of such events encountered during the initial visits and longitudinal follow-up. Medical care will be available at each Clinical Center to treat participants who develop adverse events during in-person study visits.

Potential risks associated with Aim 2 of this study include:

No more than minimal risk exists for participants within aim 2.

Confidentiality of information and identification are the risks associated with this project. Based on previous research and the protocols that have been developed, we believe that the likelihood of these risks to the participants would be minimal, i.e. "rare".

Potential risks associated with the study (all Aims) include:

Loss of confidentiality of study data: This is unlikely since data collected will be stored in locked file cabinets in locked rooms at the Clinical Centers. In addition, only participant IDs are used to identify participants in the secure server at the Data Coordinating Center.

Poor quality data: If the data collected are of poor quality such that it is not useable to achieve study aims, participants will have unnecessarily been exposed to other risks in the study.

2.3.2 KNOWN POTENTIAL BENEFITS

For Aims 1 and 3 of this study, participants could receive direct benefit as a result of their participation in this research. Current state-of-the-art COPD education is offered to all clinicians at participating PBRN sites (see aim 3 protocol) that could result in improved care for their COPD patients. Health care providers at practices randomized to the CAPTURE education arm (arm 1), will receive their participant's CAPTURE Tool scores and peak flow results. This may result in further diagnostic testing leading to a diagnosis of COPD or other respiratory disorder.

Known potential benefits for each participating clinical staff include critical review their clinical respiratory practice. In general, aim 2 offers the ability to assess and address CAPTURE-specific primary care practice feasibility issues which could augment or hamper clinical communication or implementation of COPD case-finding in real-world primary care clinical practice.

Potential benefits to society include improved understanding of how best to identify individuals with COPD in the primary care setting. This could ultimately lead to better treatments and lower morbidity and mortality for patients with COPD.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The demonstrated and potential future benefits to improved understanding of COPD case finding outweigh the minimal risks of the procedures performed.

Increased understanding of how best to diagnose individuals at risk for COPD in the primary care population has the potential to benefit both patients with COPD and society at large. The risk to individuals associated with this study protocol is small and the knowledge to be gained is substantial.

3 OBJECTIVES AND ENDPOINTS

Aims 1 and 3.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Aim 1: Define the sensitivity and specificity of CAPTURE for identifying previously undiagnosed patients with *clinically significant COPD* in a broad range of primary care settings	Sensitivity and specificity of CAPTURE to identify previously undiagnosed patients with clinically significant COPD at baseline.	Standard methodology for COPD diagnosis will be used (1).
Aim 3: Define the impact of CAPTURE information provided to clinicians in identifying and managing patients with respiratory symptoms (*CAPTURE+*) across a broad range of primary care settings.	Proportion of CAPTURE+ participants who meet at least one of the following within 12 months of study baseline (composite endpoint): 1) referral for or completion of clinical spirometry testing, 2) new diagnosis of COPD, 3) newly prescribed respiratory medication (long acting bronchodilator or anti-inflammatory for respiratory condition), or 4) referral to a specialist for respiratory evaluation/treatment.	The composite endpoint is clinically relevant and consistent with published data (45). This will test the impact of CAPTURE on clinician behavior.
Secondary		
Aim 1: Define the sensitivity and specificity of CAPTURE for patients with COPD across a broad range of racial and ethnic subgroups in a range of primary care settings	Sensitivity and specificity of CAPTURE to identify previously undiagnosed patients with COPD across sex, ethnic groups, urban vs rural location, and educational status.	Patient characteristics will be used to assess the robustness of CAPTURE.
Aim 1: Determine positive and negative predictive values (PPV and NPV) in different practice settings.	Positive and negative predictive values (PPV and NPV) in different practice settings.	PPV and NPV will be used to assess the robustness and usefulness of CAPTURE in various settings.
Aim 1: Verify the optimal use (cutoff threshold) of the CAPTURE tool in combination with FEV_1 measurements for identifying undiagnosed COPD.	AUC for various cutpoints of CAPTURE and PEF measurements to determine the best cutpoint for clinically significant COPD screen.	The best discrimination for CAPTURE combined with FEV_1 will indicate the optimal usage of the tool.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Aim 1: Determine patient and site characteristics that, with the CAPTURE assessment, will best identify persons with undiagnosed COPD.	AUC to identify the combination of patient/site characteristics which best discriminates those with clinically significant COPD.	The best discrimination will determine which site and patient characteristics best predicted undiagnosed COPD in combination with the CAPTURE tool.
Aim 1: Determine whether CAPTURE is useful in identifying other definitions of undiagnosed COPD: 1) spirometry-defined COPD, and 2) mild COPD	All primary and secondary endpoints as applied to 1) spirometry-defined COPD and 2) mild COPD	This will determine the robustness of the CAPTURE tool.
Aim 3: Define the impact of CAPTURE clinician education, and patient-level CAPTURE information to clinicians ("CAPTURE education") on selected additional therapeutic interventions in previously undiagnosed patients with *clinically significant COPD.*	Proportion of CAPTURE+ participants who meet the components of the composite endpoint.	Each endpoint is clinically relevant and consistent with published data. (45) This will test the impact of CAPTURE on clinician behavior.
Aim 3: Assess impact of CAPTURE education on clinician interventions specific to smokers.	In participants with clinically significant COPD who are current smokers, the incidence of physician referral to a formal smoking cessation program, prescribed smoking cessation medication, and referral to pulmonary rehabilitation program.	Certain outcomes are specific to only smokers and should be assessed.
Aim 3: Determine the impact of CAPTURE education on patient symptoms, exacerbations, hospitalizations, and mortality.	In participants with clinically significant COPD, change in CAT score, and proportion of patients who experience exacerbations, hospitalizations, or mortality.	This endpoint is important for quality of life, and long-term patient outlook.
Aim 3: Determine the impact of CAPTURE education when COPD is defined spirometrically.	All of the above endpoints for Aim 3, with the patient population defined as those who have COPD defined spirometrically.	This will determine the robustness of the CAPTURE tool

Aim 2.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Explore clinical practice implementation approaches to and acceptance of CAPTURE case finding for clinically significant COPD in a range of primary care practices.	Primary care clinician recommendations that inform CAPTURE RE-AIM strategies at both provider and clinical support levels of primary care practice. Primary clinician recommendations that inform CAPTURE-associated COPD education models for primary care clinicians. Primary care clinician recommendations that inform CAPTURE-associated COPD clinical quality improvement designs across a variety of primary care practice types.	Clinical improvement models that introduce new testing must investigate practice opinion and behavior and incorporate clinician recommendation.
Secondary		
Qualitatively assess primary care clinical staff COPD practice behavior – including COPD screening and diagnostic perceptions, beliefs and knowledge – that will inform strategies to improve CAPTURE RE-AIM (reach, impact, adoption, implementation and maintenance of use) characteristics.	Existing COPD screening and diagnostic and case-finding processes within a variety of primary care practices. Primary care practice beliefs about capacity to change from existing COPD screening and diagnostic assessment strategies. Practice-specific COPD screening and diagnostic continuing education preference.	Awareness of existing clinician knowledge and behavior can influence workflow implementation and overall effectiveness of new clinical tools.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Qualitatively assess primary care patient opinion of CAPTURE COPD case finding that will inform strategies to improve CAPTURE RE-AIM (reach, impact, adoption, implementation and maintenance of use) characteristics.	CAPTURE opinion survey ascertaining participant comprehension of CAPTURE instructions and testing and ease of completion.	Patient satisfaction, understanding and ease of test completion affects staff implementation and workflow decision. Participant opinion survey results will seed CAPTURE implementation planning practice staff focus groups.

4 STUDY DESIGN

4.1 OVERALL DESIGN

A prospective, multicenter study that includes three key aims: 1) cross-sectional validation to define sensitivity and specificity of CAPTURE; 2) *qualitative* research exploration engaging clinical staff at all levels from primary care practices serving US patient populations of differing gender, racial, ethnic, urban/rural and socio-economic blends, and 3) explore the impact of CAPTURE on clinical care and patient outcomes across a broad range of primary care settings in a cluster randomized controlled clinical trial. The CAPTURE tool consists of a 5-item self-administered questionnaire and selected use of peak expiratory flow (PEF) measurement, designed to identify clinically significant Chronic Obstructive Pulmonary Disease (COPD).

For Aim 1, approximately 5,000 patients will be recruited at the time of their regularly-scheduled appointment across 100 participating primary care clinics associated with practice-based research networks (PBRNs). Eligible participants will undergo a baseline visit during which the CAPTURE tool and spirometry will be obtained, as well as PEF and other participant characteristics.

For Aim 2, approximately 150 clinicians from 10 participating primary care practices across 5 US PBRNs will undergo detailed implementation investigation of the CAPTURE case finding model for clinically significant COPD. In addition, 200 primary care patients recruited as part of Aim 1 will complete a 10-minute written CAPTURE opinion survey.

To address Aim 3, participating primary care practices will be randomized in a 1:1 fashion to one of the following interventions:

- Arm 1: Practice clinicians will receive basic COPD education, and patient-level CAPTURE information with CAPTURE interpretation education (CAPTURE+ COPD education). As the second aim addresses the optimal format for delivering practice CAPTURE education this will be incorporated at the sites randomized to this arm (see Enhanced CAPTURE education in Figure 1).
- Arm 2: Practice clinicians will receive basic COPD education only (COPD education).

Basic COPD and CAPTURE specific education will use an interactive, web-based education program which will be provided to all practice personnel, including physicians, nurse practitioners, physician assistants, nurses, medical assistants, clerical staff and administrative staff. Practitioners at sites

randomized to the CAPTURE+COPD education intervention will receive the CAPTURE score from the central study coordinators soon after the baseline assessments have been completed.

Addressing Aims 1 and 3 will include a baseline visit for all participants and for Aim 3 longitudinal follow-up over 12 months for a predefined cohort of participants. Determination of the participants included in the longitudinal follow-up cohorts will be made after the baseline visit.

Baseline Data

Practices and/or study staff will pre-screen patients according to local guidelines to identify potential participants based on the following criteria: no prior COPD diagnoses, between 45 and 80 years old, and speak and read either English or Spanish. The timing of the pre-screening and the method to approach these patients for participation in the study (e.g., at the next outpatient visit, via telephone) will be flexible, depending upon site recruitment preferences. Patients who are eligible based on the pre-screening questions and agree to participate in the study will sign informed consent. After signing the consent, they will complete the CAPTURE questionnaire, PEF testing, spirometry testing, other respiratory questionnaires, and provide past medical history and demographic information. Local/PBRN study coordinators for each of the 7 PBRNs will perform the study procedures and record baseline information into the electronic data capture (EDC) system.

The EDC system will calculate a CAPTURE score for each participant, based on his/her CAPTURE questionnaire answers and PEF measurement. A binary score (positive or negative CAPTURE) will be emailed to the central study coordinator only for participants randomized to CAPTURE+COPD education intervention practices. The coordinator will communicate this information to these practitioners. Practitioners at sites randomized to the COPD education only intervention will be blinded to CAPTURE scores. Practitioners in both intervention arms will be blinded to research spirometry results.

Analyses will include a comparison of CAPTURE scores with data from spirometry testing and participant reported data to determine sensitivity and specificity of the CAPTURE tool. *The hypothesis is that a simple case finding methodology using a five-item questionnaire with selective PEF measurement will identify undiagnosed patients with clinically significant COPD.*

Based on the data collected at baseline, participants will be classified into the following groups for analyses:

Cohort	**Definition**
CAPTURE+	Participants with • CAPTURE score $\geq$ 5, or • CAPTURE score of 2, 3, or 4 with a low PEF, defined as <350 L/min for males and <250 L/min for females
CAPTURE-	Participants with • CAPTURE score < 2 or scores 2-4 with normal PEF (defined as $\geq$350 L/min for males and $\geq$250 L/min for females)
Spirometrically defined COPD	Participants with abnormal spirometry, defined as post-bronchodilator FEV_1/FVC <0.7. If a participant is unable to complete a post-bronchodilator spirometry (refusal, technical error on the part of coordinator, etc.), and the pre-bronchodilator FEV1/FVC is less than 0.65, the participant will be considered to have COPD for the purpose of follow-up in this study.

Clinically significant COPD	Participants with abnormal spirometry, defined as post-bronchodilator FEV_1/FVC <0.7, plus one of the following: 1) FEV_1 < 60% predicted or > 1 exacerbation like event within the past 12 months.
Mild COPD	Participants with abnormal spirometry, defined as post-bronchodilator $FEV_1/FVC<0.7$ plus both of the following: • $FEV_1 \geq 60\%$ and • No prior history of ECOPD

Exploratory analyses to examine the potential impact of SARS CoV-2 infection on the above operating characteristics of the CAPTURE approach will include information in the pandemic and post pandemic period collected from a simple COVID-19 questionnaire that is based on similar questionnaires from other ongoing NHLBI cohort studies.

Longitudinal Follow-up
A pre-defined subgroup of enrolled participants, who meet any of the below criteria will undergo longitudinal follow-up at 12 months,

1. Participants with a CAPTURE Score ≥ 5 or CAPTURE score of 2, 3, or 4 with a low PEF, defined as <350 L/min for males and <250 L/min for females
2. Participants who have abnormal spirometry results, defined as post-bronchodilator FEV_1/FVC < 0.7 or FEV_1 < 80% predicted at baseline. If a participant is unable to complete a post-bronchodilator spirometry (refusal, technical error on the part of coordinator, etc.), and the pre-bronchodilator FEV1/FVC is less than 0.65, the participant will be considered to have COPD for the purpose of follow-up in this study.
3. A random sample of approximately 5% who do not meet criteria 1 - 2

Participants who meet the criteria for follow-up will be sent notification shortly after enrollment, and receive reminders at 3, 6, and 9 months. Patient-reported data will be collected by COPD Foundation via telephone, secure web-based server, or mail-based methodologies, based on participant preference.

Subject medical data will be collected from the medical record to assess for changes in practice-level care.

The hypothesis for Aim 3 is that sites where COPD and CAPTURE education and patient-level CAPTURE data are provided to clinicians will exhibit improved COPD diagnosis and COPD-related care compared to sites where COPD education is provided to clinicians.

In exploratory analyses to examine the potential impact of SARS CoV-2 infection on the patient symptoms and health care utilization a simple COVID-19 questionnaire, based on other ongoing NHLBI cohort studies, has been introduced.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Aims 1 and 3

The totality of the published data confirms the clinical and economic impact of undiagnosed COPD, continuing under-diagnosis, and incomplete application of spirometric testing in the primary care community. It suggests that there is value in COPD case-finding that targets COPD patients most likely to benefit from available therapies. These points identify a pressing health care problem that requires

an innovative approach to facilitate identifying these individuals. Our preliminary studies enumerated in section 2.2 extend these concepts by demonstrating that:

- Six key domains identify patients with clinically significant COPD.
- Forty-four distinct items resonate with patients and provide important insights for COPD case-finding.
- Five items exhibit excellent sensitivity and specificity in identifying patients with clinically significant COPD.
- PEF provides incremental value in a case-finding strategy.
- The combination of a five-item questionnaire and PEF optimizes a COPD case-finding strategy in English and Spanish speaking patients.

Our proposed study will provide crucial data to address the operating characteristics and clinical translation to our COPD case-finding strategy into the primary care setting. It will also provide an important initial evaluation of the potential clinical impact of the systematic identification of previously undiagnosed COPD patients.

The impact of SARS-CoV-2 infection and its clinical illness, COVID-19, on COPD Case Finding and respiratory symptoms in primary care is unknown. In exploratory analyses a simple COVID-19 patient questionnaires and additional data elements from medical record review, based on other ongoing NHLBI cohort studies, have been introduced.

Aim 2

The rationale for this aim reflects the importance of establishing if an innovative approach to COPD case finding is considered a pragmatic tool with potential utility for primary care clinicians within real-world clinical practice settings. With the completion of this aim we anticipate confirming that future validated approaches to COPD case finding can be adopted in a broad variety of clinical care settings thereby providing further impetus for the rigorous evaluation of a) case finding guided patient outcomes as part of routine primary care clinical practice; b) case finding use in a range of primary care health professional COPD-related education approaches, clinical quality improvement models and diagnostic guidelines; and c) the capacity of clinical case finding and informed follow-up to enhance future COPD clinical care therapeutic paradigms used in primary care practice.

Consistent with Institute of Medicine criteria and US health quality standards for preventive and chronic disease care, the feasibility science qualitative research framework is designed to assist clinical and health education evaluators prepare, assess and evaluate specific implementation factors essential to the success of new diagnostic, therapeutic, educational and programmatic options in real-world clinical practice. This aim's analysis of primary care clinical practice COPD case finding feasibility considerations for CAPTURE includes an initial evaluation of existing COPD diagnostic and case finding processes within the practices, assessment of practices' capacity to change from existing respiratory symptom assessment strategies and an understanding of practice-specific learning preferences associated with new diagnostics and chronic disease diagnosis and management. Patient perceptions of the CAPTURE case-finding process are also obtained to provide a holistic perspective of the clinical feasibility of CAPTURE implementation in primary care practice. Borrowing from the RE-AIM implementation science approach, this aim explores how real-word primary care practices might potentially use CAPTURE to: a) identify target populations (Reach); b) refine current practice appraisal of patient respiratory history,

symptoms and diagnostics used to identify clinically significant COPD (Effectiveness/Impact); c) change or integrate COPD case finding into practice workflow (Adoption); d) alter practice communication, education and/or care quality improvement planning for COPD diagnosis and management (Implementation); and e) use COPD case finding consistently over time (Maintenance).

Ten primary care practices will undergo detailed implementation investigation of the CAPTURE case finding model designed to identify patients with COPD most likely to benefit from available therapeutic options. CAPTURE, a one-page questionnaire with selective PEF measurement, is presented to the clinicians of ten practices not participating in aims 1 and 3 as a prospective COPD case finding option awaiting validation. By representing CAPTURE as a model—and not introducing it into actual practice—aim 2 gains recommendation from primary care clinical practice experience with sufficient feasibility generality to circumvent interdependence between the operating characteristic exploration (aim 1) and qualitative feasibility understanding (aim 2) components of our study. The aim 2 results, that include the pooled CAPTURE clinical communication, education and implementation recommendations from real-world primary care practice, are analyzed and applied in concert with local and national research team expertise to enhance the potential impact of CAPTURE's introduction into clinical care in aim 3. Aim 2 results also provide previously unexplored qualitative information necessary for future long-term patient outcome studies of COPD case finding approaches in primary care.

The impact of SARS-CoV-2 infection and its clinical illness, COVID-19, on COPD Case Finding application in primary care is unknown. In a systematic fashion these concepts will be explored during the previously planned follow-up interviews and focus groups with clinical practice and regional PBRN personnel.

4.3 END OF STUDY DEFINITION

Participants that do not meet the criteria for, or are not selected for, longitudinal follow-up will be considered to have completed the study after completion of the baseline visit.

Participants included in the longitudinal follow-up phase will be considered to have completed the study after completion of the Month 12 Assessment as shown in the Schedule of Activities (SoA), Section 1.3.

Clinician participants in aim 2 will have completed the study after participation on their second focus group between months 14 and 16 as shown in the Figure 2, Structure of Aim 2.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Inclusion criteria for Aims 1 and 3
In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Male or female, aged 45 – 80 years

Inclusion criteria for Aim 2

Two Aim 2 practices are selected by each of their 5 affiliated PBRNs based upon willingness to participate and variability of primary care practice type within the PBRN. Differences in practice size, staffing, ownership, prior quality improvement engagement, geography, patient population socioeconomic status (SES) or languages spoken are among the among the selection criteria the PBRNs will utilize to choose.

Clinician participants (10 practices with up to 15 clinicians per practice):
1. Provision of signed and dated informed consent form.
2. Stated willingness to comply with availability and all study procedures for the duration of aim 2 by the 10 practices (through PBRN recruitment) and their up to 15 clinicians within (through informed consent).

Patient participants [200 patients (approximately 40 from each PBRN)] for CAPTURE survey:
1. Provision of signed and dated informed consent form.
2. Stated willingness to comply with all study procedures and availability for the duration of the study.
3. Male or female, aged 45 – 80 years.

5.2 EXCLUSION CRITERIA

Exclusion criteria for Aims 1 and 3
An individual who meets any of the following criteria will be excluded from participation in this study:

1. Previous clinician provided diagnosis of COPD
2. Treated respiratory infection (with antibiotics and/or systemic steroids) in the past 30 days of baseline
3. Participants unable to perform spirometry due to any of the following conditions within the past 30 days of baseline
    a) Chest surgery
    b) Abdominal surgery
    c) Eye surgery
    d) Heart attack
    e) Stroke

Exclusion criteria for Aim 2

1. Clinician participants: current employment at practices participating in aims 1 and/or 3
2. Clinician participants: from practices providing fewer than 2 clinician participants
3. Patient participants: meeting the exclusion criteria for aims 1 and 3 (above)

5.3 SCREEN FAILURES

PBRN coordinators, in conjunction with clinical study site personnel, will pre-screen individuals who are unlikely to be able to complete research spirometry. These individuals will be considered *pre-screen failures*.

Participants who are consented to participate but have a prior clinician diagnosis of COPD will be considered *screen failures*.

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment and retention strategies for Aims 1 and 3

Approximately 5,000 participants will be recruited from 100 primary care clinics affiliated with six PBRNs. Each PBRN has centrally-based research coordinators with a history of success working in PBRN practices, documented expertise in previous large diagnostic or therapeutic trials, and personnel experienced in recruitment and data collection.

IRB approval will be obtained at each PBRN for approval for patient contact, informed consent and participation in this study.

All patients who meet all inclusion and no exclusion criteria at the participating PBRN clinical site will be eligible for participation. Research coordinators will work with participating practices to identify and approach potential participants. Recruitment strategies may vary depending on the practice.

Enrollment of participants will depend on the gender, ethnic and racial makeup of those that are being recruited from the practices included in this trial. No exclusion criteria apply specifically to women or to minorities. The Data Coordinating Center (DCC) will track enrollment of participants throughout the course of this study. If women and minorities are under-represented in the initial phase of recruitment, a commitment exists to develop recruitment strategies that target these populations so the final study group is a well-balanced representation of the studied population.

Recruitment and retention strategies for Aim 2

Clinician participants: Approximately 150 clinic participants are recruited by: 1) introductory telephone contact with the practice leadership by PBRN research coordinators and the aim 2 research team; 2) follow up letter, time commitment infographic and informed consent forms sent to interested practices outlining aim 2 clinician participant activities and responsibilities; and 3) in-person aim 2 study explanation to clinician participants at the committed practices during the introductory baseline study site visit.

Clinician participant recruitment draws from both prescribing (or “provider”) staff and non-prescribing (or “clinical support”) staff. The aim 2 research team will attempt to obtain an even mix of both clinician staff types from each practice. Retention incentive of clinician participants over 2 years includes provision of on-line COPD education to all clinician participants and monetary incentive to practices as determined by each individual PBRN.

Patient participants: 200 participants (40 from each PBRN) are recruited as a sub-set of the aim 1. Each of the 200 patient participants in aim 2 are asked to complete a one-time 10-minute written opinion survey. Their aim 2 participation is concluded at the end of the opinion survey completion.

The aim 2 research team and DCC will track enrollment and retention of all aim 2 participants throughout the course of the 2-year aim 2 study.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

The study intervention is applicable to Aims 2 and 3 and consists of healthcare provider education modules.

The practitioners at the 10 sites selected for Aim 2 will receive module 1, Basic COPD education, and may elect to take modules 3-5 for supplemental information on COPD.

For Aim 3, half of the practices will receive Basic COPD education (module 1) and half will receive Basic COPD Education and CAPTURE Education (modules 1 and 2). Practitioners at practices randomized to COPD only education must take module 1 and may elect to take modules 3-5; however, they will not take module 2. Practitioners at practices randomized to COPD+CAPTURE education must take modules 1 and 2, and may elect to take modules 3-5.

1 - Basic COPD Education will be provided in order for providers to optimally manage patients with COPD. The education will incorporate evidence-based recommendations using the 2018 update of the Global Obstructive Lung Disease Strategy(45). For practices enrolled in the pandemic and post pandemic periods, additional information will be provided regarding COPD management in the pandemic era as well as information on steps to maintain patient and staff safety in the clinical sites where CAPTURE patients will be enrolled and assessed.

A 40-minute overview will be presented in the most expeditious manner at each practice site, for example by webinar for all practice personnel over the lunch hour, or audiovisual presentation available on a dedicated CAPTURE web site. The PBRNs have indicated that this module should be no longer than 40 minutes. Topics will include: CAPTURE study description and rationale, importance of COPD in the region of the local practices, COPD definition and diagnosis, patient goals, and management approach. Attendance at this mandatory training will be documented and continuing education credits will be provided for physicians and nurse practitioners by National Jewish Health, an accredited CME provider.

2 - **CAPTURE education**. An online audiovisual module will be developed to explain CAPTURE interpretation and use in patient evaluation and diagnosis of COPD. This module will only be available to practices randomized to receive the results of CAPTURE for clinical use.

With the information provided in Aim 2 about practice preferences for education, the CAPTURE education module will be revised and made available to practices enrolled in Aim 1 after the completion of Aim 2.

3 - Online advanced COPD education will be available for all practices and continuing education credits will be provided to enhance practitioner participation. Practitioner attendance at each online audiovisual module will be collected including the amount of time spent on each education module, completion of each module with a post-test and evaluation, and CME will be provided. Education will be case-based and will include role playing where appropriate. Seven basic modules of 20 minutes or less will be available both to practices randomized to receive CAPTURE results for clinician use and to control practices that will not receive CAPTURE results and will cover:

1. Diagnosis of COPD: How to diagnose COPD in primary care including medical history, physical exam and role of spirometry, severity categorization
2. Spirometry overview: Basic clinical interpretation
3. Advanced spirometry: Test performance, evaluating quality, advanced case-based interpretation
4. Management overview: Patient goals, smoking cessation, vaccination, patient education, shared decision-making

5. Pharmacotherapy: Inhaled bronchodilators, inhaled corticosteroids
6. Other therapies: Oxygen, pulmonary rehabilitation, surgical approaches
7. Inhalation devices: Patient education

4 – On-site COPD education. Additional funds will be sought to provide on-site COPD education. We have experience in successfully providing half-day on-site education to primary care practices to enhance their management of COPD.

5 – Social media and case conferences. We will use social media (Facebook and Twitter) to provide ongoing education about COPD. Facebook and Twitter posts will provide tips on managing COPD. Online conferences will be scheduled to discuss cases submitted by primary care providers.

6.2 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

For Aims 1 and 3, this study will use randomization and blinding as two of the cardinal principles of clinical trials to minimize bias.

Randomization. Practices will be randomized into one of the two interventions, COPD education or COPD education + CAPTURE education, in a 1:1 manner, stratified by PBRN. Randomization will occur at the time of site activation and each site will be assigned a unique randomization number. The DCC will prepare the randomization schedule, using computer-generated block randomization with the block size(s) known only by the DCC. A secure web-based application will be built that will be used by the central study coordinators to enter site information (e.g., site ID, stratification factor) and to obtain the randomization number. The information can be printed and sent and/or emailed directly to the study coordinator.

Blinding. This is a single-blind study with the participants blinded to whether their practitioners have received CAPTURE education and patient-level CAPTURE results. Practitioners at sites that are randomized to the control arm (COPD education alone) will be blinded to the CAPTURE questionnaire and PEF results. All practitioners and participants will be blinded to the baseline COPD status of the participants (i.e., blinded to spirometry results), except for safety reasons. In this situation, participants and their clinician will be notified if a participant's post-bronchodilator FEV_1 is less than 30% predicted. For all other participants, they and their practitioners will be blinded to research spirometry results. The coordinator should make every effort to conceal the spirometry results from the participants in these latter cases. Study coordinators should also make every effort to conceal the administration of a post-bronchodilator spirometry test from the practice staff so as not to unblind the physicians to abnormal spirometry.

6.3 STUDY INTERVENTION COMPLIANCE

In practices randomized to share the CAPTURE results with the clinician, the goal is to share results with the clinician at the time of the CAPTURE study visit. Providing results at the time of the clinical visit will allow the clinician to act on the CAPTURE results as soon as possible when the participant is in front of the clinician. Based on the workflow at each of the practices, this may not always be possible.

Sharing of the CAPTURE results with the participant's primary care clinician will be tracked by the study coordinator enrolling patients at sites randomized to receive CAPTURE results. The sharing of CAPTURE

results will be recorded on the study eCRF form. The eCRF will collect the timing of when the results were provided to the practitioner - whether the results were provided to the clinician at the time of the enrollment visit prior to the clinician visit with the patient, or were provided at another time.

If results were not shared at the time of the CAPTURE study visit, then the date of sending the CAPTURE results will be recorded on the appropriate eCRF by filling in the date (day/month/year) the exact copy of the CAPTURE Toolwere sent to the clinician through a HIPPA-compliant method and placed in the medical record. The goal is to communicate the results to the clinician. The DCC will monitor review all participants' eCRFs to assure that all those enrolled from practices randomized to CAPTURE results have been shared with clinicians..

6.4 CONCOMITANT THERAPY

Practitioners will treat participants using their own clinical judgment. No medications are prohibited. This is not an interventional therapeutic trial.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

In this cluster randomized controlled trial (Aim 3), where practices are the recipients of the intervention and where the interventions are based upon education and access to CAPTURE and PEF results, it is not anticipated that study intervention will be discontinued at the practice level. However, one of the CO-PIs will review safety data, especially SAEs related to baseline spirometry and PEF procedures, to ensure there are no untoward effects of the study on participants.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in Aims 1 and 3 of the study at any time upon request.

Clinician participants in Aim 2 are free to withdraw from participation in the study at any time upon request. If a clinician is no longer working at the participating practice then their involvement in Aim 2 activities will end and no further attempt will be made to include them in the remaining questionnaires or focus groups.

7.3 LOST TO FOLLOW-UP

If a participant selected for longitudinal follow up does not respond to the 12-month questionnaires, coordinators will attempt to contact participants first by the participant's preferred method of communication, either phone or email. At least three attempts will be made. If no response is obtained, the participant's alternate contact method will be attempted three times. Phone calls will be made at different times of the day. If there is no response, a letter will be sent to the participant. If the participant cannot be reached, the alternate contact will be called and/or emailed. If no response is

received, a letter will be sent to the alternate contact. If after all of these methods are employed and no contact with the participant results, the participant will be considered lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 BASELINE ASSESSMENTS AND DATA COLLECTION

Efficacy data will be collected by patient-reported outcomes and medical record review.

For Aim 1, CAPTURE, PEF results, acute respiratory event history and spirometry will be considered efficacy assessments. They are collected at the baseline visit.

CAPTURE. Participants will complete the 5-item *self-administered* questionnaire and measurement of Peak Expiratory Flow (PEF).

Peak Expiratory Flow (PEF). PEF using the Vitalograph® AsmaPlan® mechanical PEF meter with SafeTway® disposable mouthpieces (Vitalograph LTD, UK) will be measured for all participants. Ideally, PEF should be prior to the participant's physician appointment. The participant will perform three PEF tests. All three measurements will be recorded.

Spirometry. Before spirometry is performed, participants will be asked if they have taken a medicine which they breathed into their lungs from any puffer or inhaler within the past two hours. If participant answers yes, then spirometry will be performed but considered a post-bronchodilator spirometry test. No further spirometry will be needed. If participant answers no, then pre-bronchodilator spirometry will be performed for measurement of forced vital capacity (FVC), forced expiratory volume in one-second (FEV_1), and calculation of FEV_1/FVC (using EasyOne® Spirometer, ndd Medical Technologies Inc., Andover, MA). Testing will be performed in accordance with established American Thoracic Society/European Thoracic Society (ATS/ERS) standards. Local guidelines to minimize risk of SARS-CoV-2 infection will be adhered to, including a minimum of appropriate PPE and infection control techniques.

A Spirometry post-bronchodilator will only be performed if pre-bronchodilator spirometry FEV_1/FVC is less than 0.70 or FEV_1 is less than 80% predicted. Post-bronchodilator spirometry will be performed within 15 to 20 minutes after inhalation of 2 puffs of albuterol 180 mcg HFA using an AeroChamber Plus* Flow-Vu® spacer with one minute between the first and the second inhalation. A separate AeroChamber or comparable spacer, using a one way valve to minimize infectious risk, will be provided for each participant's testing. A standing order for albuterol administration may be used if necessary.

Spirometry is a valid, reproducible means of documenting the presence and severity of airflow limitation. When properly performed with maximum effort and attention to the details of calibration of the instrument, spirometry maneuvers are among the most reproducible of biomedical measures. In the setting of a highly trained, experienced therapist, a coefficient of variation of 2-3% is not unusual. Spirometry will be performed in a standardized manner in accordance with the ATS guidelines, as described in the manual of procedures (MOP). Spirometry is the timed-based measurement of the amount of air that can be forcefully exhaled from the lungs after a full inspiration. In the forced expiratory vital capacity maneuver, a person inhales as big a breath as possible and then blows it out as fast and as long as possible until no more air can leave the lungs. The volume of air leaving the lungs is

recorded continuously throughout the maneuver in order to allow calculation of important measures of lung function.

NHANES prediction equations, which are programmed into the Easy On PC spirometers, will be used to calculate the predicted lung function levels. These require the input of age, height, and race/ethnicity (White, Black, Hispanic). For people of mixed or unknown race the White prediction equations will be used.

PBRN Research Coordinators will be trained and certified in the performance of spirometry testing. Spirometry will be sent for central review for quality control assurance.

Adjudication of the Presence of Obstruction on Post-Bronchodilator Spirometry

The presence of obstruction is determined by the presence of an FEV_1/FVC ratio less than 0.70 after the administration of a bronchodilator. A bronchodilator will be administered to study subjects whose baseline FEV_1/FVC is less than 0.70 or whose FEV_1 is less than 80% of the predicted value.

If a subject is unable to complete a post-bronchodilator spirometry (refusal, technical error on the part of coordinator, etc.), and the pre-bronchodilator FEV_1/FVC is less than 0.65, the patient will be considered to have COPD for the purpose of follow-up in this study.

Height and weight
Height and weight will be recorded in order to determine appropriate prediction equations for spirometry and possible effect of obesity on spirometry. Height will be recorded and weight will be measured prior to spirometry testing.

Demographic Data Collection
Demographic data including date of birth, gender, ethnicity, race, educational level achieved, daily work schedule, living arrangement and health insurance will be entered into the EDC system.

Contact information including address, phone numbers and email address will be obtained. Alternate contact information will be obtained for two other people, family members not living with the participant or close contacts, who may be knowledgeable about the participant in the event that the participant cannot be contacted for subsequent longitudinal follow-up. Alternate contact information will include name, address, phone numbers and email addresses. All contact information will be stored securely at the clinical site or in a database separate from that developed for the clinical data.

Medical History
Previous medical diagnoses will include comorbidities such as cardiovascular, respiratory and malignant disorders. Influenza vaccination history will also be recorded. This questionnaire will be completed under supervision of the coordinator.

Concomitant Medication Review
Respiratory medications will be recorded at baseline for all participants. This questionnaire will be completed under supervision of the coordinator.

CAPTURE Additional Items Questionnaire
Participants will complete the 13-item *self-administered* questionnaire.

COPD Assessment Test (CAT)
Participants will complete the 8-item *self-administered* questionnaire.

Respiratory symptoms, smoke exposure and exacerbation like events
History of respiratory symptoms and exacerbation like events over the past year as well as smoke exposure (including e-cigarette or equivalent) will be recorded. This questionnaire will be completed under supervision of the coordinator.

Whenever possible, informed consent, eligibility review, CAPTURE Questionnaire and PEF will be performed prior to the participant's clinic appointment, so that CAPTURE results may be provided to the physician at the time of his/her appointment if the patient is cared for in a clinical center randomized to CAPTURE+ education.

COVID-19 Additional Items Questionnaire
Participants will complete the 18-item *self-administered* questionnaire.

Adverse events
Adverse events related to study procedures will be recorded by the coordinator.

8.2 LONGITUDINAL FOLLOW-UP ASSESSMENTS AND DATA COLLECTION

For Aim 3, the follow-up efficacy assessments are collected from the time of baseline to 12 months in selected cohorts (as described in section 4.1). Medical record abstractions completed by PBRN coordinators and participant questionnaires administered by study team members from the COPD Foundation are used.

Data collected from medical record include:

All participants undergoing 12-month follow-up as described in section 4.1	Current Smokers Only
Clinical spirometry ordered or administered	Smoking cessation counseling
Referral to specialist for respiratory evaluation/treatment	New prescription for smoking cessation medication
New recorded clinical diagnosis of COPD	Formal smoking cessation program referral/completion
New prescription for respiratory medication (long acting bronchodilator, inhaled steroids, oral anti-inflammatory)	
Exacerbation like event assessment (hospital, ED, minute clinic, antibiotic/steroid prescription/administration)	

Vaccination status	
Formal pulmonary rehabilitation program referral/completion*	
Data related to COVID-19 confirmed and suspected cases	

*only collected in relevant participants

Data from clinical visits to be collected at follow-up by telephone, secure web-based server, or mail-based methodologies directly from participants and administered by COPD Foundation study personnel include:

All participants undergoing 12-month follow-up as described in section 4.1	Current Smokers Only
Spirometry	Smoking cessation counseling
New diagnosis of COPD	Smoking cessation medications (including OTC)
Referral to pulmonologist or other respiratory specialist	
Exacerbation like event assessment	
New prescription for respiratory medication (long acting bronchodilator, inhaled steroids, oral anti-inflammatory)	
CAT score	
Attendance of pulmonary rehabilitation*	
COVID-19 related questions	

*only collected in relevant participants

8.3 AIM 2 ASSESSMENTS AND DATA COLLECTION

Practice study introduction and participation confirmation: After PBRN practice selection, the CAPTURE study Aim 2 lead together with the local PBRN Aim 2 coordinator conduct a 15-minute participation confirmation and introduction phone call with the key PBRN contact at each of the two selected practices. The study specifics and timeline are reviewed. After practice participation is confirmed, the on-site practice assessment date is scheduled. Informed consent forms for clinical staff are mailed to each confirmed practice. To reduce practice burden, completed clinical staff informed consent forms (up to 15 clinical staff per practice) can be returned by mail to the University of Michigan School of Public Health office, addressed to Dr. Randall Brown, or saved for completion and picked up at the on-site practice assessment site visit. Following the confirmation phone call, the PBRN Aim 2 coordinator completes a short (15 minute) qualitative questionnaire detailing the selected and confirmed practice demographics and PBRN parameter of practice choice for each of the two practices. The completed PBRN Practice Selection Questionnaire is returned to the Aim 2 data team and stored securely.

On-site Practice Assessment (OSPA): The OSPA is an in-person on-site practice workflow assessment. It includes 2 practice clinicians per practice choice, the PBRN Aim 2 coordinator (if available), the CAPTURE study Aim 2 lead and the CAPTURE Aim 2 research specialist (if the PBRN Aim 2 coordinator is not present). The objective of the visit is to detail specifics of practice workflow, practice physical characteristics, staff roles, clinical information gathering patterns for respiratory patients, electronic health record communication, continuing education structure, and quality improvement structure. The assessment takes place in three parts; the pre-observation practice overview (conducted with the 2 practice clinicians – 60 minutes), the ½ day practice workflow observation (observation by one member of the Aim 2 research team of common and testing areas used for the respiratory patient). There is no patient engagement and no collection of patient-specific identification or health information), and the post-observation practice summary (conducted with the same 2 practice clinicians – 30 minutes).

The 3 OSPA assessment tools are:

i) The Pre-workflow Observation Practice Assessment Review Questionnaire
ii) Respiratory Workflow Assessment Review
iii) The Post-workflow Observation Practice Assessment Review Questionnaire

Also at the OSPA, informed consent is obtained from all remaining participating staff (up to 15 clinical staff per practice) by the CAPTURE Aim 2 team and returned to the Aim 2 data team for secure storage.

Clinical Staff Questionnaires (Baseline/6/12 months). Written or on-line questionnaires are provided to participating and consented staff personnel at two practice levels -- Non-Prescribing clinical (also known as “support”) staff and Prescribing (PR) clinical (also known as “provider”) staff.

Non-Prescribing (NPR) clinical staff are clinical practice personnel involved in clinical workflow (including registered nurses, licensed practical nurses, medical assistants, medical assistants and receptionists), yet not having the role to make final and official medical diagnostic and management disposition plan decisions for and with patients. Prescribing (PR) clinical staff are prescribing clinical practice personnel involved in clinical workflow (including doctors, nurse practitioners, and physician assistants) who may independently make final medical diagnostic and management disposition plan decisions for and with patients.

Questionnaire items explore clinician demographics, including past education, duration of current employment and currently held clinical position. COPD knowledge, attitudes, beliefs, practice patterns and self-efficacy regarding COPD diagnosis, management, spirometry testing and interpretation, practice workflow and communication in the clinical primary practice care of adult patients with respiratory disease. Additional questions include preferred continuing education method and clinical staff quality improvement modalities for respiratory disease management. Specific examples of past practice chronic disease diagnostic changes and the individual and practice-wide levers of success and challenge associated with those changes are explored.

Each of the 3 (baseline, 6-month and 12-month) questionnaires are completed within 30 minutes. No identifying patient data is collected. Online questionnaires are collected and secured by the CAPTURE DCC and Aim 2 research team. The participants who complete written questionnaires (per their preference) mail completed questionnaires via pre-addressed stamped envelope to the CAPTURE DCC and Aim 2 research team.

Patient Opinion Surveys:

200 patient participants, 40 from each PBRN, are recruited as a sub-sample from Aim 1 practices. Patient participants fulfill all inclusion and exclusion criteria and receive informed consent for survey participation as part of aim 1.

Eligible participants complete a written one-time 5 to 10 minute CAPTURE opinion survey. Patient survey data is collected by Aim 1 research coordinators and is processed with Aim 1 baseline patient data. Patients receive a $15 gift card for completion of the survey Aim 2 patient participation ends at the completion on the lone opinion survey.

Participants who prefer to complete the 5 to 10-minute survey online via Qualtrics will be sent a secure, Qualtrics link via email. The Qualtrics survey will include a brief, introductory screen affirming consent, describing the survey and instructions about participation. Once the survey is complete, participants will see a screen with instructions about how to obtain their $15 gift card and how to contact study staff with questions regarding the survey.

Modular online COPD education. Access to free, COPD on-line, continuing education is provided for all clinical staff at each practice. Each module will take 20 minutes or less. Modular components of and access to COPD education is described in the protocol. Aim 2 clinician participant access and completion of COPD education modules is assessed by clinician questionnaires and focus group item response over 12 months (between months 2 and 14 of Aim 2 timeline).

COPD in Primary Care/CAPTURE Introduction Focus Groups:
Two 45 to 60-minute focus group discussions occur at each Aim 2 practice. Focus groups are informed by practice demographics, practice assessment data – including respiratory workflow, baseline clinical staff questionnaire data regarding respiratory knowledge, attitudes, beliefs and practice preference for the diagnosis and care of adult patients with respiratory disease as well as patient opinion from CAPTURE surveys and past CAPTURE study (46, 47). Focus group candidate themes and prompts are developed for non-prescribing clinical staff (NPR) and prescribing clinical staff (PR) and are presented at separate on-site focus group sessions to allow more detailed discussion of role responsibility in the context of daily practice workflow, generating a more abundant qualitative data sample. Separation of and PR clinical staffing implementation themes into two focus groups also limits potential for hierarchical work-related discussion suppression described in other short duration focus group studies (48-52).

The focus group moderator introduces the CAPTURE tool utilizing CAPTURE education components described in Section 6.1.1. The focus group moderator follows RE-AIM prompts for CAPTURE implementation planning discussion throughout the focus group. Targeted COPD self-efficacy limitation themes from questionnaire data (including awareness and/or use of validated respiratory assessment questionnaires, spirometry, COPD guidelines, inhaled medication patient education, oxygen therapy, smoking cessation education, vaccination recommendation, pulmonology specialty care and pulmonary rehabilitation referral) are explored. Questions will probe clinicians to identify and explain levers that may maximize uptake of CAPTURE use in their practices as well as potential barriers to implementation. The Aim 2 research team will record each focus group using audio and written note-taking that will allow an abridged yet detailed tape-based micro-interlocutor analysis of focus group emergent themes, questions, answers and interactions. Key themes informing consensus discussion, program modifications and key elements of the CAPTURE RE-AIM implementation dimensions will be identified. Audio-recordings will be professionally transcribed and codes will be generated for the interview topics and key research questions. Reviewing the transcripts line-by-line, all substantive information will be

assigned a priori codes as relevant for CAPTURE RE-AIM implementation planning, COPD diagnosis and CAPTURE intra-office clinical communication and COPD/CAPTURE education preference assessment. Additional codes will be developed for sub-themes and emergent themes.

Development of Practice-Based CAPTURE Implementation PBL Cases:
From analyses of the 2 NPR and 2 PR CAPTURE Introduction focus groups per PBRN, baseline clinical staff questionnaire data, online CAPTURE opinion surveys, and on-site practice assessments, 1 primary care practice CAPTURE implementation case per PBRN (total implementation cases = 5) is created by the Aim 2 research team. Given local knowledge of chronic disease management quality improvement history, effort, challenge and successes, each PBRN's participation in case creation will be instrumental. The Aim 2 research team will lead case creation using evidence-based problem based learning (PBL) techniques (53-57). The Center for Research on Learning and Teaching (CRLT) at the University of Michigan will serve as research reference for PBL case development qualification (58). Each local PBRN PBL case will be distributed to the Aim 2 clinical staff at the 2 participating PBRN practices 2 weeks prior to the CAPTURE Implementation focus groups, giving Aim 2 participants an opportunity to read the case introductions prior to the focus group session. Also, each practice will receive one additional non-PBRN case for focus group discussion as selected by the Aim 2 research team. Therein, each of the 5 CAPTURE implementation PBL cases will receive 2 comprehensive focus group reviews (see below).

CAPTURE Implementation PBL Case Presentation Focus Groups:
Each practice participates in a final pooled (NPRs and PRs together) on-site focus group. Two CAPTURE implementation cases (described above) are discussed at each focus group. The focus will explore, discuss, glean and create optimal 1) CAPTURE implementation, 2) CAPTURE clinical communication, 3) CAPTURE/COPD education and 4) CAPTURE primary care quality improvement recommendations pooled from all clinical practice levels for each of the 2 presented cases.

The Aim 2 research team will record each focus group using audio and written note-taking that will allow an abridged yet detailed tape-based micro-interlocutor analysis of focus group emergent themes, questions, answers and interactions. Key themes informing consensus discussion, program modifications and key elements of the CAPTURE RE-AIM implementation dimensions will be identified. Audio-recordings will be professionally transcribed and codes will be generated for the interview topics and key research questions. Reviewing the transcripts line-by-line, all substantive information will be assigned a priori codes as relevant for CAPTURE RE-AIM implementation planning, COPD diagnosis, CAPTURE intra-office clinical communication, and COPD and CAPTURE education preference, and COPD diagnosis quality improvement assessment. Additional codes will be developed for sub-themes and emergent themes.

8.4 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.4.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.4.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.4.2.1 SEVERITY OF EVENT

The following guidelines will be used to describe severity of AEs.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.4.2.2 RELATIONSHIP TO STUDY INTERVENTION

All AEs must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.
- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the study intervention). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.4.2.3 EXPECTEDNESS

The Principal Investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.4.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

Adverse events (AE)s that occur during the baseline visit will be recorded.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed.

8.4.4 ADVERSE EVENT REPORTING

All AEs that occur at baseline visit will be recorded in the case report form and reported to the DCC. We anticipate few adverse events due to the non-invasive nature of the study procedures. Participants will only be enrolled if they meet the study eligibility criteria, including assessment for contraindications for spirometry. Targeted safety questions will be asked of all patient participants prior to albuterol to exclude those with a previous adverse event with the medication and others at high risk due to cardiac abnormalities.

8.4.5 SERIOUS ADVERSE EVENT REPORTING

SAEs will be reported to the IRB at the institution where the event occurred and the University of Michigan IRB will be notified of any serious adverse experience within 7 calendar days of occurrence. These will be reported to the DSMB.

Follow-up of serious adverse events

All SAEs will be followed up until resolution or permanent outcome of the event. All follow-up information will be included in the case report form. The DSMB will make recommendations to ensure data integrity and the safety of study participants.

8.5 UNANTICIPATED PROBLEMS

8.5.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;

- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.5.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing IRB and to the DCC. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the DCC within 7 calendar days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC within 14 calendar days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within one month of the IRB's receipt of the report of the problem from the investigator.

8.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a DSMB (physicians with the appropriate expertise, including non-involved pulmonologists, primary care physicians, and independent statisticians with clinical experience). Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the Principal Investigators.

9 STATISTICAL AND ANALYTICAL PLANS

9.1 SAMPLE SIZE AND POWER

9.1.1 PRIMARY OBJECTIVES

Define the sensitivity and specificity of CAPTURE for identifying previously undiagnosed patients with clinically significant COPD in a broad range of primary care settings. We will also explore clinical practice implementation approaches to and acceptance of CAPTURE case finding for clinically significant COPD in a range of primary care practices. Further, we will define the impact of CAPTURE information provided to clinicians in identifying and managing patients with respiratory symptoms (CAPTURE+) across a broad range of primary care settings.

9.1.1.1 SENSITIVITY AND SPECIFICITY OF THE CAPTURE TOOL

Primary Hypothesis 1. *The CAPTURE tool will exhibit excellent sensitivity and specificity in diagnosing clinically significant COPD as defined by post-bronchodilator $FEV_1/FVC < 0.70$ in addition to either >1 exacerbation-like event (ECOPD) within the past 12 months or an $FEV_1 < 60\%$ predicted.* Approximately 5000 patients will be enrolled in the study with the expectation that 300-800 of these will have previously undiagnosed clinically significant COPD, identified through research spirometry and documentation of prior respiratory events. Amongst cases, we will calculate the proportion of individuals who are at high risk for clinically significant COPD based on CAPTURE (sensitivity). Similarly, amongst non-cases, we will calculate the proportion of individuals not classified as having clinically significant COPD based on CAPTURE (specificity). Corresponding 95% confidence intervals will be calculated.

Based on our preliminary data drawn from a research setting, we noted 89.7% sensitivity and 93.1% specificity for CAPTURE. Table 9-1 shows the range of sensitivity and specificity 95% confidence interval widths that would result if the true sensitivity or specificity is 85%, 90% or 95% across a range of sample sizes. For instance, if we find 500 individuals with confirmed clinically significant COPD and CAPTURE has 90% sensitivity, then the 95% confidence interval for sensitivity would be 90% ± 2.6%. Similarly, if 4,000 individuals are confirmed to have no evidence of clinically significant COPD and CAPTURE has 90% specificity, then the 95% confidence interval for specificity would be 90% ± 0.9%.

Table 9-1 Projected Confidence Interval Widths for Various Sensitivity/Specificity Percentages (Columns) and Sample Sizes (Rows).

	Sensitivity or Specificity		
Sample Size	**85%**	**90%**	**95%**
5000	± 1.0%	± 0.8%	± 0.6%
4000	± 1.1%	± 0.9%	± 0.7%
1000	± 2.2%	± 1.9%	± 1.4%
500	± 3.1%	± 2.6%	± 1.9%
250	± 4.4%	± 3.7%	± 2.7%
100	± 7.0%	± 5.9%	± 4.3%
50	± 9.9%	± 8.3%	± 6.0%

9.1.1.2 ADOPTION AND IMPLEMENTATION OF THE CAPTURE TOOL IN PRIMARY CARE PRACTICE

Primary Hypothesis 2: *A COPD case finding methodology using a validated one-page, five-item questionnaire with selective PEF measurement (CAPTURE) can be incorporated into the clinical practice patterns, clinical workflow, communication and practice-based quality improvement paradigms of a variety of primary care clinical settings.*

Aim 2 is a qualitative study to determine the efficacy of workflow integration of the CAPTURE tool. Statistical analysis of the clinician questionnaire will involve simple sums of each item and reviewing answers across practices and region. Standard frequencies for questions will be developed to examine patterns in responses.

The clinician focus groups will be conducted on-site at each practice at a time convenient for the participating clinicians. The number of prescribing and non-prescribing clinicians will equal 15 per practice and is based on interest with a maximum of 8 prescribing clinicians/practice. The sample size will follow a basic qualitative sampling standard of interviewing to redundancy or saturation. The number of clinicians to be interviewed (up to n=15 in each practice) is estimated based on achieving concept saturation. Reflecting regional primary care practice norms and to bolster concept saturation, PBRN Aim 2 coordinator focus group discussion participation is encouraged for very small practices where the participating prescribing and non-prescribing clinician total is less than or equal to 4. For all practice focus groups questions will explore the described Aim 2 CAPTURE RE-AIM concepts, barriers to implementation of the CAPTURE tool at other practice sites, standard processes for COPD and respiratory care diagnosis and management for each clinical role within the practice, and perception of quality improvement methods at each practice. Clinician focus groups are conducted on-site at each of the 10 practices.

Transcripts of clinician focus groups will all be digital and entered into a qualitative data analysis program, NVivo for Mac. This program allows for an investigation of the salience, patterning, and contexts of key discourse items. Grounded theory methods will be used to identify and label recurrent themes and concepts within textual materials. Texts will be examined line-by-line, key phrases assigned tentative category labels, and coded passages grouped under the themes of feasibility, barrier and utility. The analyses will look for “traces” in dialogue, including repetitions, key words, evaluation statements, and metaphors. Change in salience, patterning, or content of key themes will provide further empirical evidence regarding the efficacy of our program’s efforts to impact community norms and behaviors. An audit trail will be maintained to document the position of text material from which codes and themes are developed. We will use word/code counts of repetitive themes and concepts to indicate patterns. By allowing for open-ended responses, the narratives and notes will allow us to capture significant changes in participants’ attitudes or behaviors. Codes and themes will be discussed iteratively with the research team members to hone definitions and assure consistency of interpretation. We will establish a coding dictionary and all interviews will be coded using the complete set of themes. Two independent coders will code each document to assure inter-coder reliability. Preliminary results will be shared with our Aim 2 research team and will inform the development of the case studies for the latter part of the project.

9.1.1.3 PRACTICE BEHAVIOR IN SITES WITH VERSUS WITHOUT CAPTURE EDUCATION AND PATIENT LEVEL CAPTURE DATA PROVIDED

Primary Hypothesis 3: *Sites where basic COPD and CAPTURE education are provided to clinicians, along with patient level CAPTURE data, will have a higher probability than control sites (i.e., those receiving only basic COPD education) of meeting the composite endpoint in their CAPTURE+ patients within 12 months of baseline.* From record review, the composite endpoint is met if one of the following is recorded: (1) referral for clinical spirometry testing, 2) new clinical diagnosis of COPD, 3) newly prescribed respiratory medication (long acting bronchodilator or anti-inflammatory for respiratory condition), or 4) referral to a specialist for respiratory evaluation/ treatment.

The study will enroll 50 CAPTURE practices and 50 control practices; each practice will enroll 50 patients (for a total of 5,000 patients). We project that within each practice, there will be at least 5 patients previously undiagnosed with COPD who have a CAPTURE+ screening result. The primary analysis will be to compare the average proportion of CAPTURE+ patients per practice that meet the composite endpoint in the two intervention arms. For power and sample sizes computations, this is a cluster randomized trial of n=50 clusters (practices) per intervention arm with 5 CAPTURE+ patients per cluster (practice). The primary power calculation is based on comparing the average cluster sample proportion (average proportion of CAPTURE+ patients per practice meeting composite endpoint) between intervention arms. Table 9-2 displays power for a two-sample test comparing average cluster sample proportions, accounting for possible intra-cluster correlation coefficient (ICC) values of 0.05, 0.10 and 0.15 that are typically seen in cluster randomized trials of behavioral interventions (https://www.abdn.ac.uk/hsru/research/research-tools/study-design/). These calculations assume a type I error of 5% and that the control arm meets the composite endpoint in 5% of CAPTURE+ patients and the CAPTURE arm meets the composite endpoint in higher percentages (columns of Table 9-2). There will be variability in the actual number of CAPTURE+ patients per practice. It is standard practice to inflate the number of needed clusters by 12% to account for this extra source of variability. Therefore, our power calculations are based on 44 clusters per intervention arm.

Table 9-2. Overall power to detect a difference in rate of meeting primary endpoint in CAPTURE group (50 practices/clusters) vs usual care (50 practices/clusters), assuming 5% performance rate in usual care; 50 patients total / practice; assuming 10% prevalence gives 5 CAPTURE+/practice

Improvement over usual care	+7.5%	+10%	+15%	+25%	+50%
ICC=0.05	0.72	0.89	0.99	>0.99	>0.99
ICC=0.10	0.65	0.84	0.98	>0.99	>0.99
ICC=0.15	0.59	0.79	0.97	>0.99	>0.99

9.1.2 SECONDARY OBJECTIVES

9.1.2.1 SENSITIVITY AND SPECIFICITY IN PREDEFINED SUBGROUPS

Table 9-3. Projected numbers of clinically significant COPD cases and non-cases we expect by subgroup of interest assuming prevalence of obstructed individuals is between 6-16%. (*Non-Hispanic) This table assumes prevalence of non-clinically significant COPD similar to clinically significant COPD (not included in this table).

	Total	**Men (50%)**	**Women (50%)**	**White* (62%)**	**Black* (15%)**	**Hispanic (18%)**	**Rural (46%)**	**Urban (54%)**	**Ever-Smokers (40%)**	**Never-smokers (60%)**
Projected # confirmed clinically significant COPD by subgroup	300-800	150-400	150-400	186-496	45-120	54-144	138-368	162-432	120-320	180-480
Projected # confirmed no COPD by subgroup	3,400-4,400	1,700-2,200	1,700-2,200	2,108-2,728	510-660	612-792	1,564-2,024	1,836-2,376	1,360-1,760	2,040-2,640

We will also examine several subgroups of interest that are key to addressing our overall goal of defining the value of CAPTURE across a broad range on individuals. These will include sex, ethnic groups, rural and urban location, and educational level, among individuals with clinically significant COPD, spirometrically defined COPD and individuals with "mild" COPD as defined in this protocol. We have specifically chosen clinical sites with a diverse gender, racial and ethnic mix, and rural and urban mix with the expected prevalence of clinically significant COPD cases and controls by subgroup outlined in Table 9-3, again with corresponding sensitivity and specificity confidence interval widths in Table 9-1. For example, if sensitivity of CAPTURE in Hispanic individuals is 90%, then a sample size of approximately 100 would give a confidence interval of 90% ± 5.9%. We believe that with an overall sample size of 5,000 recruited patients we will have adequately sized subgroups to assess the operating characteristics of CAPTURE in the subgroups of interest.

9.1.2.2 FURTHER ANALYSIS OF ASSOCIATIONS BETWEEN MEETING COMPOSITE ENDPOINT AND INDIVIDUAL AND PRACTICE LEVEL OUTCOMES

Secondary analyses for evaluating practice behavior are exploratory, and therefore not included in a formal power and sample size analysis. These analyses are described further in Section 9.3.2.

9.2 POPULATIONS FOR ANALYSES

Aim 1
Population used for sensitivity calculations are all enrolled patients with clinically significant COPD as defined by post-bronchodilator $FEV_1/FVC < 0.70$ in addition to either >1 exacerbation-like event (ECOPD) within the past 12 months or an $FEV_1 < 60\%$ predicted.

Population used for specificity calculations are all enrolled patients with no demonstrable COPD as determined by research spirometry conducted upon study entry, $FEV_1/FVC \geq 0.70$.

Aim 2
Clinician participants: enrolled clinicians are from 2 primary care practices in each of five US PBRN regions that do not engage in Aims 1 or 3 investigation. Eligible clinicians include primary care providers and primary care clinical non-provider support personnel.

Patient participants: enrolled as a sub-sample of Aim 1 participants at baseline. One CAPTURE patient opinion survey is administered at baseline. Aim 2 participants fulfill the inclusion, exclusion and population analysis criteria of aim 1.

Aim 3
Populations used in 2-sample comparisons of the average proportion of CAPTURE+ patients per practice that meet the composite endpoint in the two intervention arms will be based on randomization group (intent-to-treat analysis).

9.3 STATISTICAL ANALYSES

9.3.1 SENSITIVITY AND SPECIFICITY (AIM 1)

SAS version 9.4 PROC LOGISTIC will be used for computations. Calculations of sensitivity and specificity along with their corresponding 95% confidence intervals assume independent Bernoulli outcomes for each patient. Clinically significant COPD+ and COPD- populations selected for these analyses are described in Section 9.2. CAPTURE+ patients are those with a baseline CAPTURE score $\geq$ 5 or with a baseline CAPTURE score of 2, 3, or 4 with a low PEF (defined as <350 L/min for males, <250 L/min for females).

In addition to the primary sensitivity/specificity calculations, sensitivity/specificity and associated 95% confidence intervals will be calculated in predefined subgroups: sex, ethnic subgroups, rural and urban location, and educational status. As part of secondary analyses, receiver operating characteristic (ROC) curve analyses will evaluate different thresholds of the CAPTURE questionnaire score in defining a positive clinically significant + COPD screen, separately and in combination with low PEF characteristics, **and the additional CAPTURE questions**. As part of this exploration, participant and practice level data as well as interactions with the CAPTURE tool results, will be considered as predictors of clinically significant COPD using multivariable logistic regression. Corresponding positive and negative predictive values will be estimated across the range of prevalence percentages seen at the enrolled practices. Model selection in secondary logistic regression analyses will be based on forward selection using maximum likelihood theory, with entry into the model dependent on statistical significance at the 0.05 level. Exploration of this nature has the potential to produce artificially high operating characteristics (area under the curve [AUC], sensitivity and specificity) based on overfitting the data. SAS 9.4 PROC LOGISTIC includes a cross-validation approach to ROC curve analysis [ROCOPTIONS(CROSSVALIDATE)] that we will use when assessing operating characteristics for any new prediction tool that goes beyond the original CAPTURE metric considered in primary analyses. Once a final logistic regression model has been selected, classification thresholds for predicting clinically significant COPD will be described by the investigative team from the cross-validated ROC curve. Calibration plots of observed versus predicted sensitivity, and observed versus predicted specificity, will be conducted across previously specified subgroups of interest (sex, ethnic subgroups, rural and urban location, and educational status).

All of the above analyses will be applied to these additional populations: (1) patients with spirometrically defined COPD and (2) patients with mild COPD.

9.3.2 PRACTICE BEHAVIOR (AIM 3)

The primary analysis will be to compare the average cluster sample proportion (average proportion of CAPTURE+ patients per practice meeting composite endpoint) between intervention arms. Practices that do not identify any CAPTURE + subjects will not contribute to the primary analysis, although this is felt to be an unlikely occurrence. A two-sample test comparing average cluster sample proportions will be used that explicitly takes into account correlation between individuals treated within the same practice. A two-sided p-value < 0.05 will be considered statistically significant. This analysis corresponds to a generalized estimating equation (GEE) regression analysis with (1) individual-level binary composite outcome data, (2) CAPTURE intervention group as a covariate, (3) practice id used to identify correlated outcomes, (4) exchangeable correlation matrix that assumes similar correlation between all composite outcome results for patients within the same practice, and (5) a logistic link function. The primary analysis would then correspond to a test for the CAPTURE intervention group parameter. There are no planned interim analyses for the primary endpoint, the rationale being that this is not a pharmaceutical or device trial that would benefit from standard stopping rules for efficacy. A DSMB will be monitoring the study for safety and study integrity.

Secondary analyses on meeting the composite outcome for participants who are CAPTURE+ will employ the GEE analysis framework with individual and practice level predictors in addition to the CAPTURE intervention group. Interactions will be assessed. We will also use the GEE framework to study and describe each of the individual components of the composite outcome as they relate to individual and practice level outcomes. In the subset of smoking patients, we will use GEE regression analysis to study additional binary outcomes, such as incidence of physician referral to a formal smoking cessation program, prescribed smoking cessation medication in participants who are smokers, and referral to pulmonary rehabilitation program.

In participants who are CAPTURE+, change in CAT score will be analyzed using mixed models with a random effect for practice. The average cluster sample proportion of patients who experience exacerbations will be compared between intervention groups using methodology similar to that used for the primary endpoint. Survival analysis allowing for correlation of endpoints within cluster (practice) will be used to compare mortality between intervention groups and perform multivariable analysis. We will explore differences between intervention groups in the average cluster sample rate of hospitalizations again using GEE. All additional secondary analyses will also be applied to patients with clinically significant and spirometrically defined COPD. Practices that do not have any clinically significant COPD or spirometrically defined COPD will not contribute to analyses of these secondary endpoints, respectively.

Model selection in GEE secondary analyses will be based on statistical significance at the 0.05 level using robust sandwich estimation of variability within clusters. Model fit will be checked by comparing observed versus predicted values within predefined subgroups of interest (sex, ethnic subgroups, rural and urban location, and educational status).

9.3.3 CAPTURE IMPLEMENTATION RECOMMENDATIONS (AIM 2)

Site-specific practice information, clinician knowledge and behavioral questionnaires, as well as patient opinion survey responses are recorded primarily to populate focus group themes for qualitative analysis. Secondary analyses of individual clinician and patient response using frequencies, means, ranking and dispersion by clinician type, practice and PBRN is accomplished using SAS version 9.4. Correlation with implementation recommendation is determined using GEE variance models.

Audio transcripts of clinician focus groups will all be digital and entered into a qualitative data analysis program, NVivo for Mac. This program allows for an investigation of the salience, patterning, and contexts of key discourse items. Grounded theory methods will be used to identify and label recurrent themes and concepts within textual materials. Texts will be examined line-by-line, key phrases assigned tentative category labels, and coded passages grouped under the themes of feasibility, barrier and utility. The analyses will look for “traces” in dialogue, including repetitions, key words, evaluation statements, and metaphors. Micro-interlocutor analysis of focus group emergent themes, questions, answers and interactions will account for individual gaps in focus group participation. Change in salience, patterning, or content of key themes will provide further empirical evidence regarding the efficacy of our program’s efforts to impact clinician community norms and behaviors. An audit trail will be maintained to document the position of text material from which codes and themes are developed. We will use word/code counts of repetitive themes and concepts to indicate patterns. By allowing for open-ended responses, the narratives and notes will allow us to capture significant changes in

participants' attitudes or behaviors. Codes and themes will be discussed iteratively with the research team members to hone definitions and assure consistency of interpretation. We will establish a coding dictionary and all interviews will be coded using the complete set of themes. Reviewing the transcripts line-by-line, all substantive information will be assigned a priori codes as relevant for CAPTURE RE-AIM implementation planning, COPD diagnosis, CAPTURE intra-office clinical communication, and COPD and CAPTURE education preference, and COPD diagnosis quality improvement assessment. Two independent coders will code each document to assure inter-coder reliability. Preliminary results will be shared with the Aim 2 data team and will inform the development of the CAPTURE case studies and primary care practice implementation recommendations.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise.

A HIPPA waiver will be submitted to each IRB to prescreen clinic schedules and patient panels for recruitment purposes. The PHI reviewed by the coordinator in the electronic health record (EHR) will include age, date of birth, diagnosis of COPD, respiratory medications, and other medical conditions that are contraindicated for spirometry. A waiver of written consent will be submitted to each IRB to pre-screen potential participants for eligibility criteria prior to informed consent. The pre-screening will either be by telephone prior to an upcoming clinic visit, or in person at the time of the visit. An IRB-approved telephone/in-person screening script will be submitted to each IRB.

A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. Participants will additionally have the opportunity to review the study and informed consent prior to providing consent for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

All PBRN research coordinators, COPD Foundation study staff and other clinical investigators will be certified by their local IRB in informed consent and human studies research.

Clinicians interested in participating in the qualitative, minimal risk study for Aim 2, will be given the opportunity to review the consent form below and sign it. This can happen once their practice agrees to participate in Aim 2 activities or during the first in person site visit with Dr. Brown.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

When a study is prematurely terminated, refer to Section 7, Study Intervention Discontinuation and Participant Discontinuation/Withdrawal, for handling of enrolled study participants.

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. In addition, it may be transmitted and stored at the DCC in a database separate from the clinical database (used for statistical analysis and scientific reporting) and with COPD Foundation study team access to aid in contacting participants at the 12-month follow-up. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the DCC. This will not include the participant's contact or identifying

information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by DCC research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the DCC.

For the online Aim 2 patient opinion survey, Qualtrics is used. Qualtrics is a secure University of Michigan (U-M) contracted-for cloud service that can be used to maintain or share the university's sensitive unregulated data, as well as some kinds of sensitive regulated data.

U-M's agreement with Qualtrics includes a Business Associate Agreement. This means individuals may use this service to maintain Protected Health Information (PHI) regulated by HIPAA. Complying with HIPAA's requirements is a *shared responsibility*. Users sharing and storing PHI in Qualtrics are responsible for complying with HIPAA safeguards, including:

- Using and disclosing only the minimum necessary PHI for the intended purpose.
- Obtaining all required authorizations for using and disclosing PHI.
- Ensuring that PHI is seen only by those who are authorized to see it.
- Obtaining all necessary data-sharing agreements and Business Associate Agreements for using and disclosing PHI.
- Following any additional steps required by your unit to comply with HIPAA.

Sensitive data, including PHI, may be collected and stored in Qualtrics for non-clinical, academic purposes only (for example, research and hospital quality improvement initiatives). Qualtrics cannot be used for any clinical applications, no matter the sensitivity level of the data

11 STUDY ADMINISTRATION AND OVERSIGHT

11.1 STUDY LEADERSHIP

11.1.1 PRINCIPAL INVESTIGATORS

The principal investigators are responsible for providing direction and oversight of all study activities.

Principal Investigators	
Fernando Martinez, MD, MS	MeiLan Han, MD, MS
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11.1.2 PRACTICE BASED RESEARCH NETWORKS (PBRN)

PBRNs will have the following roles and responsibilities:

CAPTURE Study Preparation

1. Review protocol to help identify operational details
2. Submit final protocol and informed consents to all IRBs necessary for the participating sites
3. Complete and maintain current human participants training for all main study personnel as required by the IRB
4. Attendance of PBRN coordinators at in person training, spirometry certification for all coordinators, update of spirometry quality assessments and training
5. Identify and recruit local practice sites to participate in the study

CAPTURE Study Implementation

1. Facilitate COPD and when appropriate CAPTURE education
2. Maintain regular contact with participating PBRN practice sites during their period of patient enrollment
3. Supervise and send PBRN Research Coordinators to enroll patients, perform study visits including completion of the CAPTURE questions, peak flow, spirometry, and collect other information on all enrolled patients
4. Complete pre bronchodilator spirometry on all participants
5. Complete post bronchodilator spirometry on participants with abnormal pre-bronchodilator spirometry as defined by study algorithm (e.g. those with pre bronchodilator results consistent with obstruction)
6. Facilitate completion of data entry to the data coordinating center
7. Follow up by research coordinator for patients failing to respond to the follow up questionnaires
8. Collect practice outcome data related to enrolled patients at close of study from either electronic medical records or if practice does not have EMR, by manual record review

Patient participants and staff participants will be recruited from the PBRNs.

PBRN	Location	Director
Atrium Health	North Carolina	Hazel Tapp, PhD
LA Net Community Health Network	Southern California	Lyndee Knox, PhD
High Plains Network	Colorado	Linda Zittleman, MD
Duke Primary Care Research Consortium Oregon Rural Practice-Based Research Network	North Carolina Oregon	Rowena Dolor, MD Nancy Elder, MD
University of Illinois, Chicago	Illinois	Min Joo, MD
Circuit Clinical, Buffalo	New York	Irfan Khan, MD

11.1.3 SPIROMETRY CORE

Led by Dr. David Mannino, the Spirometry Core will maintain quality of the research spirometry that is integral to the success of the study. The work will be done in conjunction with a research assistant. This includes the following functions:

1. Development of the operation manual for the sites
2. Training of the site staff in the use of the spirometry equipment (including travel to training and sites as needed)

3. Certification of staff in spirometry
4. Assessing staff adherence to protocols for the use of bronchodilators
5. Grading and adjudication of spirometry
6. Importing processed spirometry into spreadsheets
7. Uploading processed data to data coordinating center
8. Working with data coordinating center to verify and clean data

In addition, Dr. Mannino will be a critical part of the team that evaluates the data both from spirometry and the other components of this study (the CAPTURE tool, quality of life measures, etc.), in addition to being part of the writing team that analyzes data and disseminates the findings from this study.

11.1.4 IMPLEMENTATION CORE

Dr. Randall Brown will lead the qualitative Aim 2 activities which assess the implementation strategy and acceptance recommendations for CAPTURE use in primary care practice. His team includes an Aim 2 project manager and dedicated research assistant. Led by Dr. Brown the Aim 2 team coordinates with PBRNs and their selected Aim 2 practices and will conduct qualitative site visits and focus groups in addition to administering clinical practice behavioral questionnaires. Drs. Barbara Yawn, Barry Make, Bruce Bender and Julia Houfek will contribute to the development of the web based educational modules and the qualitative efforts on this project.

11.1.5 DATA COORDINATING CENTER (DCC)

Dr. Cathie Spino directs the DCC, housed at the University of Michigan within the Statistical Analysis of Biomedical & Educational Research (SABER) Unit of the Department of Biostatistics in the School of Public Health. The DCC staff will include a Database programmer, Data manager, Senior Unblinded Statistician, Statistical Analyst, Project Manager, Clinical Monitor, Web Programmer/Designer, and a Research Administrator. In addition, the blinded senior statistician, Dr. Susan Murray, is located at the University of Michigan. The DCC plays a pivotal role in the design, implementation, execution and administration of the study. The DCC will be responsible for randomization, eCRFs and online reporting systems, preparation of the manual of operations for data entry, addressing questions regarding entry and analysis, monitoring recruitment, follow-up and adherence to protocol, and scheduling and arranging meetings of the Executive Committee, Steering Committee, and Medical Monitor. The DCC will prepare all of the routine study reports for the Executive Committee, Operations Committee, and Medical Monitor. The DCC will interact with all of the Cores and other Committees, as needed. The DCC will compile data tables and listing for DSMB reports.

11.1.6 CLINICAL COORDINATING CENTER

The Clinical Coordinating Center (CCC) will be led by Principal Investigators Fernando Martinez, MD, MS at Weill Cornell Medicine, and MeiLan Han, MD, MS at the University of Michigan. Dr. Martinez will be responsible for overall study oversight as well as fiscal management of the overall project and capitation payments to sites for work performed. He will also be responsible for communication with NIH and submission of annual reports. Dr. Han will work with the Data Coordinating Center to oversee clinical trial enrollment and, along with her statistical team, be responsible for coordinating statistical analysis. The process for making decisions on scientific direction and allocation of resources will be made by both Drs. Martinez and Han, with input from the rest of the investigative team as needed.

Additional Clinical Coordinating Center (CCC) responsibilities:

- Establish subcontracts with enrolling sites, central laboratories, imaging service providers, and others as appropriate
- Protocol development and scientific design oversight
- Statistical analysis
- Participating study site selection
- Review of serious adverse events and unanticipated problems involving risk to participants or others, reporting to participating centers and regulatory reporting
- Prepare and maintain Clinical Coordinating Center IRB submissions
- Analyze and present data to DSMB

Clinical Coordinating Center Personnel

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11.1.7 12 MONTH SURVEY COORDINATING CENTER

The 12 month Survey Coordinating Center will be led by Co-Investigator Barbara Yawn, MD MSc, Chief Science Officer at the COPD Foundation. Dr. Yawn will be responsible for oversight of the development and implementation of the reminder notices and 12 month survey administration by COPD Foundation study personnel for participants selected to complete the 12 month follow up survey.

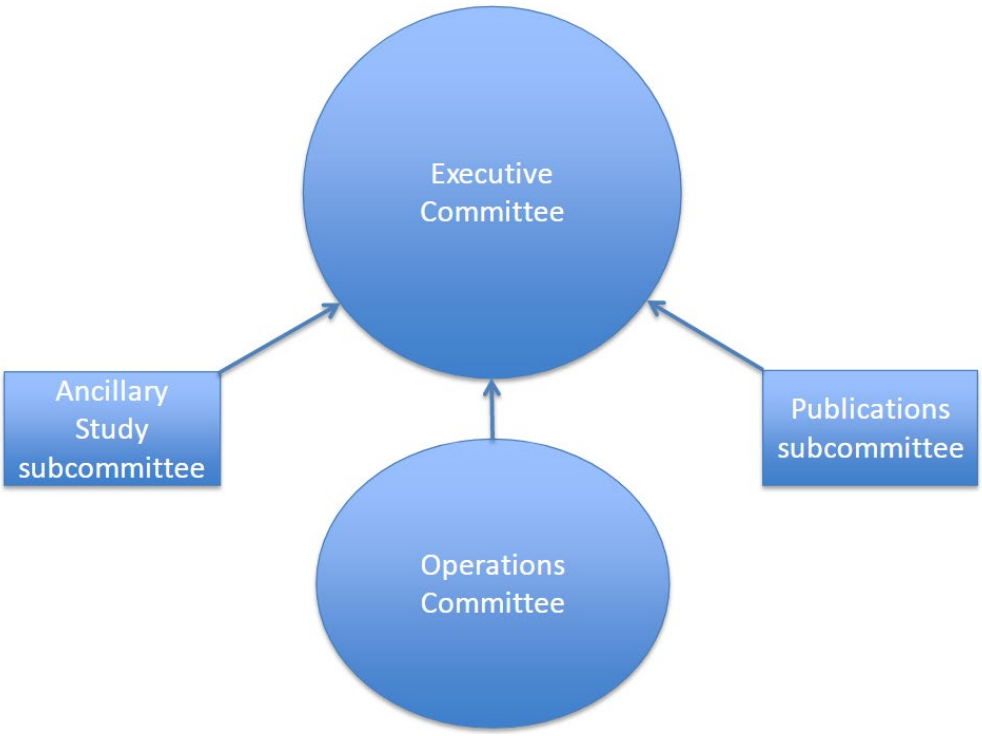
11.2 ORGANIZATIONAL STRUCTURE

The Executive Committee will be led by the Principal Investigators and will consist of the 2 elected PBRN Directors, 1 representative of the COPD Foundation, Co-Investigators, Data Coordinating Center PI and Project Manager, NIH official and Clinical Coordinating Center Project Managers. The Executive

Committee will meet every one-to-two weeks to administratively direct and monitor the progress of the study and to respond to any design, implementation or administrative issues that arise during the study.

The Operations Committee will consist of Overall Principal Investigators, PBRN Directors and lead coordinators, DCC Project Managers, and Co-Investigators. It will address implemental and administration faced by the PBRN practices that arise during the study.

Other subcommittees, such as the Publications and Ancillary Studies Subcommittees, will be constituted to support maximizing the utility of the CAPTURE study to the scientific community.



12 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data, documentation and completion. An individualized quality management plan will be developed.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

13 DATA HANDLING AND RECORD KEEPING

13.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Comprehensive data coordinating center (DCC) functions for this clinical trial, including clinical monitoring, database development, web-based data entry and management, as well as the creation and export of study reports for the DSMB will be provided by the University of Michigan Statistical Analysis of Biomedical and Education Research (SABER) group. Housed in the top nationally ranked Department of Biostatistics, SABER, in its 17-year existence, has served as the DCC for over 50 studies, including multiple NIH-sponsored networks.

The DCC will use OpenClinica® (OpenClinica Clinical Trial Software; OpenClinica, LLC, Waltham, MA), a clinical trial software platform for electronic remote (i.e., site-based entry) data capture and clinical data management, as the basis for our custom-designed data entry and management system. The majority of data will be collected via electronic Case Report Forms (CRFs); however, other data sources, such as laboratory data from the central laboratory, may be used. In these circumstances, the DCC will also utilize electronic data transfer. Protocols for the transfer of data, with careful attention to data integrity, will be written by experienced programmers and stored in the OpenClinica database or data mart.

The DCC has established a set of standard operating procedures (SOPs) governing the processes used to ensure patient privacy and data confidentiality, including the use of anonymous participant IDs on CRFs and in reports. OpenClinica® enables compliance with Good Clinical Practice (GCP) and regulatory requirements by providing differentiated user roles and privileges, password and user authentication security, electronic signatures, SSL encryption, and comprehensive auditing to record and monitor access and data changes.

Data collection is the responsibility of the central study staff at the PBRN under the supervision of the PBRN Director (investigator). The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. In addition to the protocol, the DCC will prepare a Manual of Procedures which provides additional detail on data collection procedures, including source documentation, eCRF completion guidelines, data handling procedures and procedures for data monitoring and quality control that ensure these data are accurate, consistent, complete and reliable and in accordance with ICH 36.

13.2 STUDY RECORDS RETENTION

Study documents should be retained as required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

13.3 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1

- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation or scheduled protocol-required activity. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

13.4 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers after the completion of the primary endpoint by contacting Drs. Martinez and Han.

14 PROTOCOL AMENDMENT HISTORY

Protocol Amendment 2.0 - Summary of Changes				
Location	**Page Number**	**Type of Change**	**Description**	**Rationale**
Cover Page	---	*Administrative*	Update Protocol Version to 2.0 and update version date to	Amendment version and date
Cover Page	---	*Administrative*	Add NCT # for each AIM	Add all 3 numbers to protocol since each AIM is registered in clinicaltrials.gov
Table of Contents	---	*Administrative*	Corrected page numbers for new version	Updating Table of Contents to reflect any page number shifts due to reformat
Multiple Sections	Multiple	*Administrative*	Changed Medical Chart Review to Medical Record Review throughout the protocol	Changed Medical Chart Review to Medical Record Review throughout the protocol
1.2 Schema Table 1	9	*Clarification*	Concomitant medications revised to read Respiratory Medications	Further clarification since these are limited to respiratory medication not all medications

1.2 Schema Table 1	9	*Clarification*	Foot note 3 moved to 12 month to reflect the data that will be collected for subjects who qualify for 12 month follow-up w	Clarification that 12 month column is for indicating what data will be collected for subjects who meet 12 month follow-up criteria
1.2 Schema Table 1	9	*Clarification*	X in last column for 12 month spirometry was deleted. This was originally meant to be footnote that post bronchodilator spirometry would be performed at baseline for those subjects that qualified	Further clarification that spirometry will not be done at 12 month follow-up, the footnote was meant to reflect post bronchodilator spirometry at baseline for those subjects who qualify
Section 2.3.1 Known Potential Risks	14	*Revision*	For Albuterol: A targeted safety questionnaire will be administered to all participants prior to albuterol to exclude those with a previous adverse event with the medication and others at high risk due to cardiac abnormalities.	Subjects are excluded who have had MI and therefore not necessary
Section 4.1 Overall Study Design	21	*Clarification*	Patient-reported data will be collected by telephone, secure web-based server, and mail-based methodologies <u>based on participant preference and completed by the COPD Foundation.</u>, as well as medical record abstraction, depending upon practice site preferences and feasibility.	The COPD Foundation will be collecting participant 12 month follow-up subject questionnaires
Section 4.1 Overall Study Design	21	*Clarification*	Clinic site data will also be collected from the Subject medical record data will be collected from the medical record to assess for changes in practice-level care.	Further clarification that this data will be collected from medical record
Section 6.3 Study Intervention Compliance	27	*New*	If results were not shared at the time of the CAPTURE study visit, then the date of sending the CAPTURE results will be recorded on the appropriate eCRF by filling in the date (day/month/year) the exact copy of the CAPTURE Toolresults were sent to the clinician through a inter–clinic email or other HIPPA-compliant method and placed in the medical record. The goal is to communicate the results to the clinician in a timely manner within 3 business days. The DCC will monitor review all participants' eCRFs to assure that all those enrolled from practices randomized to CAPTURE results have been shared with clinicians. in the specified timeframe.	The study team wanted to clarify that the exact copy of the CAPTURE tool should be shared with clinician. Also wanted to make timing of sharing less restrictive and the team recognized that restrictive parameters cannot always be realized in clinical practice setting

Section 8.2 Longitudinal Follow-up Assessment and Data Collection	30	*Clarification*	Medical chart abstractions completed by PBRN coordinators and participant questionnaires administered by study team members from the COPD Foundation are used.	Clarification that medical chart reviews will be done by PBRN coordinators and COPD Foundation will administer participant questionnaires at 12 months
Section 8.2 Longitudinal Follow-up Assessment and Data Collection	30	*Clarification*	Data from clinical visits to be collected at follow-up by telephone, secure web-based server, or mail-based methodologies directly from participants and administered by COPD Foundation study personnel	Clarification that COPD Foundation will administer participant questionnaires at 12 months
Section 10.1.1 Informed Consent Process	45	*New*	All PBRN research coordinators, COPD Foundation study staff and other clinical investigators will be certified by their local IRB in informed consent and human studies research.	The COPD Foundation has attained IRB approval as their team will be interacting with participants
Section 10.1.3 Confidentiality and Privacy	46	*Clarification*	In addition, it may be transmitted and stored at the DCC in a database separate from the clinical database (used for statistical analysis and scientific reporting) and with COPD Foundation study team study coordinator access to aid in contacting participants at the 12-month follow-up.	COPD Foundation will have access to participant contact information from a separate database in order to contact participants for follow-up questionnaire completion
Section 11.1.2 Practice Based Research Networks (PBRN)	47	*Administrative*	Moved Roles and Responsibilities to section 11.1.2	Moved Roles and Responsibilities to section 11.1.2
Section 11.1.2 Practice Based Research Networks (PBRN)	47	*Revision*	Change Carolinas HealthCare System to Atrium Health and add new PI for Oregon Rural Practice-Based Research Network	Carolinas HealthCare System is now Atrium Health and the new PI at Oregon, Dr. Lyle Fagnan is retiring and Dr. Nancy Elder will take his place as director and site PI for CAPTURE
Section 11.1.7 Clinical Coordinating Center	49	*Clarification*	Update titles for COPD Foundation study members	Administrative change to include titles for Dr. Yawn
Section 11.1.8 12 Month Survey Coordinating Center	50	*New*	Add 12 Month Survey Coordinating Center to Study Leadership, Section 11.	The COPD Foundation study team will be coordinating outreach to 12 month follow-up subjects and administering surveys
Section 11.2 Organizational Structure	51	*Clarification*	Includes 1 representative of the COPD Foundation in the Executive Committee Organization description.	COPD Foundation representatives are part of the Executive Committee currently
Section 4.1 Overall Study Design	9, 10, 21	*New*	Deletion of CAT Score ≥ 10 and CAPTURE Score ≥ 2 and return to CAPTURE+ and abnormal spirometry as longitudinal follow-up criteria	The study team proposes to defer longitudinal follow-up based solely on an isolated, baseline CAT or CAPTURE scores as it is outside the scope of the current CAPTURE program. The study team is also proposing to return to the original scientific approach to follow CAPTURE+ (as defined in the protocol) subjects along with abnormal post-BD spirometry and 5%

				random sample of those subjects that meet neither of these criteria. Those subjects already selected under the current algorithm would still be followed longitudinally (and noted as selected under the initial follow-up selection criteria) and would use data as appropriate. Importantly, the primary care clinician colleagues within the CAPTURE program do not feel there is a safety issue in not following this population as there are no data defining a negative impact of an isolated, elevated CAT score in primary care patients.
Section 1.1 Synopsis, Section 4.1 Overall Study Design, Section 8.1 Baseline Assessments and Data Collection	3, 20, 29	*New*	Addition of adjudication of the presence of obstruction on post-bronchodilator spirometry	As the study commenced, several instances of the faulty spirometry software reading incomplete or participant refusal of post-bronchodilator occurred and led to the need for spirometry core to determine review process in these instances and validity of pre-bronchodilator spirometry. The rationale for this is that in other databases where all patients had both pre and post-bronchodilator spirometry, those who had a pre-bronchodilator FEV1/FVC less than 0.65 had a post-bronchodilator FEV1/FVC less than 0.70 more than 95% of the time.
8.1 Baseline Assessments and Data Collection	28	*New*	Addition of spirometry instructions if participant has taken a medicine they breathed into lungs from puffer or inhaler within two hours of spirometry test	Since study start, one participant reported taking albuterol shortly before the visit. The study clinicians confirmed this scenario would constitute the participant being in a post-bronchodilator state already with no further need to proceed after initial spirometry. The data collection process has been updated to assure these values would be placed in post-bronchodilator data. Coordinators are instructed to ask this question before spirometry should this scenario occur again during the study.

Protocol Amendment 3.0 - Summary of Changes

Location	Page Number	Type of Change	Description	Rationale
Cover Page	---	*Administrative*	Update Protocol Version to 3.0 and update version date to 24 September 2019	Amendment version and date updated
Cover Page	---	*Administrative*	Add NCT # for each AIM	Add all 3 numbers to protocol since each AIM is registered in clinicaltrials.gov
Multiple Sections	Multiple	*Revision*	Number of PBRNs participating in aims 1 and 2 revised to 6 PBRNs throughout protocol.	Additional PBRN added
1.2 Schema Table 1	9	*Revision*	CAPTURE 12 additional items questionnaire	The CAPTURE 12 item additional questionnaire was renamed.
Section 8.1 Baseline	30	*Clarification*	CAPTURE Additional Items Questionnaire administration	Further instruction for administration of CAPTURE Additional Items Questionnaire,

Assessments and Data Collection			instruction added to Study Assessments.	as described in Section 1.2 Schema table, was added.
Section 11.1.2 Practice Based Research Networks (PBRN)	48	*Revision*	University of Illinois, Chicago added as a participating PBRN.	University of Illinois, Chicago added as an enrolling site in aims 1 and 3.
Protocol Amendment 4.0 - Summary of Changes				
Location	**Page Number**	**Type of Change**	**Description**	**Rationale**
Protocol Amendment Summary of Changes Table	---	*Administrative*	Protocol Amendment 2.0 – Summary of Changes was added to the Summary of Protocol Amendments Table.	Amendment 2.0 – Summary of Changes was added to provide a comprehensive list of changes across all protocol amendments.
Protocol Amendment 5.0 - Summary of Changes				
Location	**Page Number**	**Type of Change**	**Description**	**Rationale**
1.2 Schema Table 1, 8.2 Longitudinal follow-up assessment	9, 32	*New*	A COVID-19 questionnaire was added to the 12-month follow-up visit, performed by the COPD Foundation.	A COVID-19 questionnaire was added to collect information about the COVID-19 prevalence in primary care, impact on symptoms, relation to comorbidities, and impact on provider outcomes.
2.1 Study Rationale, 4.1 Overall Design, 4.2 Scientific Rationale for Study Design	11, 22, 23	*New*	Rationale for collecting COVID-19 information from participants was added.	The impact of COVID-19 on COPD Case Finding and respiratory symptoms in primary care is unknown. COVID-19 information will be used to investigate this.
4.1 Overall Study Design	21	*Revision*	The following change was made: Participants who meet the criteria for follow-up will be sent notification~~/reminder letters within the first 3 weeks of~~ **shortly after** enrollment and **receive** at 3, 6, and 9 months	Language was updated for flexibility in notification of participants in order to allow time to confirm follow-up criteria.
8.1 Baseline Assessments and Data Collection	29	*Revision*	Additional guidance for sites to follow their local institutional guidelines for spirometry was added.	Institutional guidance for minimizing the risk of COVID-19 spread during spirometry varies across sites. Sites should ensure they are following local guidance.
8.3 Aim 2 Assessments	34	*Revision*	Participants will receive a $15 gift card for completion of the opinion survey, instead of $10.	This was a typo in the prior version of the protocol.
8.2 Longitudinal follow-up assessment	31	*New*	Extraction of data related to COVID-19 confirmed and suspected cases will be added to the 12 month medical record review.	A COVID-19 questionnaire was added to collect information about the COVID-19 prevalence in primary care, impact on symptoms, relation to comorbidities, and impact on provider outcomes.
Protocol Amendment Summary of Changes Table	---	*Administrative*	Protocol Amendment 2.0 – Summary of Changes was added to the Summary of Protocol Amendments Table.	Summary of Changes for protocol versions 2.0 and 3.0 –were added to Section 14 to provide a comprehensive list of changes across all protocol amendments.

15 LITERATURE REFERENCES

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The CAPTURE Study: Validating a unique COPD case finding tool in primary care

Protocol Number: 1R01HL136682

National Clinical Trial (NCT) Identified Number:

NCT03581227, NCT03653611, NCT03583099

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Funder:

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Version Number: v. 6.0

10 JAN 2022

Protocol Amendment 6.0 - Summary of Changes				
Location	**Page Number**	**Type of Change**	**Description**	**Rationale**
Cover page	---	*Administrative*	Update Protocol Version to 6.0 and update version date to 10 JAN 2022	Amendment version and date
1.1 Synopsis Definitions	3	*Revision*	Language related to normal PEF has been changed to greater than or equal to the measurement ranges for males and females. "…defined as ≥350 L/min for males and ≥ 250 L/min for females"	The previous sentence stated that the PEF scores needed to be greater to 350 L/min or 250 L/min and not inclusive of these values.
1.1 Synopsis Definitions	3	*Revision*	Language related to exacerbations been changed to greater than or equal 1. "≥ 1 exacerbation-like event within the past 12 months."	The previous sentence stated that the number of exacerbations need to be greater than 1 but was not inclusive of 1. The new statement is to clarify that clinically significant COPD includes 1 or more exacerbations.
1.1 Study Population	6	*Revision*	The overall N has been changed to approximately 5000. (total N ~~=~~ ≈ 5000)	The DSMB approved the reduction of enrollment from 5000 but the study will aim to enroll as many participants as possible. This has been reflected throughout the document.
2.1 Study Rationale	11	*Revision*	We will conduct ~~a 5,000 participant~~ cohort study of approximately 5,000 participants	The DSMB approved the reduction of enrollment from 5000 but the study will aim to enroll as many participants as possible. This has been reflected throughout the document.
2.2 Background	13	*Revision*	Language related to exacerbations been changed to greater than or equal 1. "…COPD with ≥ 1 ECOPD"	The previous sentence stated that the number of exacerbations need to be greater than 1 but was not inclusive of 1. The new statement is to clarify that clinically significant COPD includes 1 or more exacerbations.
4.1 Overall Design	20	*Revision*	Language related to normal PEF has been changed to greater than or equal to the measurement ranges for females. "≥250 L/min for females"	The previous sentence stated that the PEF scores needed to be greater to 350 L/min or 250 L/min and not inclusive of these values. Participants with PEF values greater than or equal to 350 L/min (males) or 250 L/min (females) are CAPTURE Negative.
4.1 Overall Design	20	*Revision*	Language related to exacerbations been changed to greater than or equal 1. "…≥ 1 exacerbation like event within the past 12 months."	The previous sentence stated that the number of exacerbations need to be greater than 1 but was not inclusive of 1. The new statement is to clarify that clinically significant COPD includes 1 or more exacerbations.

9.1.1.1 Sensitivity and Specificity of the CAPTURE Tool	39	*Revision*	Language related to exacerbations been changed to greater than or equal 1. "... either >1 exacerbation-like event (ECOPD) within the past 12 months"	The previous sentence stated that the number of exacerbations need to be greater than 1 but was not inclusive of 1. The new statement is to clarify that clinically significant COPD includes 1 or more exacerbations.
9.1.1.3 Sensitivity and Specificity of the CAPTURE Tool	41	*Revision*	"(for a total of approximately 5,000-patients)."	The DSMB approved the reduction of enrollment from 5000 but the study will aim to enroll as many participants as possible. This has been reflected throughout the document.
9.2 Population for Analyses	42	*Revision*	Language related to exacerbations been changed to greater than or equal 1. "…>1 exacerbation-like event (ECOPD)"	The previous sentence stated that the number of exacerbations need to be greater than 1 but was not inclusive of 1. The new statement is to clarify that clinically significant COPD includes 1 or more exacerbations.

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STATEMENT OF COMPLIANCE

This study will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CAO	Chronic Airflow Obstruction
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
ECOPD	Exacerbation of Chronic Obstructive Pulmonary Disease
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FEV1	Forced Expiratory Volume in 1 second
FFR	Federal Financial Report
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practice
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act

IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PBRN	Practice-Based Research Network
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
RE-AIM	Reach, Effectiveness, Adoption, Implementation, Maintenance
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States
USPSTF	United States Preventive Services Task Force

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	The CAPTURE Study: Validating a unique Chronic Obstructive Pulmonary Disease (COPD) case finding tool in primary care
Study Description:	**Aims 1 and 3**. A prospective, multicenter study including a cross-sectional validation to define sensitivity and specificity of CAPTURE and its impact on clinical care across a broad range of primary care settings in a cluster randomized controlled clinical trial. The CAPTURE tool consists of a 5-item self-administered questionnaire and peak expiratory flow (PEF) measurement, designed to identify undiagnosed patients with Chronic Obstructive Pulmonary Disease (COPD). **Aim 2.** This study delivers a qualitative assessment of clinical practice acceptance of and implementation strategy for CAPTURE case finding within 10 varied primary care practices across 5 US PBRN regions. We evaluate primary care practice attitudes, beliefs and recommendations about CAPTURE's potential to feasibly integrate into clinical practice patterns, workflow and quality improvement paradigm planning in a variety of primary care clinical settings.
Definitions:	**CAPTURE+ =** Participants with • CAPTURE score $\geq$ 5, or • CAPTURE score of 2, 3, or 4 with a low PEF, defined as <350 L/min for males and <250 L/min for females **CAPTURE-** = Participants with CAPTURE score < 2 or scores 2-4 with normal PEF, defined as $\geq$350 L/min for males and $\geq$ 250 L/min for females **Spirometrically defined COPD =** Participants with abnormal spirometry, defined as post-bronchodilator FEV_1/FVC <0.7. If a participant is unable to complete a post-bronchodilator spirometry (refusal, technical error on the part of coordinator, etc.), and the pre-bronchodilator FEV1/FVC is less than 0.65, the participant will be considered to have COPD for the purpose of follow-up in this study. **Clinically significant COPD =** Participants with abnormal spirometry, defined as post-bronchodilator FEV_1/FVC <0.7, plus one of the following: • FEV_1 < 60% predicted, or • $\geq$ 1 exacerbation-like event within the past 12 months. **Mild COPD =** Participants with abnormal spirometry, defined as post-bronchodilator FEV_1/FVC<0.7 plus both of the following: • $FEV_1 \geq$ 60% and • No prior history of ECOPD
Objectives:	**Aims 1 and 3 Primary Objectives:** • **Aim 1 -** Define the sensitivity and specificity of CAPTURE for identifying previously undiagnosed patients with clinically significant COPD in a broad range of primary care settings.

	• **Aim 3 –** Define the impact of CAPTURE information provided to clinicians in identifying and managing patients with respiratory symptoms (CAPTURE+) across a broad range of primary care settings. **Aim 2 Primary Objective:** Explore clinical practice implementation approaches to and acceptance of CAPTURE case finding for clinically significant COPD in a range of primary care practices. **Aims 1 and 3 Secondary Objectives:** • **Aim 1 –** • Define the sensitivity and specificity of CAPTURE for patients with COPD across a broad range of racial and ethnic groups in a range of primary care settings. • Determine positive and negative predictive values (PPV and NPV) in different practice settings. • Verify the optimal use (cutoff threshold) of the CAPTURE tool in combination with PEF measurements for identifying undiagnosed COPD. • Determine patient and site characteristics that, with the CAPTURE assessment, will best identify persons with undiagnosed COPD. • Determine whether CAPTURE is useful in identifying other definitions of undiagnosed COPD including: 1) spirometry-defined COPD, and 2) mild COPD • Determine the potential impact of SARS CoV-2 infection on the above operating characteristics of the CAPTURE approach. • **Aim 3 -** • Define the impact of CAPTURE clinician education, and patient-level CAPTURE information to clinicians (“CAPTURE education”) on selected additional therapeutic interventions in previously undiagnosed patients with clinically significant COPD. • Assess impact of CAPTURE education on clinician interventions specific to smokers. • Determine the impact of CAPTURE education on patient symptoms, exacerbations, hospitalizations, and mortality. • Determine the impact of CAPTURE education when COPD is defined spirometrically. • Determine the potential impact of SARS CoV-2 infection on clinical actions taken in response to CAPTURE screening. **Aim 2 Secondary Objectives:** • Qualitatively assess primary care clinical staff COPD practice behavior – including COPD screening and diagnostic perceptions, beliefs and knowledge – that will inform strategies to improve CAPTURE RE-AIM (reach, impact, adoption, implementation and maintenance of use) characteristics.

	• Qualitatively assess primary care patient opinion of CAPTURE COPD case finding that will inform strategies to improve CAPTURE RE-AIM (reach, impact, adoption, implementation and maintenance of use) characteristics. • Determine the potential impact of SARS CoV-2 infection on the application of the CAPTURE approach.
Endpoints:	**Aims 1 and 3 Primary Endpoints:** • Aim 1 – ○ Sensitivity and specificity of CAPTURE to identify previously undiagnosed patients with clinically significant COPD at baseline. • Aim 3 – ○ Proportion of CAPTURE+ participants who meet at least one of the following within 12 months of study baseline (composite endpoint): 1) referral for or completion of clinical spirometry testing, 2) new diagnosis of COPD, 3) newly prescribed respiratory medication (long acting bronchodilator or anti-inflammatory for respiratory condition), or 4) referral to a specialist for respiratory evaluation/treatment **Aim 2 Primary Endpoints:** • Primary care clinician recommendations that inform CAPTURE RE-AIM strategies at both provider and clinical support levels of primary care practice. • Primary clinician recommendations that inform CAPTURE-associated COPD education models for primary care clinicians. • Primary care clinician recommendations that inform CAPTURE-associated COPD clinical quality improvement designs across a variety of primary care practice types. **Aims 1 and 3 Secondary Endpoints:** • Aim 1 – ○ Sensitivity and specificity of CAPTURE to identify previously undiagnosed patients with COPD across sex, ethnic groups, urban vs rural location, and educational level. ○ Positive and negative predictive values (PPV and NPV) in different practice settings. ○ Areas under the receiving operator characteristic curve (AUC) for various cutpoints of CAPTURE and PEF_1 measurements to determine the best cutpoint for COPD+ screen. ○ AUC to identify the combination of patient/site characteristics which best discriminates those with clinically significant COPD. ○ All primary and secondary endpoints as applied to 1) spirometry-defined COPD and 2) mild COPD • Aim 3 – ○ Proportion of CAPTURE+ patients who meet the components of the composite endpoint. ○ Proportion of patients with clinically significant COPD who meet the composite endpoint.

	○ In participants with clinically significant COPD who are current smokers, the incidence of physician referral to a formal smoking cessation program, prescribed smoking cessation medication, and referral to pulmonary rehabilitation program. ○ In participants with clinically significant COPD, change in CAT score, and proportion of patients who experience exacerbations, hospitalizations, or mortality. ○ All of the above endpoints for Aim 3, with the patient population defined as those who have COPD defined spirometrically. **Aim 2 Secondary Endpoints:** • Existing COPD screening and diagnostic and case finding processes within a variety of primary care practices. • Primary care practice belief about capacity to change from existing COPD screening and diagnostic assessment strategies. • Practice-specific COPD screening and diagnostic continuing education preference.
Study Population:	**Aims 1 and 3.** Adults 45-80 years old without a prior diagnosis of COPD (total N ~ 5000) **Aim 2.** - 10 primary care practices: 2 practices per PBRN with up to 15 clinical staff participants per practice; clinician N = up to 150 (up to 30 clinician participants per PBRN). - Aim 1 patient opinion survey population; patient N = 200 (40 patients from each PBRN; adults 45-80 years old, without a prior diagnosis of COPD). - Total N = up to 350
Phase:	N/A
Description of Sites/Facilities Enrolling Participants:	**Aims 1 and 3.** Enrollment will occur in approximately 100 primary care practices affiliated with 7 primary care based practice networks (PBRN) across the United States who exhibit a broad range of gender, ethnic, racial, socioeconomic, and regional diversity. **Aim 2.** • Two primary care practices chosen by each of the same 5 PBRN co-investigator teams make up the 10 aim 2 practices from which clinician participants are enrolled. These 10 practices are separate from the 100 chosen practices in aims 1 and 3. • Patient participants are a sub-sample of those participants enrolled in aims 1 and 3.
Description of Study Intervention:	**Aims 1 and 3.** Primary care practices will be randomized to either receive basic COPD education and patient-level CAPTURE information with CAPTURE education (initially basic then later enhanced based on data collected in Aim 2) versus COPD education only. **Aim 2.** Participating primary care clinicians from 10 varied practices are surveyed at three different time points and participate in two focus groups qualitatively assessing CAPTURE implementation strategy and COPD case

	finding approaches in primary care. Participating patients complete one 10-minute written opinion survey about CAPTURE.
Study Duration:	**Aim 1 and 3.** 4 years **Aim 2.** 2 years
Participant Duration:	**Aims 1 and 3.** Up to 12 months **Aim 2.** • Primary care practice clinicians: questionnaires and focus groups (total 3 hours/participant) over 16 months. • Primary care patients: one 10-minute questionnaire/participant over 14 months.

1.2 SCHEMA

FIGURE 1. OVERALL STRUCTURE OF AIMS

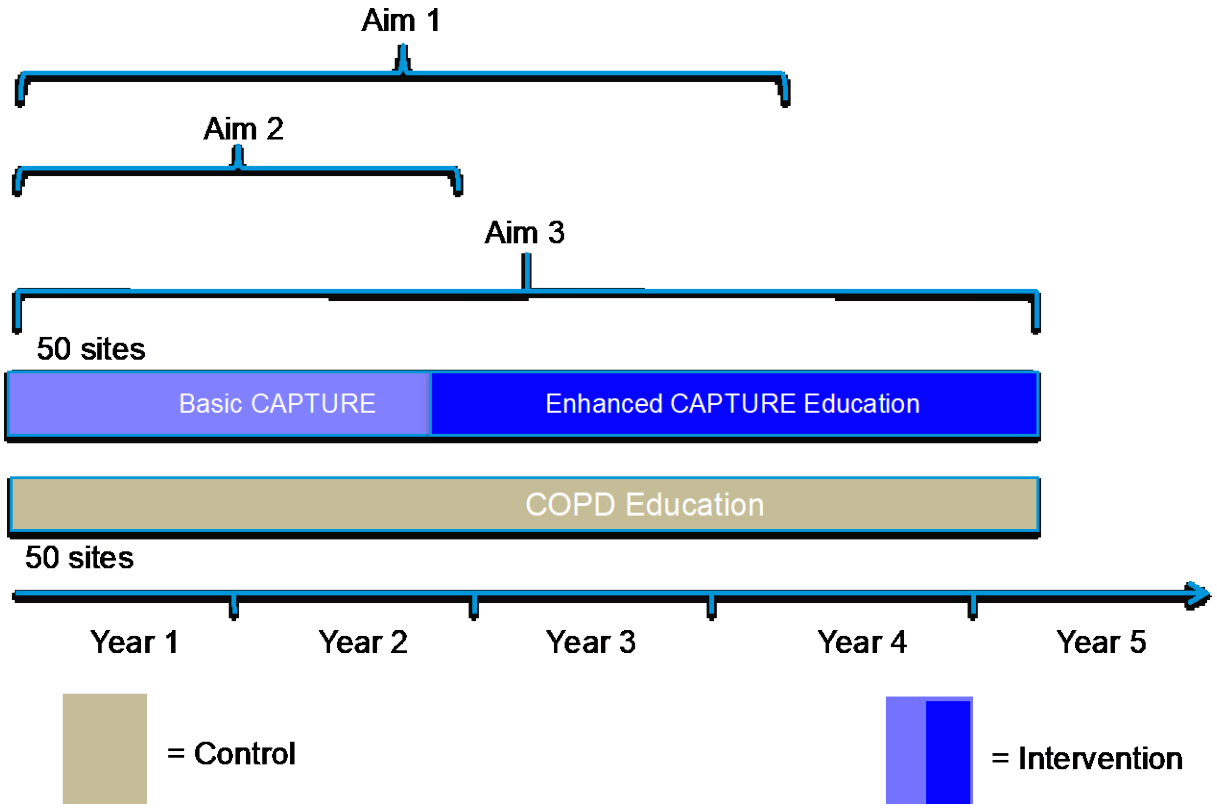

FIGURE 2. STRUCTURE OF AIM 2

1.3 SCHEDULE OF ACTIVITIES (SOA)

Table 1: Schedule of Activities (Aims 1 and 3)

	Pre-Visit Contact[1]	**Baseline**	**12 Months[3]**
Contact (C)/ Visit (V)/Medical Record Review (MRR)	**C1**	**V1**	**C2/MRR[5]**
Time point, days (Visit window)	**Prior to outpatient visit (≤-1)**	**Within 30 days of pre-visit contact**	**365 ±30 (C2)**
Contact patient re: interest in study visit[1]	X		
Informed consent		X	
Demographics		X	
Medical history (Co-morbidities)[2]		X	
Vaccination status		X	X
CAPTURE 5-item questionnaire		X	X
CAPTURE item additional questionnaire		X	
Peak Expiratory Flow (PEF)		X	
Height and weight		X	
Respiratory medications review		X	X
Spirometry[4]		X*	
Respiratory symptoms, exacerbation assessment		X	X
Smoking exposure history		X	
Smoking cessation review[6]			X
COPD Assessment Test (CAT)		X	X
COVID-19 Questionnaire		X	X
Adverse Events		X	
Medical record review Additional COVID-19 items			X X

1. Optional per site recruitment preferences
2. Comorbidities including cardiovascular, respiratory and malignant disorders
3. Recorded for a subset of participants who meet any of the following criteria: 1) CAPTURE+ subjects defined as CAPTURE Score ≥ 5 or CAPTURE score of 2, 3, or 4 with a low PEF, defined as <350 L/min for males and <250 L/min for females 2) abnormal spirometry defined as $FEV_1/FVC < 0.70$ or $FEV_1 < 80\%$ predicted at baseline; and, 3) a random sample of approximately 5% of those who do not meet criteria 1 and 2. For participants meeting criteria 1 and 2 who cannot or choose not to complete the 12-month assessment, medical record review will still be completed. For participants meeting criteria 1 and 2 who

change medical practices and medical record review cannot be completed, patients will be contacted for completion of patient reported data. For participants meeting criterion 3 where all of the protocol-specified 12-month assessments cannot be made, another participant will be selected at random to replace this participant.

4. Pre-bronchodilator spirometry will be done for all participants. Post-bronchodilator spirometry will be performed for participants with abnormal spirometry ($FEV_1/FVC < 0.70$ or $FEV_1 < 80\%$ predicted) *If the participant has taken a bronchodilator within a 2-hour window of spirometry the spirometry will be considered post-bronchodilator and a pre-bronchodilator spirometry will not be done.
5. The 12-month assessment consists of patient reported data, collected by the COPD Foundation, and medical record review completed by site coordinators.
6. This will be completed in those that are smoking at V1.

2 INTRODUCTION

2.1 STUDY RATIONALE

Undiagnosed COPD is a leading cause of morbidity and mortality. Spirometry, the 'gold standard' for diagnosis, is not recommended for screening in asymptomatic individuals or untargeted case finding and remains widely underutilized in primary care settings. Targeted case finding approaches have been strongly advocated but currently available approaches generally identify patients across the spectrum of mild to severe disease without reference to potential therapeutic benefit or exacerbation risk, thereby limiting clinical impact and acceptance in primary care. There is an urgent need to develop and implement simple case finding approaches that can identify patients with clinically significant COPD in primary care settings.

Through a multi-stage, iterative process we developed a simple case finding tool using five questions combined with selective peak expiratory flow **(PEF)** measurement that identifies individuals with 1) an $FEV_1 < 60\%$ predicted and/or 2) at risk for ECOPD. We call this tool CAPTURE (**C**OPD **A**ssessment in **P**rimary Care **T**o Identify **U**ndiagnosed **R**espiratory Disease and **E**xacerbation Risk)(1). As clinical trials have demonstrated benefit and therapeutic guidelines recommend therapy for these individuals we have labeled these patients as suffering from 'clinically significant' COPD. The long-term goal of this project is to identify these patients so that they can be treated and result in improved health status, reduced exacerbations, and decreased morbidity.

The *overall objectives* of Aims 1 and 3 of this project are to 1) validate the sensitivity, specificity, and predictive value of CAPTURE to identify undiagnosed, clinically significant COPD patients in a diverse primary care population; and explore whether identifying these patients results in improved COPD specific care and health status. Our *principal hypothesis* is that CAPTURE can effectively and efficiently identify primary care patients with undiagnosed, clinically significant COPD. We objectively test our principal hypothesis by completing to two separate and linked aims:

Aim 1 – Determine the sensitivity and specificity of CAPTURE in identifying clinically significant COPD patients in a broad range of primary care outpatient practices.

Working hypothesis - A simple case finding methodology using a five-item questionnaire with selective PEF measurement will identify undiagnosed patients with clinically significant COPD.

We will conduct a cohort study of approximately 5,000 participants in 100 primary care practices affiliated with five primary care based research networks **(PBRN)** that provide access to previously undiagnosed patients with clinically significant COPD who exhibit gender, ethnic, racial, socioeconomic and regional diversity.

Aim 3 – Define the impact of CAPTURE screening in a broad range of primary care outpatient practices and evaluate practice and patient characteristics that are associated with care implementation and clinical outcomes for patients with respiratory symptoms (CAPTURE+).

Working hypothesis – Provision of patient specific CAPTURE data to practicing clinicians will result in improved management of patients with respiratory symptoms (CAPTURE+).

We will provide basic COPD education and patient level CAPTURE information and education to site clinicians at 50 of the sites and prospectively follow selective, pre-defined subgroups of patients to define relevant outcomes. Care at the other 50 clinical sites will follow standard of care with basic COPD education to clinicians.

Assessing the potential clinical impact of a novel COPD case finding strategy includes confirmation of validity in a diverse primary care patient population and a quantitative research evaluation of its impact on clinical decision-making and COPD patient outcomes, as found in aims 1 and 3 above. Equally important is exploration through validated implementation methods that the newly designed CAPTURE tool, even if valid and impactful, can provide real-world utility within a variety of primary care practice settings. While we find no evidence in previous COPD screening studies of such detailed appraisal, ascertaining the feasibility of clinical testing is a vital component of assuring that new approaches address potential clinical practice need, capacity, knowledge and diagnostic gaps. As much as possible, clinical respiratory innovations should align with busy workflow at all practice staff levels to more effectively identify primary care patients with undiagnosed, clinically significant COPD. The SARS-CoV-2 pandemic may potentially alter the approach to COPD Case Finding in the primary care community; the protocol has been adapted to investigate this possibility. Similarly, the potential of SARS-CoV-2 infection and the COVID-19 clinical syndrome to impact respiratory symptoms in primary care patients will also be explored.

To maximize success of the CAPTURE adoption, education and implementation in this study and in future work, Aim 2 is introduced to assess practice experience, need and preference that can inform clinical COPD case finding and education in primary care settings:

Aim 2 – Explore clinical practice implementation approaches to and acceptance of CAPTURE case finding for clinically significant COPD in a range of primary care practices.

The *overall objective* of this aim is to qualitatively explore primary care clinical practice acceptance of COPD case finding implementation and define education and feasibility strategies to enhance adoption in primary care practice. This assessment includes understanding clinician and clinical staff COPD practice and perceptions in addition to the feasibility of case finding integration into existent clinical work patterns. To attain this objective, we address one *working hypothesis* – a COPD case finding methodology using a validated one-page, five-item questionnaire with selective PEF measurement (CAPTURE) can be incorporated into the clinical practice patterns, clinical workflow, communication and practice-based quality improvement paradigms in a variety of primary care clinical settings. The *rationale* for this objective reflects the importance of establishing if an innovative approach to COPD case finding (CAPTURE) is considered a pragmatic tool with potential utility for primary care clinicians within real-world clinical practice settings.

With the completion of this aim we anticipate confirming that future validated approaches to COPD case finding can be adopted in a broad variety of clinical care settings thereby providing further impetus for the rigorous evaluation of a) case finding guided patient outcomes as part of routine primary care clinical practice; b) case finding use in a range of primary care health professional COPD-related education approaches, clinical quality improvement models and diagnostic guidelines; and c) the capacity of clinical case finding with informed follow-up to enhance future COPD clinical care therapeutic paradigms used in primary care practice.

2.2 BACKGROUND

Aims 1 and 3.

COPD remains a major cause of morbidity and mortality. COPD results in substantial morbidity and mortality worldwide.(2-4) Globally, the prevalence of COPD and years lived with disability increased from 1990 to 2013.(5) This is particularly evident in older individuals.(6) These well-designed population based studies confirm the growing impact of COPD.

COPD is frequently undiagnosed. We recently documented that only 28% of participants with chronic airway obstruction **(CAO)** had physician diagnosed disease.(7) Importantly, an FEV_1 <50% predicted was noted in 10% of those with undiagnosed CAO; this is similar to other cohorts or population based surveys.(8-11) There is consistency in these well-conducted studies that confirm most COPD patients are undiagnosed.

Spirometry is underutilized. The U.S. Preventive Services Task Force **(USPSTF)** recently recommended against the use of spirometry for routine, general population or practice-based screening in asymptomatic individuals.(12) An editorial by the PI of this application highlighted the limitations of this conclusion.(13) Within primary care spirometry is often viewed as time consuming and difficult to implement and interpret.(14) As such, it is not routinely used.(15-19) Even the availability of less expensive and easily used spirometers(20) has not resulted in increased utilization.(21, 22)

Undiagnosed COPD is associated with a negative clinical impact. In a robust, population based study we confirmed that undiagnosed patients experienced impaired health status and a higher risk for all-cause mortality compared to those without CAO; this was particularly evident with more severe CAO.(7) Others have confirmed increased mortality,(23) health status impairment,(24) exacerbation-like respiratory events,(11) and increased health care costs.(25, 26) As such, there are consistent data suggesting that undiagnosed COPD patients experience negative clinical events and impaired health status.

Therapeutic interventions improve COPD clinical outcomes. Well designed, randomized controlled trials confirm that COPD therapy is effective, particularly in patients with an FEV_1 < 60% predicted who are symptomatic or at risk for ECOPD.(27, 28) Despite limited data, some have suggested that earlier detection of patients with previously undiagnosed, yet clinically significant COPD, in primary care settings could improve short- and long-term patient outcomes and may be cost-effective. (29, 30)

COPD case finding approaches to date have generally been methodologically limited. Several COPD case finding tools have been created based on existing epidemiologic literature or expert opinion.(31, 32) This includes tools created by investigators in this study.(33, 34) In general, current approaches were designed to identify COPD patients without reference to disease severity or ECOPD risk, resulting in the identification of a high proportion of patients with mild or minimally symptomatic disease.(21, 33-39) Several studies have tested the accuracy of handheld flow meters for case identification with varying sensitivity and specificity.(40) Although informative in terms of CAO, PEF meters have been unable to systematically identify patients at risk of ECOPD. We tested a three-staged approach (risk-factor

questionnaire, PEF, and spirometry) for identifying moderate to severe COPD (FEV_1<60% predicted) in a convenience sample of the general population.(41) This study was limited by the nature of the population screened and the screening questionnaire used but supported the concept that PEF can facilitate COPD case finding.

A systematic analysis of existing databases provides insight into the best variables for COPD Case Identification. To identify potential items that could be useful in the identification of undiagnosed COPD we interrogated three robust datasets of populations in which the investigators on this application had major roles [COPD Foundation Peak Flow Study Cohort (n=5761); Burden of Obstructive Lung Disease Kentucky site (n=508); and COPDGene® (n=10,214)].(42) We utilized the machine learning statistical method of random forests to identify and validate variables most important in identifying patients with clinically significant COPD. COPD case finding candidate content included items reflecting exposure, personal and family history, respiratory symptoms, recent health history, activity limitation and demographics.

A comprehensive, qualitative study identified key constructs for identifying recently diagnosed patients with clinically significant COPD. We completed a two phase study that included focus groups followed by cognitive interviews to refine the key constructs for identifying patients with clinically significant COPD.(43) Fifty participants were recruited including those with mild airflow obstruction, diagnosed within the previous six months and without previous ECOPD; those diagnosed within the previous six months and with a history of at least one ECOPD within the prior year; those with 2-3 risk factors for COPD but without CAO; and those with $\geq$ 4 risk factors for COPD but without CAO. Using a content analysis approach, key themes and constructs were identified and integrated with the content of the previous literature review and data mining. We identified 44 candidate items that resonated with patients and provided important insights into a case finding instrument.

A five-item questionnaire exhibits excellent operating characteristics to identify clinically significant COPD patients. We completed a prospective, multi-site, case-control study of four groups: cases with clinically significant COPD – COPD with $\geq$ 1 ECOPD in the previous year (n=97) and COPD with no ECOPD but an FEV_1 < 60% predicted (n=89); controls – no known COPD (n=87) and COPD with an FEV_1 > 60% predicted and no ECOPD in the previous year (n=74). Using random forest analyses the 44 candidate items were reduced to 34-item, 21-item, 8-item and two different five-item sets. Through-out the item reduction process, the item sets maintained good performance, consistently misclassifying fewer than 27% of cases and controls, and with sensitivity greater than 80% and specificity greater than 70%. A five-item questionnaire exhibited good operating characteristics for separating COPD cases from controls. These characteristics were even better when separating COPD from controls without COPD.

Selective PEF measurement enhances the operating characteristics of a COPD case finding strategy. In the above case control study PEF was measured using a mechanical PEF meter with disposable mouthpieces. To optimize sensitivity and specificity, the following cut-off scores were selected, based on our data, for identifying cases of clinically significant COPD using PEF alone: males: <350 L/min; females: <250 L/min. The best method for predicting cases was a combination of the questionnaire and PEF **(CAPTURE)**, where PEF is used only for mid-range scores. Under this scoring scenario, patients with scores of 0 or 1 are not considered at risk of clinically significant COPD; they would not require further evaluation. Those with a score of 5 or 6 are considered to be at high risk of clinically significant COPD and should be referred directly for further evaluation, including clinical spirometry. Patients scoring in the middle range (2 to 4) would undergo PEF testing, applying the 350/250 interpretation thresholds. In our sample, 52% of the participants required PEF to determine if spirometry was indicated. The other 48% needed only the five-item questionnaire. This approach provided 90% sensitivity, 93% specificity and an overall error rate of 9%.

CAPTURE exhibits similar operating characteristics in a Spanish speaking population. To broaden our target population, the five-item questionnaire was methodically translated to Spanish using previously validated, rigorous methods(44) to yield an instrument that is equivalent to the English questionnaire and linguistically and culturally applicable to persons of diverse Spanish-speaking backgrounds residing in the US. In a subset of Spanish speaking participants CAPTURE exhibited excellent sensitivity (88%), specificity (92%) and overall error rate (10%) for identifying patients with clinically significant COPD.

Aim 2.

Consistent with national criteria for preventive and chronic disease care quality, feasibility science is designed to assist clinical and health education evaluators plan for assessing and evaluating specific implementation factors essential to the success of new diagnostic, therapeutic and programmatic options in real-world clinical practice. This aim's analysis of primary care clinical practice COPD case finding feasibility includes an initial evaluation of existing COPD diagnostic and case finding processes within the practices, assessment of practices' capacity to change from existing respiratory symptom assessment strategies and an understanding of practice-specific learning preferences associated with new diagnostics in chronic disease diagnosis and management. The aim addresses through the RE-AIM feasibility approach how a new tool might a) identify target populations (Reach); b) appraise optimal targeted respiratory history and symptoms consistent with clinically significant COPD (Effectiveness or Impact); c) integrate into practice workflow (Adoption); d) deliver changes and improvements to COPD care within the scope of real-world clinical practice (Implementation); and e) persist in use and quality over time (Maintenance) (45-53).

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Potential risks associated with Aims 1 and 3 of this study are outlined below.

Spirometry: Participants may become short of breath. Syncope, light-headedness and fainting may develop during this test. These are uncommon.

Albuterol: Tremulousness, feeling of a strong, rapid heartbeat, and palpitations can occur with inhaled albuterol. A targeted safety questionnaire will be administered to all participants prior to albuterol to exclude those with a previous adverse event with the medication. Note that albuterol is only administered to those with abnormal spirometry on the baseline spirometry assessment (defined as $FEV_1/FVC < 0.70$ or $FEV_1 < 80\%$ predicted).

Peak Expiratory Flow: Participants may become short of breath. Syncope, light-headedness and fainting may develop during this test. These are uncommon.

Other non-physical risks of the study include those from economic loss from participation in the study; this will be minimized by scheduling tests and evaluations in a timely manner in the fewest number of visits possible. Patient and physician participants will be provided a modest fee to cover their time to participate in the study.

We anticipate few adverse events due to the non-invasive nature of the study procedures and the rarity of such events encountered during the initial visits and longitudinal follow-up. Medical care will be available at each Clinical Center to treat participants who develop adverse events during in-person study visits.

Potential risks associated with Aim 2 of this study include:

No more than minimal risk exists for participants within aim 2.

Confidentiality of information and identification are the risks associated with this project. Based on previous research and the protocols that have been developed, we believe that the likelihood of these risks to the participants would be minimal, i.e. "rare".

Potential risks associated with the study (all Aims) include:

Loss of confidentiality of study data: This is unlikely since data collected will be stored in locked file cabinets in locked rooms at the Clinical Centers. In addition, only participant IDs are used to identify participants in the secure server at the Data Coordinating Center.

Poor quality data: If the data collected are of poor quality such that it is not useable to achieve study aims, participants will have unnecessarily been exposed to other risks in the study.

2.3.2 KNOWN POTENTIAL BENEFITS

For Aims 1 and 3 of this study, participants could receive direct benefit as a result of their participation in this research. Current state-of-the-art COPD education is offered to all clinicians at participating PBRN sites (see aim 3 protocol) that could result in improved care for their COPD patients. Health care providers at practices randomized to the CAPTURE education arm (arm 1), will receive their participant's CAPTURE Tool scores and peak flow results. This may result in further diagnostic testing leading to a diagnosis of COPD or other respiratory disorder.

Known potential benefits for each participating clinical staff include critical review their clinical respiratory practice. In general, aim 2 offers the ability to assess and address CAPTURE-specific primary care practice feasibility issues which could augment or hamper clinical communication or implementation of COPD case-finding in real-world primary care clinical practice.

Potential benefits to society include improved understanding of how best to identify individuals with COPD in the primary care setting. This could ultimately lead to better treatments and lower morbidity and mortality for patients with COPD.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The demonstrated and potential future benefits to improved understanding of COPD case finding outweigh the minimal risks of the procedures performed.

Increased understanding of how best to diagnose individuals at risk for COPD in the primary care population has the potential to benefit both patients with COPD and society at large. The risk to individuals associated with this study protocol is small and the knowledge to be gained is substantial.

3 OBJECTIVES AND ENDPOINTS

Aims 1 and 3.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Aim 1: Define the sensitivity and specificity of CAPTURE for identifying previously undiagnosed patients with *clinically significant COPD* in a broad range of primary care settings	Sensitivity and specificity of CAPTURE to identify previously undiagnosed patients with clinically significant COPD at baseline.	Standard methodology for COPD diagnosis will be used (1).
Aim 3: Define the impact of CAPTURE information provided to clinicians in identifying and managing patients with respiratory symptoms (*CAPTURE+*) across a broad range of primary care settings.	Proportion of CAPTURE+ participants who meet at least one of the following within 12 months of study baseline (composite endpoint): 1) referral for or completion of clinical spirometry testing, 2) new diagnosis of COPD, 3) newly prescribed respiratory medication (long acting bronchodilator or anti-inflammatory for respiratory condition), or 4) referral to a specialist for respiratory evaluation/treatment.	The composite endpoint is clinically relevant and consistent with published data (45). This will test the impact of CAPTURE on clinician behavior.
Secondary		
Aim 1: Define the sensitivity and specificity of CAPTURE for patients with COPD across a broad range of racial and ethnic subgroups in a range of primary care settings	Sensitivity and specificity of CAPTURE to identify previously undiagnosed patients with COPD across sex, ethnic groups, urban vs rural location, and educational status.	Patient characteristics will be used to assess the robustness of CAPTURE.
Aim 1: Determine positive and negative predictive values (PPV and NPV) in different practice settings.	Positive and negative predictive values (PPV and NPV) in different practice settings.	PPV and NPV will be used to assess the robustness and usefulness of CAPTURE in various settings.
Aim 1: Verify the optimal use (cutoff threshold) of the CAPTURE tool in combination with FEV_1 measurements for identifying undiagnosed COPD.	AUC for various cutpoints of CAPTURE and PEF measurements to determine the best cutpoint for clinically significant COPD screen.	The best discrimination for CAPTURE combined with FEV_1 will indicate the optimal usage of the tool.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Aim 1: Determine patient and site characteristics that, with the CAPTURE assessment, will best identify persons with undiagnosed COPD.	AUC to identify the combination of patient/site characteristics which best discriminates those with clinically significant COPD.	The best discrimination will determine which site and patient characteristics best predicted undiagnosed COPD in combination with the CAPTURE tool.
Aim 1: Determine whether CAPTURE is useful in identifying other definitions of undiagnosed COPD: 1) spirometry-defined COPD, and 2) mild COPD	All primary and secondary endpoints as applied to 1) spirometry-defined COPD and 2) mild COPD	This will determine the robustness of the CAPTURE tool.
Aim 3: Define the impact of CAPTURE clinician education, and patient-level CAPTURE information to clinicians ("CAPTURE education") on selected additional therapeutic interventions in previously undiagnosed patients with *clinically significant COPD.*	Proportion of CAPTURE+ participants who meet the components of the composite endpoint.	Each endpoint is clinically relevant and consistent with published data. (45) This will test the impact of CAPTURE on clinician behavior.
Aim 3: Assess impact of CAPTURE education on clinician interventions specific to smokers.	In participants with clinically significant COPD who are current smokers, the incidence of physician referral to a formal smoking cessation program, prescribed smoking cessation medication, and referral to pulmonary rehabilitation program.	Certain outcomes are specific to only smokers and should be assessed.
Aim 3: Determine the impact of CAPTURE education on patient symptoms, exacerbations, hospitalizations, and mortality.	In participants with clinically significant COPD, change in CAT score, and proportion of patients who experience exacerbations, hospitalizations, or mortality.	This endpoint is important for quality of life, and long-term patient outlook.
Aim 3: Determine the impact of CAPTURE education when COPD is defined spirometrically.	All of the above endpoints for Aim 3, with the patient population defined as those who have COPD defined spirometrically.	This will determine the robustness of the CAPTURE tool

Aim 2.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Explore clinical practice implementation approaches to and acceptance of CAPTURE case finding for clinically significant COPD in a range of primary care practices.	Primary care clinician recommendations that inform CAPTURE RE-AIM strategies at both provider and clinical support levels of primary care practice. Primary clinician recommendations that inform CAPTURE-associated COPD education models for primary care clinicians. Primary care clinician recommendations that inform CAPTURE-associated COPD clinical quality improvement designs across a variety of primary care practice types.	Clinical improvement models that introduce new testing must investigate practice opinion and behavior and incorporate clinician recommendation.
Secondary		
Qualitatively assess primary care clinical staff COPD practice behavior – including COPD screening and diagnostic perceptions, beliefs and knowledge – that will inform strategies to improve CAPTURE RE-AIM (reach, impact, adoption, implementation and maintenance of use) characteristics.	Existing COPD screening and diagnostic and case-finding processes within a variety of primary care practices. Primary care practice beliefs about capacity to change from existing COPD screening and diagnostic assessment strategies. Practice-specific COPD screening and diagnostic continuing education preference.	Awareness of existing clinician knowledge and behavior can influence workflow implementation and overall effectiveness of new clinical tools.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Qualitatively assess primary care patient opinion of CAPTURE COPD case finding that will inform strategies to improve CAPTURE RE-AIM (reach, impact, adoption, implementation and maintenance of use) characteristics.	CAPTURE opinion survey ascertaining participant comprehension of CAPTURE instructions and testing and ease of completion.	Patient satisfaction, understanding and ease of test completion affects staff implementation and workflow decision. Participant opinion survey results will seed CAPTURE implementation planning practice staff focus groups.

4 STUDY DESIGN

4.1 OVERALL DESIGN

A prospective, multicenter study that includes three key aims: 1) cross-sectional validation to define sensitivity and specificity of CAPTURE; 2) *qualitative* research exploration engaging clinical staff at all levels from primary care practices serving US patient populations of differing gender, racial, ethnic, urban/rural and socio-economic blends, and 3) explore the impact of CAPTURE on clinical care and patient outcomes across a broad range of primary care settings in a cluster randomized controlled clinical trial. The CAPTURE tool consists of a 5-item self-administered questionnaire and selected use of peak expiratory flow (PEF) measurement, designed to identify clinically significant Chronic Obstructive Pulmonary Disease (COPD).

For Aim 1, approximately 5,000 patients will be recruited at the time of their regularly-scheduled appointment across 100 participating primary care clinics associated with practice-based research networks (PBRNs). Eligible participants will undergo a baseline visit during which the CAPTURE tool and spirometry will be obtained, as well as PEF and other participant characteristics.

For Aim 2, approximately 150 clinicians from 10 participating primary care practices across 5 US PBRNs will undergo detailed implementation investigation of the CAPTURE case finding model for clinically significant COPD. In addition, 200 primary care patients recruited as part of Aim 1 will complete a 10-minute written CAPTURE opinion survey.

To address Aim 3, participating primary care practices will be randomized in a 1:1 fashion to one of the following interventions:

- Arm 1: Practice clinicians will receive basic COPD education, and patient-level CAPTURE information with CAPTURE interpretation education (CAPTURE+ COPD education). As the second aim addresses the optimal format for delivering practice CAPTURE education this will be incorporated at the sites randomized to this arm (see Enhanced CAPTURE education in Figure 1).
- Arm 2: Practice clinicians will receive basic COPD education only (COPD education).

Basic COPD and CAPTURE specific education will use an interactive, web-based education program which will be provided to all practice personnel, including physicians, nurse practitioners, physician assistants, nurses, medical assistants, clerical staff and administrative staff. Practitioners at sites

randomized to the CAPTURE+COPD education intervention will receive the CAPTURE score from the central study coordinators soon after the baseline assessments have been completed.

Addressing Aims 1 and 3 will include a baseline visit for all participants and for Aim 3 longitudinal follow-up over 12 months for a predefined cohort of participants. Determination of the participants included in the longitudinal follow-up cohorts will be made after the baseline visit.

Baseline Data

Practices and/or study staff will pre-screen patients according to local guidelines to identify potential participants based on the following criteria: no prior COPD diagnoses, between 45 and 80 years old, and speak and read either English or Spanish. The timing of the pre-screening and the method to approach these patients for participation in the study (e.g., at the next outpatient visit, via telephone) will be flexible, depending upon site recruitment preferences. Patients who are eligible based on the pre-screening questions and agree to participate in the study will sign informed consent. After signing the consent, they will complete the CAPTURE questionnaire, PEF testing, spirometry testing, other respiratory questionnaires, and provide past medical history and demographic information. Local/PBRN study coordinators for each of the 7 PBRNs will perform the study procedures and record baseline information into the electronic data capture (EDC) system.

The EDC system will calculate a CAPTURE score for each participant, based on his/her CAPTURE questionnaire answers and PEF measurement. A binary score (positive or negative CAPTURE) will be emailed to the central study coordinator only for participants randomized to CAPTURE+COPD education intervention practices. The coordinator will communicate this information to these practitioners. Practitioners at sites randomized to the COPD education only intervention will be blinded to CAPTURE scores. Practitioners in both intervention arms will be blinded to research spirometry results.

Analyses will include a comparison of CAPTURE scores with data from spirometry testing and participant reported data to determine sensitivity and specificity of the CAPTURE tool. *The hypothesis is that a simple case finding methodology using a five-item questionnaire with selective PEF measurement will identify undiagnosed patients with clinically significant COPD.*

Based on the data collected at baseline, participants will be classified into the following groups for analyses:

Cohort	**Definition**
CAPTURE+	Participants with • CAPTURE score $\geq$ 5, or • CAPTURE score of 2, 3, or 4 with a low PEF, defined as <350 L/min for males and <250 L/min for females
CAPTURE-	Participants with • CAPTURE score < 2 or scores 2-4 with normal PEF (defined as $\geq$350 L/min for males and $\geq$250 L/min for females)
Spirometrically defined COPD	Participants with abnormal spirometry, defined as post-bronchodilator FEV_1/FVC <0.7. If a participant is unable to complete a post-bronchodilator spirometry (refusal, technical error on the part of coordinator, etc.), and the pre-bronchodilator FEV1/FVC is less than 0.65, the participant will be considered to have COPD for the purpose of follow-up in this study.

Clinically significant COPD	Participants with abnormal spirometry, defined as post-bronchodilator FEV_1/FVC <0.7, plus one of the following: 1) FEV_1 < 60% predicted or ≥ 1 exacerbation like event within the past 12 months.
Mild COPD	Participants with abnormal spirometry, defined as post-bronchodilator FEV_1/FVC<0.7 plus both of the following: • FEV_1 ≥ 60% and • No prior history of ECOPD

Exploratory analyses to examine the potential impact of SARS CoV-2 infection on the above operating characteristics of the CAPTURE approach will include information in the pandemic and post pandemic period collected from a simple COVID-19 questionnaire that is based on similar questionnaires from other ongoing NHLBI cohort studies.

Longitudinal Follow-up
A pre-defined subgroup of enrolled participants, who meet any of the below criteria will undergo longitudinal follow-up at 12 months,

1. Participants with a CAPTURE Score ≥ 5 or CAPTURE score of 2, 3, or 4 with a low PEF, defined as <350 L/min for males and <250 L/min for females
2. Participants who have abnormal spirometry results, defined as post-bronchodilator FEV_1/FVC < 0.7 or FEV_1 < 80% predicted at baseline. If a participant is unable to complete a post-bronchodilator spirometry (refusal, technical error on the part of coordinator, etc.), and the pre-bronchodilator FEV1/FVC is less than 0.65, the participant will be considered to have COPD for the purpose of follow-up in this study.
3. A random sample of approximately 5% who do not meet criteria 1 - 2

Participants who meet the criteria for follow-up will be sent notification shortly after enrollment, and receive reminders at 3, 6, and 9 months. Patient-reported data will be collected by COPD Foundation via telephone, secure web-based server, or mail-based methodologies, based on participant preference.

Subject medical data will be collected from the medical record to assess for changes in practice-level care.

The hypothesis for Aim 3 is that sites where COPD and CAPTURE education and patient-level CAPTURE data are provided to clinicians will exhibit improved COPD diagnosis and COPD-related care compared to sites where COPD education is provided to clinicians.

In exploratory analyses to examine the potential impact of SARS CoV-2 infection on the patient symptoms and health care utilization a simple COVID-19 questionnaire, based on other ongoing NHLBI cohort studies, has been introduced.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Aims 1 and 3

The totality of the published data confirms the clinical and economic impact of undiagnosed COPD, continuing under-diagnosis, and incomplete application of spirometric testing in the primary care community. It suggests that there is value in COPD case-finding that targets COPD patients most likely to benefit from available therapies. These points identify a pressing health care problem that requires

an innovative approach to facilitate identifying these individuals. Our preliminary studies enumerated in section 2.2 extend these concepts by demonstrating that:

- Six key domains identify patients with clinically significant COPD.
- Forty-four distinct items resonate with patients and provide important insights for COPD case-finding.
- Five items exhibit excellent sensitivity and specificity in identifying patients with clinically significant COPD.
- PEF provides incremental value in a case-finding strategy.
- The combination of a five-item questionnaire and PEF optimizes a COPD case-finding strategy in English and Spanish speaking patients.

Our proposed study will provide crucial data to address the operating characteristics and clinical translation to our COPD case-finding strategy into the primary care setting. It will also provide an important initial evaluation of the potential clinical impact of the systematic identification of previously undiagnosed COPD patients.

The impact of SARS-CoV-2 infection and its clinical illness, COVID-19, on COPD Case Finding and respiratory symptoms in primary care is unknown. In exploratory analyses a simple COVID-19 patient questionnaires and additional data elements from medical record review, based on other ongoing NHLBI cohort studies, have been introduced.

Aim 2

The rationale for this aim reflects the importance of establishing if an innovative approach to COPD case finding is considered a pragmatic tool with potential utility for primary care clinicians within real-world clinical practice settings. With the completion of this aim we anticipate confirming that future validated approaches to COPD case finding can be adopted in a broad variety of clinical care settings thereby providing further impetus for the rigorous evaluation of a) case finding guided patient outcomes as part of routine primary care clinical practice; b) case finding use in a range of primary care health professional COPD-related education approaches, clinical quality improvement models and diagnostic guidelines; and c) the capacity of clinical case finding and informed follow-up to enhance future COPD clinical care therapeutic paradigms used in primary care practice.

Consistent with Institute of Medicine criteria and US health quality standards for preventive and chronic disease care, the feasibility science qualitative research framework is designed to assist clinical and health education evaluators prepare, assess and evaluate specific implementation factors essential to the success of new diagnostic, therapeutic, educational and programmatic options in real-world clinical practice. This aim's analysis of primary care clinical practice COPD case finding feasibility considerations for CAPTURE includes an initial evaluation of existing COPD diagnostic and case finding processes within the practices, assessment of practices' capacity to change from existing respiratory symptom assessment strategies and an understanding of practice-specific learning preferences associated with new diagnostics and chronic disease diagnosis and management. Patient perceptions of the CAPTURE case-finding process are also obtained to provide a holistic perspective of the clinical feasibility of CAPTURE implementation in primary care practice. Borrowing from the RE-AIM implementation science approach, this aim explores how real-word primary care practices might potentially use CAPTURE to: a) identify target populations (Reach); b) refine current practice appraisal of patient respiratory history,

symptoms and diagnostics used to identify clinically significant COPD (Effectiveness/Impact); c) change or integrate COPD case finding into practice workflow (Adoption); d) alter practice communication, education and/or care quality improvement planning for COPD diagnosis and management (Implementation); and e) use COPD case finding consistently over time (Maintenance).

Ten primary care practices will undergo detailed implementation investigation of the CAPTURE case finding model designed to identify patients with COPD most likely to benefit from available therapeutic options. CAPTURE, a one-page questionnaire with selective PEF measurement, is presented to the clinicians of ten practices not participating in aims 1 and 3 as a prospective COPD case finding option awaiting validation. By representing CAPTURE as a model—and not introducing it into actual practice—aim 2 gains recommendation from primary care clinical practice experience with sufficient feasibility generality to circumvent interdependence between the operating characteristic exploration (aim 1) and qualitative feasibility understanding (aim 2) components of our study. The aim 2 results, that include the pooled CAPTURE clinical communication, education and implementation recommendations from real-world primary care practice, are analyzed and applied in concert with local and national research team expertise to enhance the potential impact of CAPTURE's introduction into clinical care in aim 3. Aim 2 results also provide previously unexplored qualitative information necessary for future long-term patient outcome studies of COPD case finding approaches in primary care.

The impact of SARS-CoV-2 infection and its clinical illness, COVID-19, on COPD Case Finding application in primary care is unknown. In a systematic fashion these concepts will be explored during the previously planned follow-up interviews and focus groups with clinical practice and regional PBRN personnel.

4.3 END OF STUDY DEFINITION

Participants that do not meet the criteria for, or are not selected for, longitudinal follow-up will be considered to have completed the study after completion of the baseline visit.

Participants included in the longitudinal follow-up phase will be considered to have completed the study after completion of the Month 12 Assessment as shown in the Schedule of Activities (SoA), Section 1.3.

Clinician participants in aim 2 will have completed the study after participation on their second focus group between months 14 and 16 as shown in the Figure 2, Structure of Aim 2.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Inclusion criteria for Aims 1 and 3
In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Male or female, aged 45 – 80 years

Inclusion criteria for Aim 2

Two Aim 2 practices are selected by each of their 5 affiliated PBRNs based upon willingness to participate and variability of primary care practice type within the PBRN. Differences in practice size,

staffing, ownership, prior quality improvement engagement, geography, patient population socioeconomic status (SES) or languages spoken are among the among the selection criteria the PBRNs will utilize to choose.

Clinician participants (10 practices with up to 15 clinicians per practice):
1. Provision of signed and dated informed consent form.
2. Stated willingness to comply with availability and all study procedures for the duration of aim 2 by the 10 practices (through PBRN recruitment) and their up to 15 clinicians within (through informed consent).

Patient participants [200 patients (approximately 40 from each PBRN)] for CAPTURE survey:
1. Provision of signed and dated informed consent form.
2. Stated willingness to comply with all study procedures and availability for the duration of the study.
3. Male or female, aged 45 – 80 years.

5.2 EXCLUSION CRITERIA

Exclusion criteria for Aims 1 and 3
An individual who meets any of the following criteria will be excluded from participation in this study:

1. Previous clinician provided diagnosis of COPD
2. Treated respiratory infection (with antibiotics and/or systemic steroids) in the past 30 days of baseline
3. Participants unable to perform spirometry due to any of the following conditions within the past 30 days of baseline
    a) Chest surgery
    b) Abdominal surgery
    c) Eye surgery
    d) Heart attack
    e) Stroke

Exclusion criteria for Aim 2

1. Clinician participants: current employment at practices participating in aims 1 and/or 3
2. Clinician participants: from practices providing fewer than 2 clinician participants
3. Patient participants: meeting the exclusion criteria for aims 1 and 3 (above)

5.3 SCREEN FAILURES

PBRN coordinators, in conjunction with clinical study site personnel, will pre-screen individuals who are unlikely to be able to complete research spirometry. These individuals will be considered *pre-screen failures*.

Participants who are consented to participate but have a prior clinician diagnosis of COPD will be considered *screen failures*.

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment and retention strategies for Aims 1 and 3

Approximately 4800 participants will be recruited from 100 primary care clinics affiliated with six PBRNs. Each PBRN has centrally-based research coordinators with a history of success working in PBRN practices, documented expertise in previous large diagnostic or therapeutic trials, and personnel experienced in recruitment and data collection.

IRB approval will be obtained at each PBRN for approval for patient contact, informed consent and participation in this study.

All patients who meet all inclusion and no exclusion criteria at the participating PBRN clinical site will be eligible for participation. Research coordinators will work with participating practices to identify and approach potential participants. Recruitment strategies may vary depending on the practice.

Enrollment of participants will depend on the gender, ethnic and racial makeup of those that are being recruited from the practices included in this trial. No exclusion criteria apply specifically to women or to minorities. The Data Coordinating Center (DCC) will track enrollment of participants throughout the course of this study. If women and minorities are under-represented in the initial phase of recruitment, a commitment exists to develop recruitment strategies that target these populations so the final study group is a well-balanced representation of the studied population.

Recruitment and retention strategies for Aim 2

Clinician participants: Approximately 150 clinic participants are recruited by: 1) introductory telephone contact with the practice leadership by PBRN research coordinators and the aim 2 research team; 2) follow up letter, time commitment infographic and informed consent forms sent to interested practices outlining aim 2 clinician participant activities and responsibilities; and 3) in-person aim 2 study explanation to clinician participants at the committed practices during the introductory baseline study site visit.

Clinician participant recruitment draws from both prescribing (or "provider") staff and non-prescribing (or "clinical support") staff. The aim 2 research team will attempt to obtain an even mix of both clinician staff types from each practice. Retention incentive of clinician participants over 2 years includes provision of on-line COPD education to all clinician participants and monetary incentive to practices as determined by each individual PBRN.

Patient participants: 200 participants (40 from each PBRN) are recruited as a sub-set of the aim 1. Each of the 200 patient participants in aim 2 are asked to complete a one-time 10-minute written opinion survey. Their aim 2 participation is concluded at the end of the opinion survey completion.

The aim 2 research team and DCC will track enrollment and retention of all aim 2 participants throughout the course of the 2-year aim 2 study.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

The study intervention is applicable to Aims 2 and 3 and consists of healthcare provider education modules.

The practitioners at the 10 sites selected for Aim 2 will receive module 1, Basic COPD education, and may elect to take modules 3-5 for supplemental information on COPD.

For Aim 3, half of the practices will receive Basic COPD education (module 1) and half will receive Basic COPD Education and CAPTURE Education (modules 1 and 2). Practitioners at practices randomized to COPD only education must take module 1 and may elect to take modules 3-5; however, they will not take module 2. Practitioners at practices randomized to COPD+CAPTURE education must take modules 1 and 2, and may elect to take modules 3-5.

1 - Basic COPD Education will be provided in order for providers to optimally manage patients with COPD. The education will incorporate evidence-based recommendations using the 2018 update of the Global Obstructive Lung Disease Strategy(45). For practices enrolled in the pandemic and post pandemic periods, additional information will be provided regarding COPD management in the pandemic era as well as information on steps to maintain patient and staff safety in the clinical sites where CAPTURE patients will be enrolled and assessed.

A 40-minute overview will be presented in the most expeditious manner at each practice site, for example by webinar for all practice personnel over the lunch hour, or audiovisual presentation available on a dedicated CAPTURE web site. The PBRNs have indicated that this module should be no longer than 40 minutes. Topics will include: CAPTURE study description and rationale, importance of COPD in the region of the local practices, COPD definition and diagnosis, patient goals, and management approach. Attendance at this mandatory training will be documented and continuing education credits will be provided for physicians and nurse practitioners by National Jewish Health, an accredited CME provider.

2 - **CAPTURE education**. An online audiovisual module will be developed to explain CAPTURE interpretation and use in patient evaluation and diagnosis of COPD. This module will only be available to practices randomized to receive the results of CAPTURE for clinical use.

With the information provided in Aim 2 about practice preferences for education, the CAPTURE education module will be revised and made available to practices enrolled in Aim 1 after the completion of Aim 2.

3 - Online advanced COPD education will be available for all practices and continuing education credits will be provided to enhance practitioner participation. Practitioner attendance at each online audiovisual module will be collected including the amount of time spent on each education module, completion of each module with a post-test and evaluation, and CME will be provided. Education will be case-based and will include role playing where appropriate. Seven basic modules of 20 minutes or less will be available both to practices randomized to receive CAPTURE results for clinician use and to control practices that will not receive CAPTURE results and will cover:

1. Diagnosis of COPD: How to diagnose COPD in primary care including medical history, physical exam and role of spirometry, severity categorization
2. Spirometry overview: Basic clinical interpretation
3. Advanced spirometry: Test performance, evaluating quality, advanced case-based interpretation
4. Management overview: Patient goals, smoking cessation, vaccination, patient education, shared decision-making
5. Pharmacotherapy: Inhaled bronchodilators, inhaled corticosteroids
6. Other therapies: Oxygen, pulmonary rehabilitation, surgical approaches
7. Inhalation devices: Patient education

4 – On-site COPD education. Additional funds will be sought to provide on-site COPD education. We have experience in successfully providing half-day on-site education to primary care practices to enhance their management of COPD.

5 – Social media and case conferences. We will use social media (Facebook and Twitter) to provide ongoing education about COPD. Facebook and Twitter posts will provide tips on managing COPD. Online conferences will be scheduled to discuss cases submitted by primary care providers.

6.2 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

For Aims 1 and 3, this study will use randomization and blinding as two of the cardinal principles of clinical trials to minimize bias.

Randomization. Practices will be randomized into one of the two interventions, COPD education or COPD education + CAPTURE education, in a 1:1 manner, stratified by PBRN. Randomization will occur at the time of site activation and each site will be assigned a unique randomization number. The DCC will prepare the randomization schedule, using computer-generated block randomization with the block size(s) known only by the DCC. A secure web-based application will be built that will be used by the central study coordinators to enter site information (e.g., site ID, stratification factor) and to obtain the randomization number. The information can be printed and sent and/or emailed directly to the study coordinator.

Blinding. This is a single-blind study with the participants blinded to whether their practitioners have received CAPTURE education and patient-level CAPTURE results. Practitioners at sites that are randomized to the control arm (COPD education alone) will be blinded to the CAPTURE questionnaire and PEF results. All practitioners and participants will be blinded to the baseline COPD status of the participants (i.e., blinded to spirometry results), except for safety reasons. In this situation, participants and their clinician will be notified if a participant's post-bronchodilator FEV_1 is less than 30% predicted. For all other participants, they and their practitioners will be blinded to research spirometry results. The coordinator should make every effort to conceal the spirometry results from the participants in these latter cases. Study coordinators should also make every effort to conceal the administration of a post-bronchodilator spirometry test from the practice staff so as not to unblind the physicians to abnormal spirometry.

6.3 STUDY INTERVENTION COMPLIANCE

In practices randomized to share the CAPTURE results with the clinician, the goal is to share results with the clinician at the time of the CAPTURE study visit. Providing results at the time of the clinical visit will allow the clinician to act on the CAPTURE results as soon as possible when the participant is in front of the clinician. Based on the workflow at each of the practices, this may not always be possible.

Sharing of the CAPTURE results with the participant's primary care clinician will be tracked by the study coordinator enrolling patients at sites randomized to receive CAPTURE results. The sharing of CAPTURE

results will be recorded on the study eCRF form. The eCRF will collect the timing of when the results were provided to the practitioner - whether the results were provided to the clinician at the time of the enrollment visit prior to the clinician visit with the patient, or were provided at another time.

If results were not shared at the time of the CAPTURE study visit, then the date of sending the CAPTURE results will be recorded on the appropriate eCRF by filling in the date (day/month/year) the exact copy of the CAPTURE Toolwere sent to the clinician through a HIPPA-compliant method and placed in the medical record. The goal is to communicate the results to the clinician. The DCC will monitor review all participants' eCRFs to assure that all those enrolled from practices randomized to CAPTURE results have been shared with clinicians.

6.4 CONCOMITANT THERAPY

Practitioners will treat participants using their own clinical judgment. No medications are prohibited. This is not an interventional therapeutic trial.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

In this cluster randomized controlled trial (Aim 3), where practices are the recipients of the intervention and where the interventions are based upon education and access to CAPTURE and PEF results, it is not anticipated that study intervention will be discontinued at the practice level. However, one of the CO-PIs will review safety data, especially SAEs related to baseline spirometry and PEF procedures, to ensure there are no untoward effects of the study on participants.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in Aims 1 and 3 of the study at any time upon request.

Clinician participants in Aim 2 are free to withdraw from participation in the study at any time upon request. If a clinician is no longer working at the participating practice then their involvement in Aim 2 activities will end and no further attempt will be made to include them in the remaining questionnaires or focus groups.

7.3 LOST TO FOLLOW-UP

If a participant selected for longitudinal follow up does not respond to the 12-month questionnaires, coordinators will attempt to contact participants first by the participant’s preferred method of communication, either phone or email. At least three attempts will be made. If no response is obtained, the participant’s alternate contact method will be attempted three times. Phone calls will be made at different times of the day. If there is no response, a letter will be sent to the participant. If the participant cannot be reached, the alternate contact will be called and/or emailed. If no response is received, a letter will be sent to the alternate contact. If after all of these methods are employed and no contact with the participant results, the participant will be considered lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 BASELINE ASSESSMENTS AND DATA COLLECTION

Efficacy data will be collected by patient-reported outcomes and medical record review.

For Aim 1, CAPTURE, PEF results, acute respiratory event history and spirometry will be considered efficacy assessments. They are collected at the baseline visit.

CAPTURE. Participants will complete the 5-item *self-administered* questionnaire and measurement of Peak Expiratory Flow (PEF).

Peak Expiratory Flow (PEF). PEF using the Vitalograph® AsmaPlan® mechanical PEF meter with SafeTway® disposable mouthpieces (Vitalograph LTD, UK) will be measured for all participants. Ideally, PEF should be prior to the participant's physician appointment. The participant will perform three PEF tests. All three measurements will be recorded.

Spirometry. Before spirometry is performed, participants will be asked if they have taken a medicine which they breathed into their lungs from any puffer or inhaler within the past two hours. If participant answers yes, then spirometry will be performed but considered a post-bronchodilator spirometry test. No further spirometry will be needed. If participant answers no, then pre-bronchodilator spirometry will be performed for measurement of forced vital capacity (FVC), forced expiratory volume in one-second (FEV_1), and calculation of FEV_1/FVC (using EasyOne® Spirometer, ndd Medical Technologies Inc., Andover, MA). Testing will be performed in accordance with established American Thoracic Society/European Thoracic Society (ATS/ERS) standards. Local guidelines to minimize risk of SARS-CoV-2 infection will be adhered to, including a minimum of appropriate PPE and infection control techniques.

A Spirometry post-bronchodilator will only be performed if pre-bronchodilator spirometry FEV_1/FVC is less than 0.70 or FEV_1 is less than 80% predicted. Post-bronchodilator spirometry will be performed within 15 to 20 minutes after inhalation of 2 puffs of albuterol 180 mcg HFA using an AeroChamber Plus* Flow-Vu® spacer with one minute between the first and the second inhalation. A separate AeroChamber or comparable spacer, using a one way valve to minimize infectious risk, will be provided for each participant's testing. A standing order for albuterol administration may be used if necessary.

Spirometry is a valid, reproducible means of documenting the presence and severity of airflow limitation. When properly performed with maximum effort and attention to the details of calibration of the instrument, spirometry maneuvers are among the most reproducible of biomedical measures. In the setting of a highly trained, experienced therapist, a coefficient of variation of 2-3% is not unusual. Spirometry will be performed in a standardized manner in accordance with the ATS guidelines, as described in the manual of procedures (MOP). Spirometry is the timed-based measurement of the amount of air that can be forcefully exhaled from the lungs after a full inspiration. In the forced expiratory vital capacity maneuver, a person inhales as big a breath as possible and then blows it out as fast and as long as possible until no more air can leave the lungs. The volume of air leaving the lungs is recorded continuously throughout the maneuver in order to allow calculation of important measures of lung function.

NHANES prediction equations, which are programmed into the Easy On PC spirometers, will be used to calculate the predicted lung function levels. These require the input of age, height, and race/ethnicity

(White, Black, Hispanic). For people of mixed or unknown race the White prediction equations will be used.

PBRN Research Coordinators will be trained and certified in the performance of spirometry testing. Spirometry will be sent for central review for quality control assurance.

Adjudication of the Presence of Obstruction on Post-Bronchodilator Spirometry

The presence of obstruction is determined by the presence of an FEV_1/FVC ratio less than 0.70 after the administration of a bronchodilator. A bronchodilator will be administered to study subjects whose baseline FEV_1/FVC is less than 0.70 or whose FEV_1 is less than 80% of the predicted value.

If a subject is unable to complete a post-bronchodilator spirometry (refusal, technical error on the part of coordinator, etc.), and the pre-bronchodilator FEV_1/FVC is less than 0.65, the patient will be considered to have COPD for the purpose of follow-up in this study.

Height and weight
Height and weight will be recorded in order to determine appropriate prediction equations for spirometry and possible effect of obesity on spirometry. Height will be recorded and weight will be measured prior to spirometry testing.

Demographic Data Collection
Demographic data including date of birth, gender, ethnicity, race, educational level achieved, daily work schedule, living arrangement and health insurance will be entered into the EDC system.

Contact information including address, phone numbers and email address will be obtained. Alternate contact information will be obtained for two other people, family members not living with the participant or close contacts, who may be knowledgeable about the participant in the event that the participant cannot be contacted for subsequent longitudinal follow-up. Alternate contact information will include name, address, phone numbers and email addresses. All contact information will be stored securely at the clinical site or in a database separate from that developed for the clinical data.

Medical History
Previous medical diagnoses will include comorbidities such as cardiovascular, respiratory and malignant disorders. Influenza vaccination history will also be recorded. This questionnaire will be completed under supervision of the coordinator.

Concomitant Medication Review
Respiratory medications will be recorded at baseline for all participants. This questionnaire will be completed under supervision of the coordinator.

CAPTURE Additional Items Questionnaire
Participants will complete the 13-item *self-administered* questionnaire.

COPD Assessment Test (CAT)
Participants will complete the 8-item *self-administered* questionnaire.

Respiratory symptoms, smoke exposure and exacerbation like events
History of respiratory symptoms and exacerbation like events over the past year as well as smoke exposure (including e-cigarette or equivalent) will be recorded. This questionnaire will be completed under supervision of the coordinator.

Whenever possible, informed consent, eligibility review, CAPTURE Questionnaire and PEF will be performed prior to the participant's clinic appointment, so that CAPTURE results may be provided to the physician at the time of his/her appointment if the patient is cared for in a clinical center randomized to CAPTURE+ education.

COVID-19 Additional Items Questionnaire
Participants will complete the 18-item *self-administered* questionnaire.

Adverse events
Adverse events related to study procedures will be recorded by the coordinator.

8.2 LONGITUDINAL FOLLOW-UP ASSESSMENTS AND DATA COLLECTION

For Aim 3, the follow-up efficacy assessments are collected from the time of baseline to 12 months in selected cohorts (as described in section 4.1). Medical record abstractions completed by PBRN coordinators and participant questionnaires administered by study team members from the COPD Foundation are used.

Data collected from medical record include:

All participants undergoing 12-month follow-up as described in section 4.1	Current Smokers Only
Clinical spirometry ordered or administered	Smoking cessation counseling
Referral to specialist for respiratory evaluation/treatment	New prescription for smoking cessation medication
New recorded clinical diagnosis of COPD	Formal smoking cessation program referral/completion
New prescription for respiratory medication (long acting bronchodilator, inhaled steroids, oral anti-inflammatory)	
Exacerbation like event assessment (hospital, ED, minute clinic, antibiotic/steroid prescription/administration)	
Vaccination status	
Formal pulmonary rehabilitation program referral/completion*	
Data related to COVID-19 confirmed and suspected cases	

*only collected in relevant participants

Data from clinical visits to be collected at follow-up by telephone, secure web-based server, or mail-based methodologies directly from participants and administered by COPD Foundation study personnel include:

All participants undergoing 12-month follow-up as described in section 4.1	Current Smokers Only
Spirometry	Smoking cessation counseling
New diagnosis of COPD	Smoking cessation medications (including OTC)
Referral to pulmonologist or other respiratory specialist	
Exacerbation like event assessment	
New prescription for respiratory medication (long acting bronchodilator, inhaled steroids, oral anti-inflammatory)	
CAT score	
Attendance of pulmonary rehabilitation*	
COVID-19 related questions	

*only collected in relevant participants

8.3 AIM 2 ASSESSMENTS AND DATA COLLECTION

Practice study introduction and participation confirmation: After PBRN practice selection, the CAPTURE study Aim 2 lead together with the local PBRN Aim 2 coordinator conduct a 15-minute participation confirmation and introduction phone call with the key PBRN contact at each of the two selected practices. The study specifics and timeline are reviewed. After practice participation is confirmed, the on-site practice assessment date is scheduled. Informed consent forms for clinical staff are mailed to each confirmed practice. To reduce practice burden, completed clinical staff informed consent forms (up to 15 clinical staff per practice) can be returned by mail to the University of Michigan School of Public Health office, addressed to Dr. Randall Brown, or saved for completion and picked up at the on-site practice assessment site visit. Following the confirmation phone call, the PBRN Aim 2 coordinator completes a short (15 minute) qualitative questionnaire detailing the selected and confirmed practice demographics and PBRN parameter of practice choice for each of the two practices. The completed PBRN Practice Selection Questionnaire is returned to the Aim 2 data team and stored securely.

On-site Practice Assessment (OSPA): The OSPA is an in-person on-site practice workflow assessment. It includes 2 practice clinicians per practice choice, the PBRN Aim 2 coordinator (if available), the CAPTURE study Aim 2 lead and the CAPTURE Aim 2 research specialist (if the PBRN Aim 2 coordinator is not present). The objective of the visit is to detail specifics of practice workflow, practice physical characteristics, staff roles, clinical information gathering patterns for respiratory patients, electronic health record communication, continuing education structure, and quality improvement structure. The assessment takes place in three parts; the pre-observation practice overview (conducted with the 2 practice clinicians – 60 minutes), the ½ day practice workflow observation (observation by one member of the Aim 2 research team of common and testing areas used for the respiratory patient). There is no patient engagement and no collection of patient-specific identification or health information), and the post-observation practice summary (conducted with the same 2 practice clinicians – 30 minutes).

The 3 OSPA assessment tools are:

i) The Pre-workflow Observation Practice Assessment Review Questionnaire
ii) Respiratory Workflow Assessment Review
iii) The Post-workflow Observation Practice Assessment Review Questionnaire

Also at the OSPA, informed consent is obtained from all remaining participating staff (up to 15 clinical staff per practice) by the CAPTURE Aim 2 team and returned to the Aim 2 data team for secure storage.

Clinical Staff Questionnaires (Baseline/6/12 months). Written or on-line questionnaires are provided to participating and consented staff personnel at two practice levels -- Non-Prescribing clinical (also known as "support") staff and Prescribing (PR) clinical (also known as "provider") staff.

Non-Prescribing (NPR) clinical staff are clinical practice personnel involved in clinical workflow (including registered nurses, licensed practical nurses, medical assistants, medical assistants and receptionists), yet not having the role to make final and official medical diagnostic and management disposition plan decisions for and with patients. Prescribing (PR) clinical staff are prescribing clinical practice personnel involved in clinical workflow (including doctors, nurse practitioners, and physician assistants) who may independently make final medical diagnostic and management disposition plan decisions for and with patients.

Questionnaire items explore clinician demographics, including past education, duration of current employment and currently held clinical position. COPD knowledge, attitudes, beliefs, practice patterns and self-efficacy regarding COPD diagnosis, management, spirometry testing and interpretation, practice workflow and communication in the clinical primary practice care of adult patients with respiratory disease. Additional questions include preferred continuing education method and clinical staff quality improvement modalities for respiratory disease management. Specific examples of past practice chronic disease diagnostic changes and the individual and practice-wide levers of success and challenge associated with those changes are explored.

Each of the 3 (baseline, 6-month and 12-month) questionnaires are completed within 30 minutes. No identifying patient data is collected. Online questionnaires are collected and secured by the CAPTURE DCC and Aim 2 research team. The participants who complete written questionnaires (per their preference) mail completed questionnaires via pre-addressed stamped envelope to the CAPTURE DCC and Aim 2 research team.

Patient Opinion Surveys:
200 patient participants, 40 from each PBRN, are recruited as a sub-sample from Aim 1 practices. Patient participants fulfill all inclusion and exclusion criteria and receive informed consent for survey participation as part of aim 1.

Eligible participants complete a written one-time 5 to 10 minute CAPTURE opinion survey. Patient survey data is collected by Aim 1 research coordinators and is processed with Aim 1 baseline patient data. Patients receive a $15 gift card for completion of the survey Aim 2 patient participation ends at the completion on the lone opinion survey.

Participants who prefer to complete the 5 to 10-minute survey online via Qualtrics will be sent a secure, Qualtrics link via email. The Qualtrics survey will include a brief, introductory screen affirming consent, describing the survey and instructions about participation. Once the survey is complete, participants will see a screen with instructions about how to obtain their $15 gift card and how to contact study staff with questions regarding the survey.

Modular online COPD education. Access to free, COPD on-line, continuing education is provided for all clinical staff at each practice. Each module will take 20 minutes or less. Modular components of and access to COPD education is described in the protocol. Aim 2 clinician participant access and completion of COPD education modules is assessed by clinician questionnaires and focus group item response over 12 months (between months 2 and 14 of Aim 2 timeline).

COPD in Primary Care/CAPTURE Introduction Focus Groups:
Two 45 to 60-minute focus group discussions occur at each Aim 2 practice. Focus groups are informed by practice demographics, practice assessment data – including respiratory workflow, baseline clinical staff questionnaire data regarding respiratory knowledge, attitudes, beliefs and practice preference for the diagnosis and care of adult patients with respiratory disease as well as patient opinion from CAPTURE surveys and past CAPTURE study (46, 47). Focus group candidate themes and prompts are developed for non-prescribing clinical staff (NPR) and prescribing clinical staff (PR) and are presented at separate on-site focus group sessions to allow more detailed discussion of role responsibility in the context of daily practice workflow, generating a more abundant qualitative data sample. Separation of and PR clinical staffing implementation themes into two focus groups also limits potential for hierarchical work-related discussion suppression described in other short duration focus group studies (48-52).

The focus group moderator introduces the CAPTURE tool utilizing CAPTURE education components described in Section 6.1.1. The focus group moderator follows RE-AIM prompts for CAPTURE implementation planning discussion throughout the focus group. Targeted COPD self-efficacy limitation themes from questionnaire data (including awareness and/or use of validated respiratory assessment questionnaires, spirometry, COPD guidelines, inhaled medication patient education, oxygen therapy, smoking cessation education, vaccination recommendation, pulmonology specialty care and pulmonary rehabilitation referral) are explored. Questions will probe clinicians to identify and explain levers that may maximize uptake of CAPTURE use in their practices as well as potential barriers to implementation. The Aim 2 research team will record each focus group using audio and written note-taking that will allow an abridged yet detailed tape-based micro-interlocutor analysis of focus group emergent themes, questions, answers and interactions. Key themes informing consensus discussion, program modifications and key elements of the CAPTURE RE-AIM implementation dimensions will be identified. Audio-recordings will be professionally transcribed and codes will be generated for the interview topics and key research questions. Reviewing the transcripts line-by-line, all substantive information will be assigned a priori codes as relevant for CAPTURE RE-AIM implementation planning, COPD diagnosis and CAPTURE intra-office clinical communication and COPD/CAPTURE education preference assessment. Additional codes will be developed for sub-themes and emergent themes.

Development of Practice-Based CAPTURE Implementation PBL Cases:
From analyses of the 2 NPR and 2 PR CAPTURE Introduction focus groups per PBRN, baseline clinical staff questionnaire data, online CAPTURE opinion surveys, and on-site practice assessments, 1 primary care practice CAPTURE implementation case per PBRN (total implementation cases = 5) is created by the Aim 2 research team. Given local knowledge of chronic disease management quality improvement history, effort, challenge and successes, each PBRN's participation in case creation will be instrumental. The Aim 2 research team will lead case creation using evidence-based problem based learning (PBL) techniques (53-57). The Center for Research on Learning and Teaching (CRLT) at the University of Michigan will serve as research reference for PBL case development qualification (58). Each local PBRN PBL case will be distributed to the Aim 2 clinical staff at the 2 participating PBRN practices 2 weeks prior to the CAPTURE Implementation focus groups, giving Aim 2 participants an opportunity to read the case introductions prior to the focus group session. Also, each practice will receive one additional non-PBRN case for focus group discussion as selected by the Aim 2 research team. Therein, each of the 5 CAPTURE implementation PBL cases will receive 2 comprehensive focus group reviews (see below).

CAPTURE Implementation PBL Case Presentation Focus Groups:
Each practice participates in a final pooled (NPRs and PRs together) on-site focus group. Two CAPTURE implementation cases (described above) are discussed at each focus group. The focus will explore, discuss, glean and create optimal 1) CAPTURE implementation, 2) CAPTURE clinical communication, 3)

CAPTURE/COPD education and 4) CAPTURE primary care quality improvement recommendations pooled from all clinical practice levels for each of the 2 presented cases.

The Aim 2 research team will record each focus group using audio and written note-taking that will allow an abridged yet detailed tape-based micro-interlocutor analysis of focus group emergent themes, questions, answers and interactions. Key themes informing consensus discussion, program modifications and key elements of the CAPTURE RE-AIM implementation dimensions will be identified. Audio-recordings will be professionally transcribed and codes will be generated for the interview topics and key research questions. Reviewing the transcripts line-by-line, all substantive information will be assigned a priori codes as relevant for CAPTURE RE-AIM implementation planning, COPD diagnosis, CAPTURE intra-office clinical communication, and COPD and CAPTURE education preference, and COPD diagnosis quality improvement assessment. Additional codes will be developed for sub-themes and emergent themes.

8.4 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.4.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.4.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.4.2.1 SEVERITY OF EVENT

The following guidelines will be used to describe severity of AEs.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.4.2.2 RELATIONSHIP TO STUDY INTERVENTION

All AEs must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.
- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the study intervention). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.4.2.3 EXPECTEDNESS

The Principal Investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.4.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

Adverse events (AE)s that occur during the baseline visit will be recorded.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed.

8.4.4 ADVERSE EVENT REPORTING

All AEs that occur at baseline visit will be recorded in the case report form and reported to the DCC. We anticipate few adverse events due to the non-invasive nature of the study procedures. Participants will only be enrolled if they meet the study eligibility criteria, including assessment for contraindications for spirometry. Targeted safety questions will be asked of all patient participants prior to albuterol to exclude those with a previous adverse event with the medication and others at high risk due to cardiac abnormalities.

8.4.5 SERIOUS ADVERSE EVENT REPORTING

SAEs will be reported to the IRB at the institution where the event occurred and the University of Michigan IRB will be notified of any serious adverse experience within 7 calendar days of occurrence. These will be reported to the DSMB.

Follow-up of serious adverse events

All SAEs will be followed up until resolution or permanent outcome of the event. All follow-up information will be included in the case report form. The DSMB will make recommendations to ensure data integrity and the safety of study participants.

8.5 UNANTICIPATED PROBLEMS

8.5.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;

- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.5.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing IRB and to the DCC. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the DCC within 7 calendar days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC within 14 calendar days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within one month of the IRB's receipt of the report of the problem from the investigator.

8.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a DSMB (physicians with the appropriate expertise, including non-involved pulmonologists, primary care physicians, and independent statisticians with clinical experience). Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the Principal Investigators.

9 STATISTICAL AND ANALYTICAL PLANS

9.1 SAMPLE SIZE AND POWER

9.1.1 PRIMARY OBJECTIVES

Define the sensitivity and specificity of CAPTURE for identifying previously undiagnosed patients with clinically significant COPD in a broad range of primary care settings. We will also explore clinical practice implementation approaches to and acceptance of CAPTURE case finding for clinically significant COPD in a range of primary care practices. Further, we will define the impact of CAPTURE information provided to clinicians in identifying and managing patients with respiratory symptoms (CAPTURE+) across a broad range of primary care settings.

9.1.1.1 SENSITIVITY AND SPECIFICITY OF THE CAPTURE TOOL

Primary Hypothesis 1. *The CAPTURE tool will exhibit excellent sensitivity and specificity in diagnosing clinically significant COPD as defined by post-bronchodilator $FEV_1/FVC < 0.70$ in addition to either ≥ 1 exacerbation-like event (ECOPD) within the past 12 months or an $FEV_1 < 60\%$ predicted.* Approximately 5000 patients will be enrolled in the study with the expectation that 300-800 of these will have previously undiagnosed clinically significant COPD, identified through research spirometry and documentation of prior respiratory events. Amongst cases, we will calculate the proportion of individuals who are at high risk for clinically significant COPD based on CAPTURE (sensitivity). Similarly, amongst non-cases, we will calculate the proportion of individuals not classified as having clinically significant COPD based on CAPTURE (specificity). Corresponding 95% confidence intervals will be calculated.

Based on our preliminary data drawn from a research setting, we noted 89.7% sensitivity and 93.1% specificity for CAPTURE. Table 9-1 shows the range of sensitivity and specificity 95% confidence interval widths that would result if the true sensitivity or specificity is 85%, 90% or 95% across a range of sample sizes. For instance, if we find 500 individuals with confirmed clinically significant COPD and CAPTURE has 90% sensitivity, then the 95% confidence interval for sensitivity would be 90% ± 2.6%. Similarly, if 4,000 individuals are confirmed to have no evidence of clinically significant COPD and CAPTURE has 90% specificity, then the 95% confidence interval for specificity would be 90% ± 0.9%.

Table 9-1 Projected Confidence Interval Widths for Various Sensitivity/Specificity Percentages (Columns) and Sample Sizes (Rows).

	Sensitivity or Specificity		
Sample Size	**85%**	**90%**	**95%**
5000	± 1.0%	± 0.8%	± 0.6%
4000	± 1.1%	± 0.9%	± 0.7%
1000	± 2.2%	± 1.9%	± 1.4%
500	± 3.1%	± 2.6%	± 1.9%
250	± 4.4%	± 3.7%	± 2.7%
100	± 7.0%	± 5.9%	± 4.3%
50	± 9.9%	± 8.3%	± 6.0%

9.1.1.2 ADOPTION AND IMPLEMENTATION OF THE CAPTURE TOOL IN PRIMARY CARE PRACTICE

Primary Hypothesis 2: *A COPD case finding methodology using a validated one-page, five-item questionnaire with selective PEF measurement (CAPTURE) can be incorporated into the clinical practice patterns, clinical workflow, communication and practice-based quality improvement paradigms of a variety of primary care clinical settings.*

Aim 2 is a qualitative study to determine the efficacy of workflow integration of the CAPTURE tool. Statistical analysis of the clinician questionnaire will involve simple sums of each item and reviewing answers across practices and region. Standard frequencies for questions will be developed to examine patterns in responses.

The clinician focus groups will be conducted on-site at each practice at a time convenient for the participating clinicians. The number of prescribing and non-prescribing clinicians will equal 15 per practice and is based on interest with a maximum of 8 prescribing clinicians/practice. The sample size will follow a basic qualitative sampling standard of interviewing to redundancy or saturation. The number of clinicians to be interviewed (up to n=15 in each practice) is estimated based on achieving concept saturation. Reflecting regional primary care practice norms and to bolster concept saturation, PBRN Aim 2 coordinator focus group discussion participation is encouraged for very small practices where the participating prescribing and non-prescribing clinician total is less than or equal to 4. For all practice focus groups questions will explore the described Aim 2 CAPTURE RE-AIM concepts, barriers to implementation of the CAPTURE tool at other practice sites, standard processes for COPD and respiratory care diagnosis and management for each clinical role within the practice, and perception of quality improvement methods at each practice. Clinician focus groups are conducted on-site at each of the 10 practices.

Transcripts of clinician focus groups will all be digital and entered into a qualitative data analysis program, NVivo for Mac. This program allows for an investigation of the salience, patterning, and contexts of key discourse items. Grounded theory methods will be used to identify and label recurrent themes and concepts within textual materials. Texts will be examined line-by-line, key phrases assigned tentative category labels, and coded passages grouped under the themes of feasibility, barrier and utility. The analyses will look for “traces” in dialogue, including repetitions, key words, evaluation statements, and metaphors. Change in salience, patterning, or content of key themes will provide further empirical evidence regarding the efficacy of our program’s efforts to impact community norms and behaviors. An audit trail will be maintained to document the position of text material from which codes and themes are developed. We will use word/code counts of repetitive themes and concepts to indicate patterns. By allowing for open-ended responses, the narratives and notes will allow us to capture significant changes in participants’ attitudes or behaviors. Codes and themes will be discussed iteratively with the research team members to hone definitions and assure consistency of

interpretation. We will establish a coding dictionary and all interviews will be coded using the complete set of themes. Two independent coders will code each document to assure inter-coder reliability. Preliminary results will be shared with our Aim 2 research team and will inform the development of the case studies for the latter part of the project.

9.1.1.3 PRACTICE BEHAVIOR IN SITES WITH VERSUS WITHOUT CAPTURE EDUCATION AND PATIENT LEVEL CAPTURE DATA PROVIDED

Primary Hypothesis 3: *Sites where basic COPD and CAPTURE education are provided to clinicians, along with patient level CAPTURE data, will have a higher probability than control sites (i.e., those receiving only basic COPD education) of meeting the composite endpoint in their CAPTURE+ patients within 12 months of baseline.* From record review, the composite endpoint is met if one of the following is recorded: (1) referral for clinical spirometry testing, 2) new clinical diagnosis of COPD, 3) newly prescribed respiratory medication (long acting bronchodilator or anti-inflammatory for respiratory condition), or 4) referral to a specialist for respiratory evaluation/ treatment.

The study will enroll 50 CAPTURE practices and 50 control practices; each practice will enroll 50 patients (for a total of approximately5,000 patients). We project that within each practice, there will be at least 5 patients previously undiagnosed with COPD who have a CAPTURE+ screening result. The primary analysis will be to compare the average proportion of CAPTURE+ patients per practice that meet the composite endpoint in the two intervention arms. For power and sample sizes computations, this is a cluster randomized trial of n=50 clusters (practices) per intervention arm with 5 CAPTURE+ patients per cluster (practice). The primary power calculation is based on comparing the average cluster sample proportion (average proportion of CAPTURE+ patients per practice meeting composite endpoint) between intervention arms. Table 9-2 displays power for a two-sample test comparing average cluster sample proportions, accounting for possible intra-cluster correlation coefficient (ICC) values of 0.05, 0.10 and
0.15 that are typically seen in cluster randomized trials of behavioral interventions (https://www.abdn.ac.uk/hsru/research/research-tools/study-design/). These calculations assume a type I error of 5% and that the control arm meets the composite endpoint in 5% of CAPTURE+ patients and the CAPTURE arm meets the composite endpoint in higher percentages (columns of Table 9-2). There will be variability in the actual number of CAPTURE+ patients per practice. It is standard practice to inflate the number of needed clusters by 12% to account for this extra source of variability. Therefore, our power calculations are based on 44 clusters per intervention arm.

Table 9-2. Overall power to detect a difference in rate of meeting primary endpoint in CAPTURE group (50 practices/clusters) vs usual care (50 practices/clusters), assuming 5% performance rate in usual care; 50 patients total / practice; assuming 10% prevalence gives 5 CAPTURE+/practice

Improvement over usual care	+7.5%	+10%	+15%	+25%	+50%
ICC=0.05	0.72	0.89	0.99	>0.99	>0.99
ICC=0.10	0.65	0.84	0.98	>0.99	>0.99
ICC=0.15	0.59	0.79	0.97	>0.99	>0.99

9.1.2 SECONDARY OBJECTIVES

9.1.2.1 SENSITIVITY AND SPECIFICITY IN PREDEFINED SUBGROUPS

Table 9-3. Projected numbers of clinically significant COPD cases and non-cases we expect by subgroup of interest assuming prevalence of obstructed individuals is between 6-16%. (*Non-Hispanic) This table assumes prevalence of non-clinically significant COPD similar to clinically significant COPD (not included in this table).

	Total	**Men (50%)**	**Women (50%)**	**White* (62%)**	**Black* (15%)**	**Hispanic (18%)**	**Rural (46%)**	**Urban (54%)**	**Ever-Smokers (40%)**	**Never-smokers (60%)**
Projected # confirmed clinically significant COPD by subgroup	300-800	150-400	150-400	186-496	45-120	54-144	138-368	162-432	120-320	180-480
Projected # confirmed no COPD by subgroup	3,400-4,400	1,700-2,200	1,700-2,200	2,108-2,728	510-660	612-792	1,564-2,024	1,836-2,376	1,360-1,760	2,040-2,640

We will also examine several subgroups of interest that are key to addressing our overall goal of defining the value of CAPTURE across a broad range on individuals. These will include sex, ethnic groups, rural and urban location, and educational level, among individuals with clinically significant COPD, spirometrically defined COPD and individuals with "mild" COPD as defined in this protocol. We have specifically chosen clinical sites with a diverse gender, racial and ethnic mix, and rural and urban mix with the expected prevalence of clinically significant COPD cases and controls by subgroup outlined in Table 9-3, again with corresponding sensitivity and specificity confidence interval widths in Table 9-1. For example, if sensitivity of CAPTURE in Hispanic individuals is 90%, then a sample size of approximately 100 would give a confidence interval of 90% ± 5.9%. We believe that with an overall sample size of 5,000 recruited patients we will have adequately sized subgroups to assess the operating characteristics of CAPTURE in the subgroups of interest.

9.1.2.2 FURTHER ANALYSIS OF ASSOCIATIONS BETWEEN MEETING COMPOSITE ENDPOINT AND INDIVIDUAL AND PRACTICE LEVEL OUTCOMES

Secondary analyses for evaluating practice behavior are exploratory, and therefore not included in a formal power and sample size analysis. These analyses are described further in Section 9.3.2.

9.2 POPULATIONS FOR ANALYSES

Aim 1
Population used for sensitivity calculations are all enrolled patients with clinically significant COPD as defined by post-bronchodilator $FEV_1/FVC < 0.70$ in addition to either $\geq$1 exacerbation-like event (ECOPD) within the past 12 months or an $FEV_1 < 60\%$ predicted.

Population used for specificity calculations are all enrolled patients with no demonstrable COPD as determined by research spirometry conducted upon study entry, $FEV_1/FVC \geq 0.70$.

Aim 2
Clinician participants: enrolled clinicians are from 2 primary care practices in each of five US PBRN regions that do not engage in Aims 1 or 3 investigation. Eligible clinicians include primary care providers

and primary care clinical non-provider support personnel.

Patient participants: enrolled as a sub-sample of Aim 1 participants at baseline. One CAPTURE patient opinion survey is administered at baseline. Aim 2 participants fulfill the inclusion, exclusion and population analysis criteria of aim 1.

Aim 3
Populations used in 2-sample comparisons of the average proportion of CAPTURE+ patients per practice that meet the composite endpoint in the two intervention arms will be based on randomization group (intent-to-treat analysis).

9.3 STATISTICAL ANALYSES

9.3.1 SENSITIVITY AND SPECIFICITY (AIM 1)

SAS version 9.4 PROC LOGISTIC will be used for computations. Calculations of sensitivity and specificity along with their corresponding 95% confidence intervals assume independent Bernoulli outcomes for each patient. Clinically significant COPD+ and COPD- populations selected for these analyses are described in Section 9.2. CAPTURE+ patients are those with a baseline CAPTURE score $\geq$ 5 or with a baseline CAPTURE score of 2, 3, or 4 with a low PEF (defined as <350 L/min for males, <250 L/min for females).

In addition to the primary sensitivity/specificity calculations, sensitivity/specificity and associated 95% confidence intervals will be calculated in predefined subgroups: sex, ethnic subgroups, rural and urban location, and educational status. As part of secondary analyses, receiver operating characteristic (ROC) curve analyses will evaluate different thresholds of the CAPTURE questionnaire score in defining a positive clinically significant + COPD screen, separately and in combination with low PEF characteristics, **and the additional CAPTURE questions**. As part of this exploration, participant and practice level data as well as interactions with the CAPTURE tool results, will be considered as predictors of clinically significant COPD using multivariable logistic regression. Corresponding positive and negative predictive values will be estimated across the range of prevalence percentages seen at the enrolled practices. Model selection in secondary logistic regression analyses will be based on forward selection using maximum likelihood theory, with entry into the model dependent on statistical significance at the 0.05 level. Exploration of this nature has the potential to produce artificially high operating characteristics (area under the curve [AUC], sensitivity and specificity) based on overfitting the data. SAS 9.4 PROC LOGISTIC includes a cross-validation approach to ROC curve analysis [ROCOPTIONS(CROSSVALIDATE)] that we will use when assessing operating characteristics for any new prediction tool that goes beyond the original CAPTURE metric considered in primary analyses. Once a final logistic regression model has been selected, classification thresholds for predicting clinically significant COPD will be described by the investigative team from the cross-validated ROC curve. Calibration plots of observed versus predicted sensitivity, and observed versus predicted specificity, will be conducted across previously specified subgroups of interest (sex, ethnic subgroups, rural and urban location, and educational status).

All of the above analyses will be applied to these additional populations: (1) patients with spirometrically defined COPD and (2) patients with mild COPD.

9.3.2 PRACTICE BEHAVIOR (AIM 3)

The primary analysis will be to compare the average cluster sample proportion (average proportion of CAPTURE+ patients per practice meeting composite endpoint) between intervention arms. Practices that do not identify any CAPTURE + subjects will not contribute to the primary analysis, although this is felt to be an unlikely occurrence. A two-sample test comparing average cluster sample proportions will be used that explicitly takes into account correlation between individuals treated within the same practice. A two-sided p-value < 0.05 will be considered statistically significant. This analysis corresponds to a generalized estimating equation (GEE) regression analysis with (1) individual-level binary composite outcome data, (2) CAPTURE intervention group as a covariate, (3) practice id used to identify correlated outcomes, (4) exchangeable correlation matrix that assumes similar correlation between all composite outcome results for patients within the same practice, and (5) a logistic link function. The primary analysis would then correspond to a test for the CAPTURE intervention group parameter. There are no planned interim analyses for the primary endpoint, the rationale being that this is not a pharmaceutical or device trial that would benefit from standard stopping rules for efficacy. A DSMB will be monitoring the study for safety and study integrity.

Secondary analyses on meeting the composite outcome for participants who are CAPTURE+ will employ the GEE analysis framework with individual and practice level predictors in addition to the CAPTURE intervention group. Interactions will be assessed. We will also use the GEE framework to study and describe each of the individual components of the composite outcome as they relate to individual and practice level outcomes. In the subset of smoking patients, we will use GEE regression analysis to study additional binary outcomes, such as incidence of physician referral to a formal smoking cessation program, prescribed smoking cessation medication in participants who are smokers, and referral to pulmonary rehabilitation program.

In participants who are CAPTURE+, change in CAT score will be analyzed using mixed models with a random effect for practice. The average cluster sample proportion of patients who experience exacerbations will be compared between intervention groups using methodology similar to that used for the primary endpoint. Survival analysis allowing for correlation of endpoints within cluster (practice) will be used to compare mortality between intervention groups and perform multivariable analysis. We will explore differences between intervention groups in the average cluster sample rate of hospitalizations again using GEE. All additional secondary analyses will also be applied to patients with clinically significant and spirometrically defined COPD. Practices that do not have any clinically significant COPD or spirometrically defined COPD will not contribute to analyses of these secondary endpoints, respectively.

Model selection in GEE secondary analyses will be based on statistical significance at the 0.05 level using robust sandwich estimation of variability within clusters. Model fit will be checked by comparing observed versus predicted values within predefined subgroups of interest (sex, ethnic subgroups, rural and urban location, and educational status).

9.3.3 CAPTURE IMPLEMENTATION RECOMMENDATIONS (AIM 2)

Site-specific practice information, clinician knowledge and behavioral questionnaires, as well as patient opinion survey responses are recorded primarily to populate focus group themes for qualitative analysis. Secondary analyses of individual clinician and patient response using frequencies, means, ranking and dispersion by clinician type, practice and PBRN is accomplished using SAS version 9.4. Correlation with implementation recommendation is determined using GEE variance models.

Audio transcripts of clinician focus groups will all be digital and entered into a qualitative data analysis program, NVivo for Mac. This program allows for an investigation of the salience, patterning, and contexts of key discourse items. Grounded theory methods will be used to identify and label recurrent themes and concepts within textual materials. Texts will be examined line-by-line, key phrases assigned tentative category labels, and coded passages grouped under the themes of feasibility, barrier and utility. The analyses will look for "traces" in dialogue, including repetitions, key words, evaluation statements, and metaphors. Micro-interlocutor analysis of focus group emergent themes, questions, answers and interactions will account for individual gaps in focus group participation. Change in salience, patterning, or content of key themes will provide further empirical evidence regarding the efficacy of our program's efforts to impact clinician community norms and behaviors. An audit trail will be maintained to document the position of text material from which codes and themes are developed. We will use word/code counts of repetitive themes and concepts to indicate patterns. By allowing for open-ended responses, the narratives and notes will allow us to capture significant changes in participants' attitudes or behaviors. Codes and themes will be discussed iteratively with the research team members to hone definitions and assure consistency of interpretation. We will establish a coding dictionary and all interviews will be coded using the complete set of themes. Reviewing the transcripts line-by-line, all substantive information will be assigned a priori codes as relevant for CAPTURE RE-AIM implementation planning, COPD diagnosis, CAPTURE intra-office clinical communication, and COPD and CAPTURE education preference, and COPD diagnosis quality improvement assessment. Two independent coders will code each document to assure inter-coder reliability. Preliminary results will be shared with the Aim 2 data team and will inform the development of the CAPTURE case studies and primary care practice implementation recommendations.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise.

A HIPPA waiver will be submitted to each IRB to prescreen clinic schedules and patient panels for recruitment purposes. The PHI reviewed by the coordinator in the electronic health record (EHR) will include age, date of birth, diagnosis of COPD, respiratory medications, and other medical conditions that are contraindicated for spirometry. A waiver of written consent will be submitted to each IRB to pre-screen potential participants for eligibility criteria prior to informed consent. The pre-screening will either be by telephone prior to an upcoming clinic visit, or in person at the time of the visit. An IRB-approved telephone/in-person screening script will be submitted to each IRB.

A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. Participants will additionally have the opportunity to review the study and informed consent prior to providing consent for the study. Participants must be informed that participation is

voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

All PBRN research coordinators, COPD Foundation study staff and other clinical investigators will be certified by their local IRB in informed consent and human studies research.

Clinicians interested in participating in the qualitative, minimal risk study for Aim 2, will be given the opportunity to review the consent form below and sign it. This can happen once their practice agrees to participate in Aim 2 activities or during the first in person site visit with Dr. Brown.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

When a study is prematurely terminated, refer to Section 7, Study Intervention Discontinuation and Participant Discontinuation/Withdrawal, for handling of enrolled study participants.

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. In addition, it may be transmitted and stored at the DCC in a database separate from

the clinical database (used for statistical analysis and scientific reporting) and with COPD Foundation study team access to aid in contacting participants at the 12-month follow-up. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the DCC. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by DCC research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the DCC.

For the online Aim 2 patient opinion survey, Qualtrics is used. Qualtrics is a secure University of Michigan (U-M) contracted-for cloud service that can be used to maintain or share the university's sensitive unregulated data, as well as some kinds of sensitive regulated data.

U-M's agreement with Qualtrics includes a Business Associate Agreement. This means individuals may use this service to maintain Protected Health Information (PHI) regulated by HIPAA. Complying with HIPAA's requirements is a *shared responsibility*. Users sharing and storing PHI in Qualtrics are responsible for complying with HIPAA safeguards, including:

- Using and disclosing only the minimum necessary PHI for the intended purpose.
- Obtaining all required authorizations for using and disclosing PHI.
- Ensuring that PHI is seen only by those who are authorized to see it.
- Obtaining all necessary data-sharing agreements and Business Associate Agreements for using and disclosing PHI.
- Following any additional steps required by your unit to comply with HIPAA.

Sensitive data, including PHI, may be collected and stored in Qualtrics for non-clinical, academic purposes only (for example, research and hospital quality improvement initiatives). Qualtrics cannot be used for any clinical applications, no matter the sensitivity level of the data

11 STUDY ADMINISTRATION AND OVERSIGHT

11.1 STUDY LEADERSHIP

11.1.1 PRINCIPAL INVESTIGATORS

The principal investigators are responsible for providing direction and oversight of all study activities.

Principal Investigators	
Fernando Martinez, MD, MS	MeiLan Han, MD, MS
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11.1.2 PRACTICE BASED RESEARCH NETWORKS (PBRN)

PBRNs will have the following roles and responsibilities:

CAPTURE Study Preparation

1. Review protocol to help identify operational details
2. Submit final protocol and informed consents to all IRBs necessary for the participating sites
3. Complete and maintain current human participants training for all main study personnel as required by the IRB
4. Attendance of PBRN coordinators at in person training, spirometry certification for all coordinators, update of spirometry quality assessments and training
5. Identify and recruit local practice sites to participate in the study

CAPTURE Study Implementation

1. Facilitate COPD and when appropriate CAPTURE education
2. Maintain regular contact with participating PBRN practice sites during their period of patient enrollment
3. Supervise and send PBRN Research Coordinators to enroll patients, perform study visits including completion of the CAPTURE questions, peak flow, spirometry, and collect other information on all enrolled patients
4. Complete pre bronchodilator spirometry on all participants
5. Complete post bronchodilator spirometry on participants with abnormal pre-bronchodilator spirometry as defined by study algorithm (e.g. those with pre bronchodilator results consistent with obstruction)
6. Facilitate completion of data entry to the data coordinating center
7. Follow up by research coordinator for patients failing to respond to the follow up questionnaires
8. Collect practice outcome data related to enrolled patients at close of study from either electronic medical records or if practice does not have EMR, by manual record review

Patient participants and staff participants will be recruited from the PBRNs.

PBRN	**Location**	**Director**
Atrium Health	North Carolina	Hazel Tapp, PhD
LA Net Community Health Network	Southern California	Lyndee Knox, PhD
High Plains Network	Colorado	Linda Zittleman, MD
Duke Primary Care Research Consortium Oregon Rural Practice-Based Research Network	North Carolina Oregon	Rowena Dolor, MD Nancy Elder, MD
University of Illinois, Chicago	Illinois	Min Joo, MD
Circuit Clinical, Buffalo	New York	Irfan Khan, MD

11.1.3 SPIROMETRY CORE

Led by Dr. David Mannino, the Spirometry Core will maintain quality of the research spirometry that is integral to the success of the study. The work will be done in conjunction with a research assistant. This includes the following functions:

1. Development of the operation manual for the sites
2. Training of the site staff in the use of the spirometry equipment (including travel to training and sites as needed)
3. Certification of staff in spirometry
4. Assessing staff adherence to protocols for the use of bronchodilators
5. Grading and adjudication of spirometry
6. Importing processed spirometry into spreadsheets
7. Uploading processed data to data coordinating center
8. Working with data coordinating center to verify and clean data

In addition, Dr. Mannino will be a critical part of the team that evaluates the data both from spirometry and the other components of this study (the CAPTURE tool, quality of life measures, etc.), in addition to being part of the writing team that analyzes data and disseminates the findings from this study.

11.1.4 IMPLEMENTATION CORE

Dr. Randall Brown will lead the qualitative Aim 2 activities which assess the implementation strategy and acceptance recommendations for CAPTURE use in primary care practice. His team includes an Aim 2 project manager and dedicated research assistant. Led by Dr. Brown the Aim 2 team coordinates with PBRNs and their selected Aim 2 practices and will conduct qualitative site visits and focus groups in addition to administering clinical practice behavioral questionnaires. Drs. Barbara Yawn, Barry Make, Bruce Bender and Julia Houfek will contribute to the development of the web based educational modules and the qualitative efforts on this project.

11.1.5 DATA COORDINATING CENTER (DCC)

Dr. Cathie Spino directs the DCC, housed at the University of Michigan within the Statistical Analysis of Biomedical & Educational Research (SABER) Unit of the Department of Biostatistics in the School of Public Health. The DCC staff will include a Database programmer, Data manager, Senior Unblinded Statistician, Statistical Analyst, Project Manager, Clinical Monitor, Web Programmer/Designer, and a Research Administrator. In addition, the blinded senior statistician, Dr. Susan Murray, is located at the University of Michigan. The DCC plays a pivotal role in the design, implementation, execution and administration of the study. The DCC will be responsible for randomization, eCRFs and online reporting systems, preparation of the manual of operations for data entry, addressing questions regarding entry and analysis, monitoring recruitment, follow-up and adherence to protocol, and scheduling and arranging meetings of the Executive Committee, Steering Committee, and Medical Monitor. The DCC will prepare all of the routine study reports for the Executive Committee, Operations Committee, and Medical Monitor. The DCC will interact with all of the Cores and other Committees, as needed. The DCC will compile data tables and listing for DSMB reports.

11.1.6 CLINICAL COORDINATING CENTER

The Clinical Coordinating Center (CCC) will be led by Principal Investigators Fernando Martinez, MD, MS at Weill Cornell Medicine, and MeiLan Han, MD, MS at the University of Michigan. Dr. Martinez will be responsible for overall study oversight as well as fiscal management of the overall project and capitation payments to sites for work performed. He will also be responsible for communication with NIH and submission of annual reports. Dr. Han will work with the Data Coordinating Center to oversee clinical trial enrollment and, along with her statistical team, be responsible for coordinating statistical analysis. The process for making decisions on scientific direction and allocation of resources will be made by both Drs. Martinez and Han, with input from the rest of the investigative team as needed.

Additional Clinical Coordinating Center (CCC) responsibilities:

- Establish subcontracts with enrolling sites, central laboratories, imaging service providers, and others as appropriate
- Protocol development and scientific design oversight
- Statistical analysis
- Participating study site selection
- Review of serious adverse events and unanticipated problems involving risk to participants or others, reporting to participating centers and regulatory reporting
- Prepare and maintain Clinical Coordinating Center IRB submissions
- Analyze and present data to DSMB

Clinical Coordinating Center Personnel

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11.1.7 12 MONTH SURVEY COORDINATING CENTER

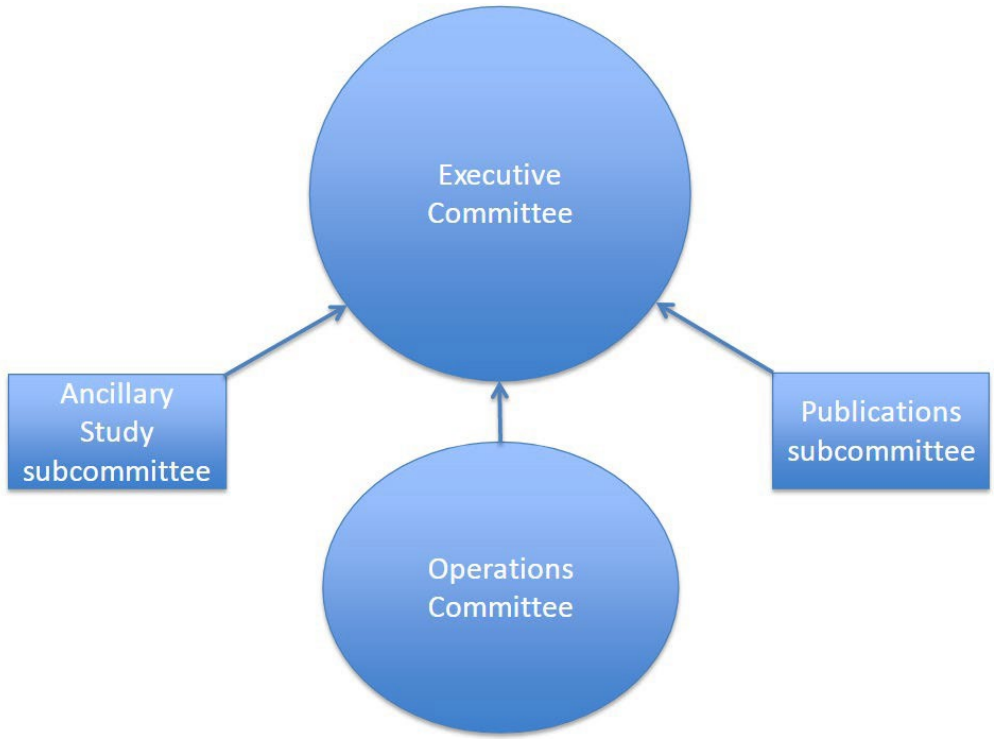
The 12 month Survey Coordinating Center will be led by Co-Investigator Barbara Yawn, MD MSc, Chief Science Officer at the COPD Foundation. Dr. Yawn will be responsible for oversight of the development and implementation of the reminder notices and 12 month survey administration by COPD Foundation study personnel for participants selected to complete the 12 month follow up survey.

11.2 ORGANIZATIONAL STRUCTURE

The Executive Committee will be led by the Principal Investigators and will consist of the 2 elected PBRN Directors, 1 representative of the COPD Foundation, Co-Investigators, Data Coordinating Center PI and Project Manager, NIH official and Clinical Coordinating Center Project Managers. The Executive Committee will meet every one-to-two weeks to administratively direct and monitor the progress of the study and to respond to any design, implementation or administrative issues that arise during the study.

The Operations Committee will consist of Overall Principal Investigators, PBRN Directors and lead coordinators, DCC Project Managers, and Co-Investigators. It will address implemental and administration faced by the PBRN practices that arise during the study.

Other subcommittees, such as the Publications and Ancillary Studies Subcommittees, will be constituted to support maximizing the utility of the CAPTURE study to the scientific community.



12 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data, documentation and completion. An individualized quality management plan will be developed.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

13 DATA HANDLING AND RECORD KEEPING

13.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Comprehensive data coordinating center (DCC) functions for this clinical trial, including clinical monitoring, database development, web-based data entry and management, as well as the creation and export of study reports for the DSMB will be provided by the University of Michigan Statistical Analysis of Biomedical and Education Research (SABER) group. Housed in the top nationally ranked Department of Biostatistics, SABER, in its 17-year existence, has served as the DCC for over 50 studies, including multiple NIH-sponsored networks.

The DCC will use OpenClinica® (OpenClinica Clinical Trial Software; OpenClinica, LLC, Waltham, MA), a clinical trial software platform for electronic remote (i.e., site-based entry) data capture and clinical data management, as the basis for our custom-designed data entry and management system. The majority of data will be collected via electronic Case Report Forms (CRFs); however, other data sources, such as laboratory data from the central laboratory, may be used. In these circumstances, the DCC will also utilize electronic data transfer. Protocols for the transfer of data, with careful attention to data integrity, will be written by experienced programmers and stored in the OpenClinica database or data mart.

The DCC has established a set of standard operating procedures (SOPs) governing the processes used to ensure patient privacy and data confidentiality, including the use of anonymous participant IDs on CRFs and in reports. OpenClinica® enables compliance with Good Clinical Practice (GCP) and regulatory requirements by providing differentiated user roles and privileges, password and user authentication security, electronic signatures, SSL encryption, and comprehensive auditing to record and monitor access and data changes.

Data collection is the responsibility of the central study staff at the PBRN under the supervision of the PBRN Director (investigator). The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. In addition to the protocol, the DCC will prepare a Manual of Procedures which provides additional detail on data collection procedures, including source documentation, eCRF completion guidelines, data handling procedures and procedures for data monitoring and quality control that ensure these data are accurate, consistent, complete and reliable and in accordance with ICH 36.

13.2 STUDY RECORDS RETENTION

Study documents should be retained as required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

13.3 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1

- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation or scheduled protocol-required activity. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

13.4 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers after the completion of the primary endpoint by contacting Drs. Martinez and Han.

14 PROTOCOL AMENDMENT HISTORY

Protocol Amendment 2.0 - Summary of Changes				
Location	**Page Number**	**Type of Change**	**Description**	**Rationale**
Cover Page	---	*Administrative*	Update Protocol Version to 2.0 and update version date to	Amendment version and date
Cover Page	---	*Administrative*	Add NCT # for each AIM	Add all 3 numbers to protocol since each AIM is registered in clinicaltrials.gov
Table of Contents	---	*Administrative*	Corrected page numbers for new version	Updating Table of Contents to reflect any page number shifts due to reformat
Multiple Sections	Multiple	*Administrative*	Changed Medical Chart Review to Medical Record Review throughout the protocol	Changed Medical Chart Review to Medical Record Review throughout the protocol
1.2 Schema Table 1	9	*Clarification*	Concomitant medications revised to read Respiratory Medications	Further clarification since these are limited to respiratory medication not all medications

1.2 Schema Table 1	9	*Clarification*	Foot note 3 moved to 12 month to reflect the data that will be collected for subjects who qualify for 12 month follow-up w	Clarification that 12 month column is for indicating what data will be collected for subjects who meet 12 month follow-up criteria
1.2 Schema Table 1	9	*Clarification*	X in last column for 12 month spirometry was deleted. This was originally meant to be footnote that post bronchodilator spirometry would be performed at baseline for those subjects that qualified	Further clarification that spirometry will not be done at 12 month follow-up, the footnote was meant to reflect post bronchodilator spirometry at baseline for those subjects who qualify
Section 2.3.1 Known Potential Risks	14	*Revision*	For Albuterol: A targeted safety questionnaire will be administered to all participants prior to albuterol to exclude those with a previous adverse event with the medication and others at high risk due to cardiac abnormalities.	Subjects are excluded who have had MI and therefore not necessary
Section 4.1 Overall Study Design	21	*Clarification*	Patient-reported data will be collected by telephone, secure web-based server, and mail-based methodologies <u>based on participant preference and completed by the COPD Foundation.</u>, as well as medical record abstraction, depending upon practice site preferences and feasibility.	The COPD Foundation will be collecting participant 12 month follow-up subject questionnaires
Section 4.1 Overall Study Design	21	*Clarification*	Clinic site data will also be collected from the Subject medical record data will be collected from the medical record to assess for changes in practice-level care.	Further clarification that this data will be collected from medical record
Section 6.3 Study Intervention Compliance	27	*New*	If results were not shared at the time of the CAPTURE study visit, then the date of sending the CAPTURE results will be recorded on the appropriate eCRF by filling in the date (day/month/year) the exact copy of the CAPTURE Toolresults were sent to the clinician through a inter–clinic email or other HIPPA-compliant method and placed in the medical record. The goal is to communicate the results to the clinician in a timely manner within 3 business days. The DCC will monitor review all participants' eCRFs to assure that all those enrolled from practices randomized to CAPTURE results have been shared with clinicians. in the specified timeframe.	The study team wanted to clarify that the exact copy of the CAPTURE tool should be shared with clinician. Also wanted to make timing of sharing less restrictive and the team recognized that restrictive parameters cannot always be realized in clinical practice setting

Section 8.2 Longitudinal Follow-up Assessment and Data Collection	30	*Clarification*	Medical chart abstractions <u>completed by PBRN coordinators</u> and participant questionnaires <u>administered by study team members from the COPD Foundation are used.</u>	Clarification that medical chart reviews will be done by PBRN coordinators and COPD Foundation will administer participant questionnaires at 12 months
Section 8.2 Longitudinal Follow-up Assessment and Data Collection	30	*Clarification*	Data from clinical visits to be collected at follow-up by telephone, secure web-based server, or mail-based methodologies directly from participants <u>and administered by COPD Foundation study personnel</u>	Clarification that COPD Foundation will administer participant questionnaires at 12 months
Section 10.1.1 Informed Consent Process	45	*New*	All PBRN research coordinators, <u>COPD Foundation study staff</u> and other clinical investigators will be certified by their local IRB in informed consent and human studies research.	The COPD Foundation has attained IRB approval as their team will be interacting with participants
Section 10.1.3 Confidentiality and Privacy	46	*Clarification*	In addition, it may be transmitted and stored at the DCC in a database separate from the clinical database (used for statistical analysis and scientific reporting) and with <u>COPD Foundation study team</u> study coordinator access to aid in contacting participants at the 12-month follow-up.	COPD Foundation will have access to participant contact information from a separate database in order to contact participants for follow-up questionnaire completion
Section 11.1.2 Practice Based Research Networks (PBRN)	47	*Administrative*	Moved Roles and Responsibilities to section 11.1.2	Moved Roles and Responsibilities to section 11.1.2
Section 11.1.2 Practice Based Research Networks (PBRN)	47	*Revision*	Change Carolinas HealthCare System to Atrium Health and add new PI for Oregon Rural Practice-Based Research Network	Carolinas HealthCare System is now Atrium Health and the new PI at Oregon, Dr. Lyle Fagnan is retiring and Dr. Nancy Elder will take his place as director and site PI for CAPTURE
Section 11.1.7 Clinical Coordinating Center	49	*Clarification*	Update titles for COPD Foundation study members	Administrative change to include titles for Dr. Yawn
Section 11.1.8 12 Month Survey Coordinating Center	50	*New*	Add 12 Month Survey Coordinating Center to Study Leadership, Section 11.	The COPD Foundation study team will be coordinating outreach to 12 month follow-up subjects and administering surveys
Section 11.2 Organizational Structure	51	*Clarification*	Includes 1 representative of the COPD Foundation in the Executive Committee Organization description.	COPD Foundation representatives are part of the Executive Committee currently
Section 4.1 Overall Study Design	9, 10, 21	*New*	Deletion of CAT Score ≥ 10 and CAPTURE Score ≥ 2 and return to CAPTURE+ and abnormal spirometry as longitudinal follow-up criteria	The study team proposes to defer longitudinal follow-up based solely on an isolated, baseline CAT or CAPTURE scores as it is outside the scope of the current CAPTURE program. The study team is also proposing to return to the original scientific approach to follow CAPTURE+ (as defined in the protocol) subjects along with abnormal post-BD spirometry and 5%

				random sample of those subjects that meet neither of these criteria. Those subjects already selected under the current algorithm would still be followed longitudinally (and noted as selected under the initial follow-up selection criteria) and would use data as appropriate. Importantly, the primary care clinician colleagues within the CAPTURE program do not feel there is a safety issue in not following this population as there are no data defining a negative impact of an isolated, elevated CAT score in primary care patients.
Section 1.1 Synopsis, Section 4.1 Overall Study Design, Section 8.1 Baseline Assessments and Data Collection	3, 20, 29	*New*	Addition of adjudication of the presence of obstruction on post-bronchodilator spirometry	As the study commenced, several instances of the faulty spirometry software reading incomplete or participant refusal of post-bronchodilator occurred and led to the need for spirometry core to determine review process in these instances and validity of pre-bronchodilator spirometry. The rationale for this is that in other databases where all patients had both pre and post-bronchodilator spirometry, those who had a pre-bronchodilator FEV1/FVC less than 0.65 had a post-bronchodilator FEV1/FVC less than 0.70 more than 95% of the time.
8.1 Baseline Assessments and Data Collection	28	*New*	Addition of spirometry instructions if participant has taken a medicine they breathed into lungs from puffer or inhaler within two hours of spirometry test	Since study start, one participant reported taking albuterol shortly before the visit. The study clinicians confirmed this scenario would constitute the participant being in a post-bronchodilator state already with no further need to proceed after initial spirometry. The data collection process has been updated to assure these values would be placed in post-bronchodilator data. Coordinators are instructed to ask this question before spirometry should this scenario occur again during the study.

Protocol Amendment 3.0 - Summary of Changes

Location	Page Number	Type of Change	Description	Rationale
Cover Page	---	*Administrative*	Update Protocol Version to 3.0 and update version date to 24 September 2019	Amendment version and date updated
Cover Page	---	*Administrative*	Add NCT # for each AIM	Add all 3 numbers to protocol since each AIM is registered in clinicaltrials.gov
Multiple Sections	Multiple	*Revision*	Number of PBRNs participating in aims 1 and 2 revised to 6 PBRNs throughout protocol.	Additional PBRN added
1.2 Schema Table 1	9	*Revision*	CAPTURE 12 additional items questionnaire	The CAPTURE 12 item additional questionnaire was renamed.
Section 8.1 Baseline	30	*Clarification*	CAPTURE Additional Items Questionnaire administration	Further instruction for administration of CAPTURE Additional Items Questionnaire,

Assessments and Data Collection			instruction added to Study Assessments.	as described in Section 1.2 Schema table, was added.
Section 11.1.2 Practice Based Research Networks (PBRN)	48	*Revision*	University of Illinois, Chicago added as a participating PBRN.	University of Illinois, Chicago added as an enrolling site in aims 1 and 3.
Protocol Amendment 4.0 - Summary of Changes				
Location	**Page Number**	**Type of Change**	**Description**	**Rationale**
Protocol Amendment Summary of Changes Table	---	*Administrative*	Protocol Amendment 2.0 – Summary of Changes was added to the Summary of Protocol Amendments Table.	Amendment 2.0 – Summary of Changes was added to provide a comprehensive list of changes across all protocol amendments.
Protocol Amendment 5.0 - Summary of Changes				
Location	**Page Number**	**Type of Change**	**Description**	**Rationale**
1.2 Schema Table 1, 8.2 Longitudinal follow-up assessment	9, 32	*New*	A COVID-19 questionnaire was added to the 12-month follow-up visit, performed by the COPD Foundation.	A COVID-19 questionnaire was added to collect information about the COVID-19 prevalence in primary care, impact on symptoms, relation to comorbidities, and impact on provider outcomes.
2.1 Study Rationale, 4.1 Overall Design, 4.2 Scientific Rationale for Study Design	11, 22, 23	*New*	Rationale for collecting COVID-19 information from participants was added.	The impact of COVID-19 on COPD Case Finding and respiratory symptoms in primary care is unknown. COVID-19 information will be used to investigate this.
4.1 Overall Study Design	21	*Revision*	The following change was made: Participants who meet the criteria for follow-up will be sent notification~~/reminder letters within the first 3 weeks of~~ **shortly after** enrollment and **receive** at 3, 6, and 9 months	Language was updated for flexibility in notification of participants in order to allow time to confirm follow-up criteria.
8.1 Baseline Assessments and Data Collection	29	*Revision*	Additional guidance for sites to follow their local institutional guidelines for spirometry was added.	Institutional guidance for minimizing the risk of COVID-19 spread during spirometry varies across sites. Sites should ensure they are following local guidance.
8.3 Aim 2 Assessments	34	*Revision*	Participants will receive a $15 gift card for completion of the opinion survey, instead of $10.	This was a typo in the prior version of the protocol.
8.2 Longitudinal follow-up assessment	31	*New*	Extraction of data related to COVID-19 confirmed and suspected cases will be added to the 12 month medical record review.	A COVID-19 questionnaire was added to collect information about the COVID-19 prevalence in primary care, impact on symptoms, relation to comorbidities, and impact on provider outcomes.
Protocol Amendment Summary of Changes Table	---	*Administrative*	Protocol Amendment 2.0 – Summary of Changes was added to the Summary of Protocol Amendments Table.	Summary of Changes for protocol versions 2.0 and 3.0 –were added to Section 14 to provide a comprehensive list of changes across all protocol amendments.

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CAPTURE Statistical Analysis Plan

TRIAL FULL TITLE	Validating a unique COPD case finding tool in primary care
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TRIAL PRINCIPAL INVESTIGATORS	Fernando J. Martinez, MD, MeiLan K. Han, MD
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2 Table of Contents

3 Abbreviations and Definitions

AE	Adverse Event
ANCOVA	Analysis of Covariance
CAO	Chronic Airflow Obstruction
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
ECOPD	Exacerbation of Chronic Obstructive Pulmonary Disease
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FEV1	Forced Expiratory Volume in 1 second
FFR	Federal Financial Report
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practice
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act

4 Introduction

4.1 Preface

This Statistical Analysis Plan (SAP) describes statistical methods and analyses for the CAPTURE (**C**OPD **A**ssessment in **P**rimary Care **T**o Identify **U**ndiagnosed **R**espiratory Disease and **E**xacerbation Risk) study, with emphasis on methods and analyses for the clinical trial component () of the CAPTURE Study Protocol version 3.0, dated September 26, 2019. This document should be read in tandem with the CAPTURE Study Protocol. When mentioned, CAPTURE Study Protocol Aims 1 and Aim 2 goals and analyses are grayed out in this document because they are out of scope of this SAP.

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the US and a major cause of morbidity, mortality and health care expenditures. In primary care settings, the primary contact point for individuals seeking health care, COPD is often under diagnosed and associated opportunities for correct disease management are missed. The CAPTURE tool was developed to identify individuals with undiagnosed COPD, and preliminary data has shown high sensitivity and specificity towards this goal. However, its use in primary care settings, where its potential impact on improved health care

utilization is high, has not yet been studied.

The clinical trial component () of the CAPTURE study is a cluster-randomized trial of 100 primary care practices affiliated with six practice-based research networks (PBRNs). Randomization to one of two interventions takes place at the practice level. Both interventions provide clinicians in participating practices with basic COPD education (enhanced usual care). Clinicians from practices randomized to the CAPTURE intervention additionally receive an educational module (CAPTURE education) on the CAPTURE tool. Each of the 100 practices enrolled 50 patients (5000 total patients). In a single visit, each enrolled patient participant completes CAPTURE screening, pre- and post-bronchodilator spirometry and completes demographic, and general and respiratory related health questionnaires. Practices randomized to the CAPTURE intervention are provided with patient-level CAPTURE tool results for the patients it has enrolled in the study. One-year follow-up chart reviews and participant surveys are used for a pre-identified subset of participants to assess whether CAPTURE screening and sharing of results with clinicians results in higher rates of guideline-concordant COPD care in those with a positive CAPTURE tool result (CAPTURE+). Study investigators hypothesize that providing CAPTURE screening results to primary care clinicians will increase rates of COPD diagnosis and increase guideline concordant COPD care.

4.2 Scope of the Analyses

The primary analysis of the cluster-randomized trial is to compare the average proportion of CAPTURE+ patients per practice that meet the composite endpoint of guideline-concordant COPD care in the two intervention arms. From record review, the composite endpoint is met if one of the following is recorded: 1) referral for clinical spirometry testing, 2) new clinical diagnosis of COPD, 3) newly prescribed respiratory medication (long acting bronchodilator or anti-inflammatory for respiratory condition), or 4) referral to a specialist for respiratory evaluation/ treatment. In addition to providing more details on the primary analysis, this document will describe secondary and exploratory analyses of interest that make use of data collected as part of the cluster-randomized trial (CAPTURE Aims 3). Analyses relating to the ancillary study objectives outlined in Aims 1 and 2 of the CAPTURE protocol are not the focus of this SAP; when mentioned, details of those analyses are grayed out.

5 Study Objectives and End Points

5.1 Primary Objectives

The Aims 1 objective from the CAPTURE protocol is to define the sensitivity and specificity of CAPTURE for identifying previously undiagnosed patients with clinically significant COPD in a broad range of primary care settings. The Aim 2 objective of the CAPTURE protocol is to explore clinical practice implementation approaches to and acceptance of CAPTURE case finding for clinically significant COPD in a range of primary care practices. The objective of the cluster-randomized trial described in Aims 3 of the CAPTURE protocol is to define the impact of CAPTURE information provided to clinicians in identifying and managing patients with respiratory symptoms (CAPTURE+) across a broad range of primary care settings. Table 1 below outlines primary and secondary objectives and endpoints for Aims 1 of the CAPTURE protocol (grayed out) and the cluster-randomized trial described in Aims 3 of the CAPTURE protocol.

Table 1. CAPTURE Study Objectives, Endpoints for Aims 3.

OBJECTIVES	ENDPOINTS
Primary	
Define the impact of CAPTURE information provided to clinicians in identifying and managing patients with respiratory symptoms (*CAPTURE+*) across a broad range of primary care settings.	Proportion of CAPTURE + participants who meet at least one of the following within 12 months after baseline study visits (composite endpoint): 1. Referral for or completion of spirometry testing , 2. New diagnosis of COPD, 3. Newly prescribed inhaled respiratory medication, or 4. Referral to a respiratory specialist.
Secondary	
Assess impact of CAPTURE clinician education, and receipt of patient-level CAPTURE results on selected measures of guideline concordant care.	Proportion of CAPTURE+ participants who meet the components of the composite endpoint with addition of measure of guideline concordant care---smoking cessation support, referral to pulmonary rehabilitation and influenza immunization to above endpoints.
Assess impact of CAPTURE education and receipt of patient level CAPTURE results on clinician interventions specific to current smokers in CAPTURE+ participants.	Proportion of current smokers who receive referral to smoking cessation program, prescribed smoking cessation medication, or referral to quit line.
Determine the impact of CAPTURE education on clinical outcomes of patient symptoms, exacerbations, hospitalizations, and mortality.	Change in COPD Assessment Test (CAT) score, occurrence of one or more exacerbations and respiratory related hospitalizations, and all-cause mortality.
Determine the impact of CAPTURE education and receipt of patient level CAPTURE results in those who meet research spirometry criteria for COPD.	All of the above diagnostic, care and patient outcome endpoints for Longitudinal Aim in those that are CAPTURE + and whose research spirometry results meet criteria consistent with COPD (FEV_1/FVC < 0.7 and FEV1 <80% predicted.

6 6. Study Methods for Cluster Randomized Trial (CAPTURE Protocol Aims 3)

6.1 General Study Design and Plan

Overview: This is a prospective multi-PBRN, cluster randomized clinical trial to assess the operating characteristics of the CAPTURE COPD screening approach and compare respiratory related clinical actions and patient health status during the year following clinician receipt vs non-receipt of the CAPTURE results. Figure 1 provides a summary of the details of the study flow and data collection.

PBRNS: The six PBRNs were selected from a pool of PBRNs with prior experience in large scale clinical trials. The selection process included surveying each candidate PBRN, reviewing survey responses and conducting telephone interviews with the director of each of those PBRNs. The final six were selected based on interest, availability, prior experience in respiratory related clinical trials, geographic spread, socioeconomic, and racial/ethnic diversity of patients within the PBRN practices as well as willingness to participate in a five-year trial. These PBRNs were enrolled (collectively) 100 practices with 50 enrolled patients per practice completing spirometry and other study entry materials.

Practices and Clinicians: Each PBRN identified and enrolled practices based on interest and availability of space to complete the research visit within the practice building and willingness of the practice's clinicians to view the required educational modules. Enrolled practices were randomized in a 1:1 ratio to

receive either basic COPD education or basic COPD education augmented with education on the CAPTURE Tool.

Patient Participants: Within each enrolled practice, potentially eligible patients of clinicians completing the required education are identified and invited to participate using one of two methods: (1) eligible patients identified by research and clinical staff are approached as they visit the clinic or (2) research staff are provided a list of patients with future appointments, and those aged 45-80 years are sent invitation letters by the PBRN to allow further contact and evaluation of eligibility and interest. The chosen method is based on prior PBRN experience and requirements of the local health systems and Institutional Review Boards (IRBs).

Patients who are eligible and agree to participate in the study sign informed consent, complete the CAPTURE questionnaire, PEF testing, spirometry testing, other respiratory questionnaires, provide past medical history, and demographic information. Local/PBRN study coordinators perform the study procedures and record baseline information into the electronic data capture (EDC) system. The EDC system calculates a CAPTURE score for each participant. For patients in a practice randomized to CAPTURE+COPD education, their practitioner is provided with CAPTURE results for their patient. Practitioners at sites randomized to the COPD education only intervention are blinded to CAPTURE scores. Practitioners in both intervention arms are blinded to research spirometry results.

Based on the data collected at baseline, participants will be classified into the following groups for analyses:

Cohort	**Definition**
CAPTURE+	Participants with • CAPTURE score $\geq$ 5, or • CAPTURE score of 2, 3, or 4 with a low PEF, defined as <350 L/min for males and <250 L/min for females
CAPTURE-	Participants with • CAPTURE score < 2 or scores 2-4 with normal PEF (defined as $\geq$350 L/min for males and $\geq$250 L/min for females)
Spirometrically Defined COPD	Participants with abnormal spirometry, defined as post-bronchodilator FEV_1/FVC <0.7. If a participant is unable to complete a post-bronchodilator spirometry (refusal, technical error on the part of coordinator, etc.), and the pre-bronchodilator FEV1/FVC is less than 0.65, the participant will be considered to have COPD for the purpose of follow-up in this study.
Clinically Significant COPD	Participants with abnormal spirometry, defined as post-bronchodilator FEV_1/FVC <0.7, plus one of the following: 1) FEV_1 < 60% predicted or > 1 exacerbation like event within the past 12 months.
Mild COPD	Participants with abnormal spirometry, defined as post-bronchodilator FEV_1/FVC<0.7 plus both of the following: • $FEV_1 \geq 60\%$ and • No prior history of ECOPD

Longitudinal Follow-up

A pre-defined subgroup of enrolled participants, who meet any of the below criteria, will undergo longitudinal follow-up at 12 months:

1. CAPTURE+ participants, as defined above.
2. Participants who have spirometrically defined COPD, as defined above.
3. A random sample of approximately 5% who do not meet criteria 1 – 2.

Participants who meet the criteria for follow-up will be sent notification/reminder letters within the first three weeks of enrollment and at three, six, and nine months. Patient-reported data will be collected by COPD Foundation via telephone, secure web-based server, or mail-based methodologies, based on participant preference.

Subject medical data will be collected from the medical record to assess for changes in practice-level care.

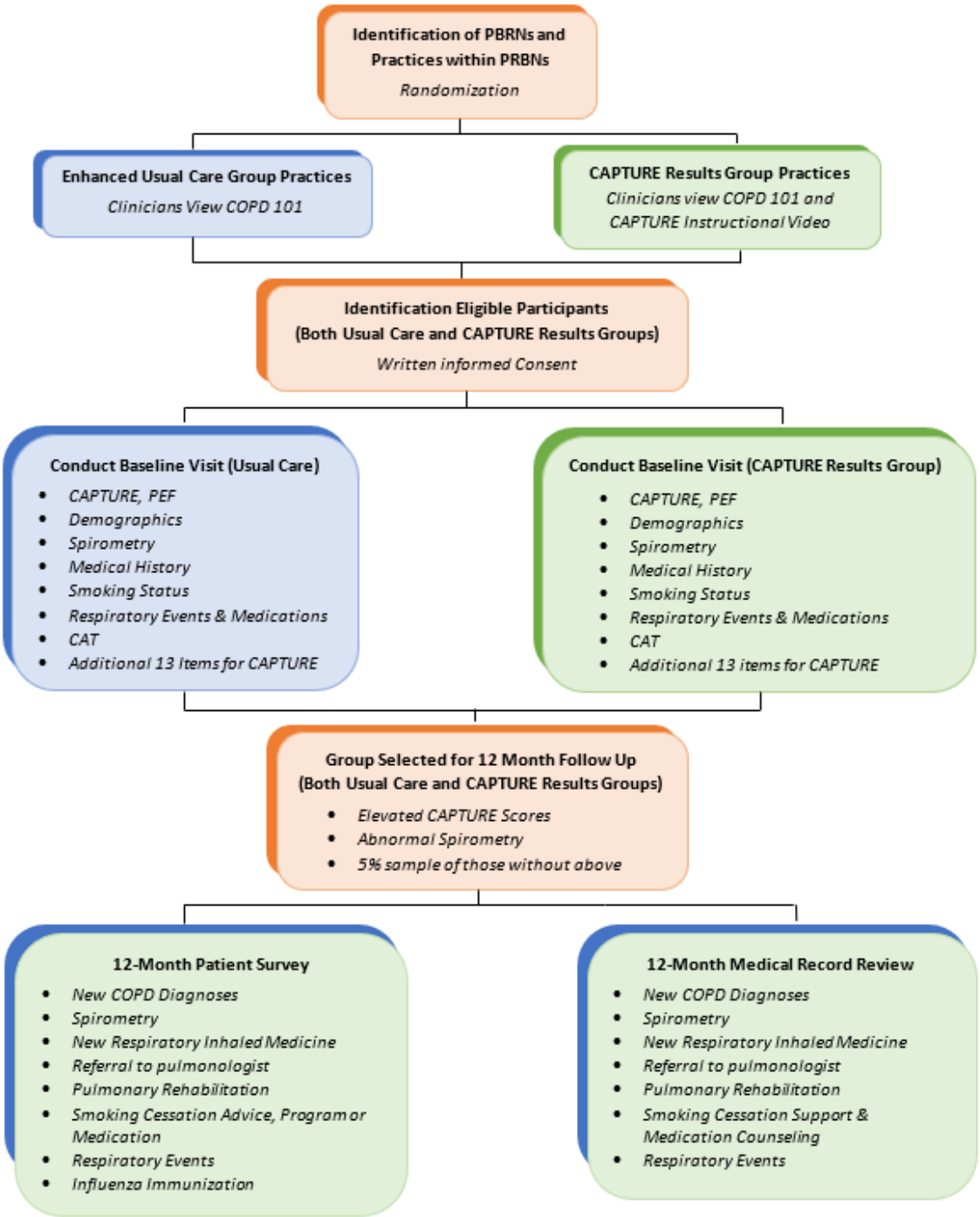

Figure 1

The hypothesis for Aims 3 is that sites where COPD and CAPTURE education and patient-level CAPTURE data are provided to clinicians will exhibit improved COPD diagnosis and COPD-related care compared to sites where COPD education is provided to clinicians.

7 Inclusion-Exclusion Criteria and General Study Population for Aims 3

7.1 Inclusion Criteria

- Men or women between the ages of 45 and 80 years of age
- Ability to read and complete visit in English or Spanish
- Stated willingness to comply with all study procedures and availability for the one-year duration of the study
- Provision of signed and dated informed consent form

7.2 Exclusion Criteria

- Previous clinician diagnosis of COPD
- Treated respiratory illness (with antibiotics and/or systemic steroids) in the past 30 days prior to study visit
- Unable to perform spirometry due to any of the following conditions within the past 30 days of baseline
    - Chest surgery
    - Abdominal surgery
    - Eye surgery
    - Heart attack
    - Stroke
- Unwilling or unable to complete all components of the single study visit

7.3 Randomization and Blinding

Randomization: Practices will be randomized into one of the two interventions, COPD education or COPD education + CAPTURE education, in a 1:1 manner, stratified by PBRN. Randomization will occur at the time of site activation and each site will be assigned a unique randomization number. The DCC will prepare the randomization schedule, using computer-generated block randomization with the block size(s) known only by the DCC. A secure web-based application will be built that will be used by the central study *coordinators to enter site information (e.g., site ID, stratification factor) and to obtain the* randomization number. The information can be printed and sent and/or emailed directly to the study coordinator.

Blinding: This is a single-blind study with the participants blinded to whether their practitioners have received CAPTURE education and patient-level CAPTURE results. Practitioners at sites that are randomized to the control arm (COPD education alone) will be blinded to the CAPTURE questionnaire and PEF results. All practitioners and participants will be blinded to the baseline COPD status of the participants (i.e., blinded to spirometry results), except for safety reasons. In this situation, participants and their clinician will be notified if a participant's post-bronchodilator FEV_1 is less than 30% predicted. For all other

participants, they and their practitioners will be blinded to research spirometry results. The coordinator should make every effort to conceal the spirometry results from the participants in these latter cases. Study coordinators should also make every effort to conceal the administration of a post- bronchodilator spirometry test from the practice staff so as not to unblind the physicians to abnormal spirometry.

7.4 Study Assessments

The following table provides the Schedule of Evaluations used in the study:

7.5 Schedule of Activities (Aims 1 and 3)

Table 2:

	Pre-Visit Contact[1]	**Baseline**	**12 Months**[3]
Contact (C)/ Visit (V)/Medical Record Review (MRR)	**C1**	**V1**	**C2/MRR**[5]
Time point, days (Visit window)	**Prior to outpatient visit (≤-1)**	**Within 30 days of pre-visit contact**	**365 ±30 (C2)**
Contact patient re: interest in study visit[1]	X		
Informed consent		X	
Demographics		X	
Medical history (Co-morbidities)[2]		X	
Vaccination status		X	X
CAPTURE 5-item questionnaire		X	X
CAPTURE item additional questionnaire		X	
Peak Expiratory Flow (PEF)		X	
Height and weight		X	
Respiratory medications review		X	X
Spirometry[4]		X*	
Respiratory symptoms, exacerbation assessment		X	X
Smoking exposure history		X	
Smoking cessation review[6]			X
COPD Assessment Test (CAT)		X	X
Adverse Events		X	
Medical record review			X

1. Optional per site recruitment preferences
2. Comorbidities including cardiovascular, respiratory and malignant disorders
3. Recorded for a subset of participants who meet any of the following criteria: 1) CAPTURE+ subjects defined as CAPTURE Score $\geq$ 5 or CAPTURE score of 2, 3, or 4 with a low PEF, defined as <350 L/min for males and <250 L/min for females 2) abnormal spirometry defined as $FEV_1/FVC < 0.70$ or $FEV_1 < 80\%$ predicted at baseline; and, 3) a random sample of approximately 5% of those who do not meet criteria 1 and 2. For participants meeting criteria 1 and 2 who cannot or choose not to complete the 12-month assessment, medical record review will still be completed. For participants meeting criteria 1 and 2 who change medical practices and medical record review cannot be completed, patients will be contacted for completion of patient reported data. For participants meeting criterion 3 where all of the protocol-specified 12-month assessments cannot be made, another participant will be selected at random to replace this participant.
4. Pre-bronchodilator spirometry will be done for all participants. Post-bronchodilator spirometry will be performed for participants with abnormal spirometry (FEV1/FVC < 0.70 or FEV1 < 80% predicted) *If the participant has taken a bronchodilator within a 2-hour window of spirometry the spirometry will be considered post-bronchodilator and a pre-bronchodilator spirometry will not be done.
5. The 12-month assessment consists of patient reported data, collected by the COPD Foundation, and medical record review completed by site coordinators.
6. This will be completed in those that are smoking at V1.

7.6 Baseline Assessments and Data Collection

CAPTURE Questionnaire: Participants will complete the five-item self-administered questionnaire. The questionnaire will be scored on a scale of 0-6, with higher scores indicating a higher likelihood of COPD diagnosis.

Peak Expiratory Flow (PEF): PEF will be measured for all participants in L/min, with a quality assurance range of 100-1000 L/min. The participant will perform three PEF tests. All three measurements will be recorded, and the largest of the measurements will be used in the CAPTURE Tool.

Spirometry: Spirometry will be performed for measurement of forced vital capacity (FVC), forced expiratory volume in one-second (FEV1), and calculation of FEV1/FVC. FEV1 and FVC are measured in liters and have expected ranges of 0.4-8.0 liters. FEV1 values less than 30% of the predicted values will be adjudicated by the study chair.

NHANES prediction equations, which are programmed into the Easy On PC spirometers, will be used to calculate the predicted lung function levels. These require the input of age, height, race, and ethnicity. For people of mixed or unknown race the White prediction equations will be used.

Adjudication of the Presence of Obstruction on Post-Bronchodilator Spirometry: The presence of obstruction is determined by the presence of an FEV1/FVC ratio less than 0.70 after the administration of a bronchodilator. A bronchodilator will be administered to study subjects whose baseline FEV1/FVC is less than 0.70 or whose FEV1 is less than 80% of the predicted value.

If a subject is unable to complete a post-bronchodilator spirometry (refusal, technical error on the part of coordinator, etc.), and the pre-bronchodilator FEV1/FVC is less than 0.65, the patient will be considered to have COPD for the purpose of follow-up in this study.

Height and Weight:Height and weight will be recorded in order to determine appropriate prediction equations for spirometry and possible effect of obesity on spirometry. Height will be recorded in inches, and weight will be measured in pounds.

Demographic Data Collection: Demographic data including date of birth, gender, ethnicity, race, educational level, current employment status, living arrangement and health insurance will be entered into the EDC system.

Medical History: Previous medical diagnoses will include comorbidities such as cardiovascular, respiratory, and malignant disorders. Influenza vaccination history will also be recorded.

Concomitant Medication Review: Respiratory medications will be recorded at baseline for all participants.

CAPTURE Additional Items Questionnaire: Participants will complete the 13 item self-administered questionnaire.

COPD Assessment Test (CAT): Participants will complete the eight item self-administered questionnaire. Each item is on a scale of 0-5 with higher scores indicating worse health status.

Respiratory Symptoms, Smoke Exposure and Exacerbation-Like Events: History of respiratory symptoms and exacerbation like events over the past year as well as smoke exposure (including e-cigarette or equivalent) will be recorded.

Adverse Events: Adverse events related to study procedures will be recorded by the coordinator.

6.6.2: Longitudinal follow-up

Follow-up efficacy assessments are collected from the time of baseline to 12 months in selected cohorts (as described in section 6.1).

Table 3: Data collected from medical records include:

All participants undergoing 12-month follow-up as described in section 6.1	Current Smokers Only
Clinical spirometry ordered or administered	Smoking cessation counseling
Referral to specialist for respiratory evaluation/treatment	New prescription for smoking cessation medication
New recorded clinical diagnosis of COPD	Formal smoking cessation program referral/completion
New prescription for respiratory medication (long acting bronchodilator, inhaled steroids, oral anti-inflammatory)	
Exacerbation like event assessment (hospital, ED, minute clinic, antibiotic/steroid prescription/administration)	
Vaccination status	
Formal pulmonary rehabilitation program referral/completion*	

*only collected in relevant participants

Table 4: Data from clinical visits to be collected at follow-up by telephone, secure web-based server, or mail- based methodologies directly from participants and administered by COPD Foundation study personnel includes:

All participants undergoing 12-month follow-up as described in section 6.1	Current Smokers Only
Spirometry	Smoking cessation counseling
New diagnosis of COPD	Smoking cessation medications (including OTC)
Referral to pulmonologist or other respiratory	
specialist	
Exacerbation like event assessment	
New prescription for respiratory medication (long acting bronchodilator, inhaled steroids,	
oral anti-inflammatory)	

*only collected in relevant participants

7.7 Imputation of Dates

If partial dates occur, the convention for replacing missing dates for the purpose of calculating derived variables is as follows:

- Missing day is imputed as the 15th of the month.
- In 12-month follow-up forms and chart reviews, missing month is imputed as 12 months from the patient's enrollment into the study.

Missing year is imputed as the year the practice enrolled the participant for baseline forms and the following year for 12-month follow-up forms.

7.8 Laboratory Reporting

No safety laboratory values are collected in the CAPTURE study.

8 Sample Size

8.1 Primary Objectives

Aims 3: Define the impact of CAPTURE information provided to clinicians in identifying and managing patients with respiratory symptoms (CAPTURE+) across a broad range of primary care settings.

8.2 Practice Behavior in Sites With Vs Without Capture Education and Patient Level Capture Data Provided

Primary Hypothesis 3: Sites where basic COPD and CAPTURE education are provided to clinicians, along with patient level CAPTURE data, will have a higher probability than control sites (i.e., those receiving only basic COPD education) of meeting the composite endpoint in their CAPTURE+ patients within 12 months of baseline.

From record review, the composite endpoint is met if one of the following is recorded: (1) referral for clinical spirometry testing, 2) new clinical diagnosis of COPD, 3) newly prescribed respiratory medication (long acting bronchodilator or anti-inflammatory for respiratory condition), or 4) referral to a specialist for respiratory evaluation/ treatment.

The study will enroll 50 CAPTURE practices and 50 control practices; each practice will enroll 50 patients (for a total of 5,000 patients). We project that within each practice there will be at least five patients previously undiagnosed with COPD who have a CAPTURE+ screening result. The primary analysis will be to compare the average proportion of CAPTURE+ patients per practice that meet the composite endpoint in the two intervention arms. For power and sample size computations, this is a cluster randomized trial of n=50 clusters (practices) per intervention arm with 5 CAPTURE+ patients per cluster (practice). The primary power calculation is based on comparing the average cluster sample proportion (average proportion of CAPTURE+ patients per practice meeting composite endpoint) between intervention arms. Table 9-2 displays power for a two-sample test comparing average cluster sample proportions, accounting for possible intra-cluster correlation coefficient (ICC) values of 0.05, 0.10 and 0.15 that are typically seen in cluster randomized trials of behavioral interventions

(https://www.abdn.ac.uk/hsru/research/research-tools/study-design/). These calculations assume a type I error of 5% and that the control arm meets the composite endpoint in 5% of CAPTURE+ patients, and the CAPTURE arm meets the composite endpoint in higher percentages (columns of Table 9-2). There will be variability in the actual number of CAPTURE+ patients per practice. It is standard practice to inflate the number of needed clusters by 12% to account for this extra source of variability. Therefore, our power calculations are based on 44 clusters per intervention arm.

Table 5:. Overall power to detect a difference in rate of meeting primary endpoint in CAPTURE group (50 practices/clusters) vs usual care (50 practices/clusters),

assuming 5% performance rate in usual care; 50 patients total / practice; assuming 10% prevalence gives 5 CAPTURE+/practice					
Improvement over usual care	+7.5%	+10%	+15%	+25%	+50%
ICC=0.05	0.72	0.89	0.99	>0.99	>0.99
ICC=0.10	0.65	0.84	0.98	>0.99	>0.99
ICC=0.15	0.59	0.79	0.97	>0.99	>0.99

9 General Analysis Considerations

9.1 Timing of Analyses

The final analyses will be performed after
(1) All 100 practices and 5000 participants have been enrolled
(2) Participants selected for follow-up have completed their 12-month data assessments or been lost-to-follow-up
(3) Chart review has been completed for those selected for follow-up
(4) All corresponding data have been entered, cleaned, locked and unblinded as per SABER SOPs.

This SAP document was finalized and approved prior to the double-blind database lock and unblinding.

9.2 Blinded Data Review

Prior to database lock and the start of any formal analyses, blinded data reviews will be completed, including summary statistics of key variables. This will allow the data for key variables to be examined to identify unusual values that need to be queried and patterns of missing values. In addition, the data reviews will allow the Executive and Publication Committees to assess the format of the data presentations. Note that blinded data reviews incorporate real data but random intervention assignment (i.e., investigators do not receive data summarized by actual intervention group, rather they review data on two randomly formed groups). All decisions will be made and documented in this SAP document prior to unblinding and database lock.

9.3 Analysis Populations for the Cluster-Randomized Clinical Trial (Aims 3)

All enrolled practices will be used in descriptions of practice characteristics. Because the CAPTURE study involves a cluster randomized design, with the intervention given at the cluster level, we have natural intent-to-treat populations for analysis at the practice level. That is, patient and practice outcomes will be ascribed to the assigned intervention group for that practice. We will not define a per-protocol analysis population as part of this study. Protocol deviations will be described, but not used to adjust analyses populations inappropriately. The safety population is all patient participants selected for follow-up as part of the cluster-randomized trial described in AIMS 3 of the CAPTURE

protocol.

There are six analyses populations:

1) CAPTURE + (Primary Analysis Population)
2) CAPTURE –
3) Spirometrically defined COPD
4) Clinically Significant COPD
5) Mild COPD
6) No COPD

9.4 Covariates and Subgroups

The effect of the CAPTURE intervention will be explored in predefined subgroups of interest with results tabulated (estimated difference in average proportion of CAPTURE+ patients per practice meeting composite endpoint between intervention arms by subgroup, corresponding 95% confidence interval and p-value) as well as displayed via forest plots. These analyses will proceed similarly to that described for the primary endpoint in section 10.1. Individual-level covariates used to define subgroups of interest are categorical age (45-59 years, 60-69 years, 70-80 years), sex (Male, Female), race (American Indian/Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, Black or African American, White, Unknown or Not Reported), ethnicity (Hispanic/Latino, Non-Hispanic/Latino, Unknown or Not Reported), educational status (Less than High School Graduate, High School Graduate/GED, Vocational/Some College, College Degree, Professional/Graduate Degree, or Not Reported), insurance status (private, public, none), living arrangements (alone, not alone), employment status (working, not working, unknown), smoking status (Current, Former, Never), as well as cohorts defined in section 6.1 (Spirometrically Defined COPD, Clinically Significant COPD, Mild COPD, no COPD by Spirometry), COPD Assessment Test (CAT) score (10 or above versus less than 10), BMI (Below 18.5 [Underweight], 18.5-24.9 [Normal], 25.0-29.9 [Overweight], 30.0 and Above [Obese]). Practice level covariates include location (Rural, Urban). Because of the possibly impact of the SARS-COV-2 pandemic on study outcomes, these analyses will be repeated in cohorts with complete follow-up as of March 15, 2020 (general date when SARS-COV-2 could have plausibly affected study outcomes)and separately in cohorts with follow-up completed after March 15, 2020.

9.5 Missing Data

Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution. We will summarize the extent of missing data over time for the primary end point. Differences in patient demographics and baseline characteristics between those with and without missing follow-up data, in those who were prospectively selected for follow-up, will be given overall and by intervention group. The primary analysis of the primary endpoint is based on a complete case approach. A sensitivity analysis for the analysis of the primary endpointwill be performed via multiple imputation using SAS PROC MI and PROC MIANALYZE.

9.6 Interim Analyses and Data Monitoring

There are no planned interim analyses for the primary endpoint, the rationale being that this is not a pharmaceutical or device trial that would benefit from standard stopping rules for efficacy. A DSMB will be monitoring the study for safety and study integrity every 6 months.

9.7 Multiple Testing

Two-sided p-values will be reported, and no adjustments for multiplicity will be made. Thus, p-values for secondary and exploratory outcomes will be interpreted with caution. Confidence

intervals will be provided to summarize treatment differences for efficacy end points.

10 Summary of Study Conduct Data

Descriptive summary statistics will be tabulated for baseline patient demographics and clinical characteristics as well as practice characteristics, separately by intervention group and overall. Intervention groups will be characterized as "Basic COPD Education" and "Basic COPD plus CAPTURE Education". For pooled summaries, "All" will be used as the column heading. All tables will be annotated with the total population size relevant to that table, including any missing observations.

For continuous variables, the estimated mean and 95% confidence intervals for the mean will be reported. P-values corresponding to two-sample t-tests[1] comparing mean differences between intervention groups will be reported. For categorical variables, number and percentages will be reported (excluding missing values). P-values corresponding to Pearson's[2] chi squared statistic or Fisher's[3] Exact test for testing association between categorical predictors and intervention groups, as appropriate, will be given.

10.1 Practice and Subject Disposition

Practice Disposition: The number of practices approached for study participation, those that subsequently enrolled in the study and those that declined will be given in a Consort Diagram.

Subject Disposition: The number of participants approached for study participation either by phone or in person, the number that subsequently consented and enrolled versus not enrolled (including reasons: screen failures, refusals) will be summarized in a CONSORT diagram. The number of participants selected for 12-month follow-up, and who subsequently had complete versus incomplete follow-up will also be given.

10.2 Protocol Deviations

In this cluster randomized controlled trial (Aims 3), where practices are the recipients of the intervention and where the interventions are based upon education and access to CAPTURE and PEF results, it is not anticipated that study intervention will be discontinued at the practice level.

The most likely protocol deviation is missing 12-month follow-up data in those selected for follow-up, which will be summarized in a CONSORT diagram as described in section 9.1.

10.3 Demographic and Baseline Variables

Demographic and baseline variables for patient participants include:

- Age in years at consent
- Sex (Male, Female)
- BMI
- Race (American Indian/Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, Black or African American, White, Unknown or Not Reported)
- Ethnicity (Hispanic/Latino, Non-Hispanic/Latino, Unknown or Not Reported)
- Educational status (Less than High School Graduate, High School Graduate/GED, Vocational/Some College, College Degree, Professional/Graduate Degree, or Not Reported)
- Employment status (Working, Not working, or Not Reported)
- Smoking status (Current, Former, Never, or Not Reported)
- Living arrangement (Alone, Not alone, or Not Reported)
- Insurance provider (Private, Public, None, or Not Reported)

- Baseline FVC
- Baseline FEV1
- Baseline FEV1/FVC
- Use of rescue respiratory medication (Yes if participant uses at least one short-acting bronchodilator, No, or Not Reported)
- Use of maintenance respiratory medication (Yes if participant uses at least one of the following: LABA, LAMA or anti-inflammatories, No, or Not Reported)
- Cardiac comorbidity (Yes if participant lists angina, coronary artery disease, heart attack, coronary artery bypass surgery, angioplasty/cardiac stents or congestive heart failure, No, or Not Reported)
- Use of supplemental oxygen (Yes, No, or Not Reported)
- COPD Assessment Test (CAT) Score
- Cohort membership as defined in section 6.1 (Spirometrically Defined COPD, Clinically Significant COPD, Mild COPD, No COPD by Spirometry).

Practice-level baseline covariates include:

- Location (Rural, Urban)
- Type of practice (Federally Qualified Health Care Center
  Part of large health system, ACO or similar (not affiliated with a medical school),
  Part of academic medical center/health system, Independent practice, Other)
- Presence of a residency program (Yes, No)
- Practice size as defined as the total number of primary care MD/DOs and NP/PAse
- Ability to perform in-house spirometry (Yes, No).

The primary study demographic and baseline variables table will have columns for CAPTURE positive, CAPTURE negative, and overall study populations. A separate demographics table will be constructed with columns depicting spirometrically defined COPD populations.

10.4 Intervention Fidelity

Completion of the clinician education is confirmed by either review of an attendance sheet for group education or online registration of the required educational videos. For patient participants who are enrolled in a CAPTURE intervention site, confirmation of giving the completed and scored CAPTURE screening tool to the patient participant's clinician is confirmed by written affirmation of the research associate completing the patient's study visit. For each practice, we will summarize the percentage of participating clinicians who completed educational training. For practices randomized to the CAPTURE intervention arm, we will summarize the percentage of enrolled participants whose CAPTURE information is provided to clinicians. Summary statistics for each of these variables across practices will be provided.

On-site monitoring visits are conducted to review all scoring of the CAPTURE tool. In the subset of participants where on-site monitoring is conducted, we record: 1) whether or not the CAPTURE Tool is scored correctly on the source document and 2) whether or not the score is transcribed correctly into the clinical database. We will provide percentages for 1 and 2 overall and by practice.

Additionally, all spirometry tests are reviewed and graded for quality by one of the investigators (DMM). Quality results are reviewed with PBRN teams and any needed retraining completed to achieve the goals of 100% CAPTURE scoring accuracy and 90+% interpretable spirometry results. We will define a usable spirometry value for each participant as being of quality A-D. Using this information, we will summarize the percentage of participants with usable spirometry, overall and by practice.

11 Efficacy Analyses for the Cluster Randomized Trial (AIMS 3)

11.1 Primary Efficacy Analysis

The primary efficacy analysis is restricted to CAPTURE+ participants, denoted in section 8.3 as population 1 (Primary Analysis Population). The primary analysis will be to compare the average cluster sample proportion (average proportion of CAPTURE+ patients per practice meeting composite endpoint) between intervention arms. Practices that do not identify any CAPTURE + subjects will not contribute to the primary analysis, although this is felt to be an unlikely occurrence. A two-sample test comparing average cluster sample proportions will be used that explicitly takes into account correlation between individuals treated within the same practice. A two-sided p-value < 0.05 will be considered statistically significant. This analysis corresponds to a generalized estimating equation (GEE)[4] regression analysis with (1) individual-level binary composite outcome data, (2) CAPTURE intervention group as a covariate, (3) practice id used to identify correlated outcomes, (4) exchangeable correlation matrix that assumes similar correlation between all composite outcome results for patients within the same practice, and (5) a logistic link function. The primary analysis would then correspond to a test for the CAPTURE intervention group parameter.

Technical Details of the Primary Analysis:

This analysis is restricted to CAPTURE+ participants (Primary Analysis Population)

Let $\pi_{ij} = P(\text{Participant } j \text{ from Practice } i \text{ Meets the Primary Endpoint})$.

Let $CAPTURE_i = I(\text{Practice } i \text{ Received Basic COPD plus CAPTURE education intervention})$

Let PRACTICE take on values $1, \ldots, 100$ denoting the enrolled practices

For the primary analysis, the GEE model takes the form

$\log\left(\frac{\pi_{ij}}{1-\pi_{ij}}\right) = \beta_0 + \beta_1 CAPTURE_i$, where binary outcomes from the same practice are assumed to follow a compound symmetry correlation structure.

SAS code for the Primary Analysis:

If the SAS dataset if called **final** and variables are

MetComp=1 if individual met primary (composite) outcome, 0 otherwise

CAPTURE=1 if individual was from a practice randomized to the Basic COPD plus CAPTURE education intervention, 0 otherwise

Practice is a categorical variable with values $1, \ldots, 100$ denoting the enrolled practices

Then the SAS code to run the primary analysis is

```
PROC GENMOD data= final descending;
CLASS Practice CAPTURE (ref="0" param=ref);
MODEL MetComp = CAPTURE /
        dist=bin link=logit type3 wald;
REPEATED subject=Practice /type=cs covb corrb modelse;
ESTIMATE 'OR for meeting Composite Endpoint for CAPTURE Yes versus No'
        intercept 0 CAPTURE 1 / exp;
RUN;
```

The p-value for the intervention effect (parameter for CAPTURE variable) will be taken from the SAS Output Table called Analysis of GEE Parameter Estimates (Empirical Standard Error Estimates). The intervention effect and 95% confidence interval will be taken from the Estimate Statement Output: Intervention effect is from row designated Exp(OR for meeting Composite Endpoint for CAPTURE Yes

versus No) and column L'Beta Estimate. 95% confidence interval is from row designated Exp(OR for meeting Composite Endpoint for CAPTURE Yes versus No) and column L'Beta Confidence Limits.

11.2 Secondary Efficacy Analyses

Secondary Analyses of Primary Outcome:The primary analysis as described in section 10.1 will be repeated in analysis populations 2-6 as given in section 8.3.

In addition, multivariable GEE regression analyses will be conducted separately in populations 1-6 from section 8.3, where the primary composite outcome is modelled using individual and practice level predictors in addition to the CAPTURE intervention group. Interactions will be assessed.

Efficacy Analyses of Secondary Outcomes: All analyses in this section will be conducted (separately) for each study population 1 through 6 described in section 8.3.

We will use the GEE framework to study and describe each of the individual components of the composite outcome as they relate to the CAPTURE intervention group.

Multivariable GEE models will incorporate individual and practice level outcomes into the analysis of individual components of the composite outcome. In the subset of smoking patients, we will use GEE regression analysis to study additional binary outcomes, such as incidence of physician referral to a formal smoking cessation program, prescribed smoking cessation medication in participants who are smokers, and referral to pulmonary rehabilitation program. Model selection in GEE secondary analyses will be based on statistical significance at the 0.05 level using robust sandwich estimation of variability within clusters. Model fit will be checked by comparing observed versus predicted values within predefined subgroups of interest as given in section 8.4.

Change in CAT score will be analyzed using mixed[5] models with a random effect for practice. The average cluster sample proportion of patients who experience exacerbations will be compared between intervention groups using methodology similar to that used for the primary endpoint. Survival analysis[6] allowing for correlation of endpoints within cluster (practice) will be used to compare mortality between intervention groups and perform multivariable analysis. We will explore differences between intervention groups in the average cluster sample rate of hospitalizations again using GEE.

12 Safety Analyses

Safety data, including AEs and SAEs will be summarized descriptively overall and by treatment group for the safety population. Coding into organ system will be performed by the study chairs for AEs and SAEs. The following organ systems will be summarized: cardiovascular disorders, dermatological disorders, gastrointestinal disorders, hematological disorders, metabolic disorders, musculoskeletal and connective tissue disorders, neurological disorders, psychological disorders, pulmonary disorders, renal and urinary disorders, hepatobiliary disorders, and other disorders.

12.1 Extent of Exposure

The summary statistics will be produced using intervention fidelity measures given in section 9.

12.2 Adverse Events

Descriptive summary statistics for adverse events (AEs) during the baseline visit will be reported. The number of AEs during baseline and the frequencies (number and percentage) of participants with one or more AEs will be summarized by treatment group and overall.

In accordance with clinicaltrials.gov reporting requirements, the following table summarizing adverse events is required and will be provided:

- Other (Not Including Serious) Adverse Events: A table of anticipated and unanticipated events (not included in the serious adverse event table) that exceed 5% within either treatment group, grouped by organ system, with number and frequency of such events in each treatment group.

The summary statistics will be produced in accordance with section nine.

12.3 Deaths, Serious Adverse Events and other Significant Adverse Events

Descriptive summary statistics for serious adverse events (SAEs) during baseline will be reported. The number of SAEs during baseline and the frequencies (number and percentage) of participants with one or more SAEs during baseline will be summarized overall, by treatment group, and by body system.

A subject listing of all SAEs during baseline, SAEs during baseline causing study discontinuation, and deaths will be presented.

In accordance with clinicaltrials.gov reporting requirements, the tables below summarizing deaths and SAEs are required:

- All-Cause Mortality: A table of all anticipated and unanticipated deaths due to any cause, with number and frequency of such events in each treatment group.
- Serious Adverse Events: A table of all anticipated and unanticipated serious adverse events, grouped by organ system, with number and frequency of such events in each treatment group.

The summary statistics will be produced in accordance with section 9.

12.4 Pregnancies

No relevant measures are collected as part of the CAPTURE study.

12.5 Clinical Laboratory Evaluations

No relevant measures are collected as part of the CAPTURE study.

12.6 Prior and Concurrent Medications

Prior relevant medications are summarized as baseline variables in section 9.3:

- Use of rescue respiratory medication (Yes if participant uses at least one short-acting bronchodilator, No, or Not Reported)
- Use of maintenance respiratory medication (Yes if participant uses at least one of the following: LABA, LAMA or anti-inflammatories, No, or Not Reported)
- Use of supplemental oxygen (Yes, No, or Not Reported)

12-month follow-up assessments record new prescriptions for respiratory medication after the baseline visit (long acting bronchodilator, inhaled steroids, oral anti-inflammatory), vaccination status, and in smokers, a new prescription for smoking cessation medication

12.7 Other Safety Measures

No additional safety measures are collected as part of the CAPTURE study.

13 Other Analyses

13.1 **SARS-COV-2** Impact on Study Enrollment, Follow-up and Power

We have performed additional analyses for the CAPTURE DSMB regarding the impact of SARS-COV-2 on study power for the cluster randomized clinical trial described in AIMS 3 of the CAPTURE protocol, summarized in a Memo dated March 30, 2020. Sections of the memo relevant to the SAP are repeated below.

At the time of placing enrollment on hold, the CAPTURE study was ahead of enrollment projections with a goal of completion of all patient enrollment by January 31, 2021. Table 1 displays enrollment data for each of the CAPTURE study's six enrolling PBRNs as of March 19, 2020, the date the last of the six PBRNs temporarily stopped enrollment.

Table 6.

PBRN site	Date enrollment put on hold	Number of practices enrolled as of 19MAR2020 (goal)	Number of patients enrolled as of 19MAR2020 (goal)	Estimated date of resumption of enrollment
A	13MAR2020	15 (20)	663 (1000)	Indeterminate
B	16MAR2020	15 (20)	750 (1000)	Indeterminate
C	16MAR2020	9 (20)	431 (1000)	Indeterminate
D	19MAR2020	6 (8)	280 (400)	Indeterminate
E	13MAR2020	11 (20)	468 (1000)	Indeterminate
F	16MAR2020	12 (13)	446 (650)	Indeterminate

As of April 1, 2020, none of the sites has an estimate of when enrollment will be able to resume. This information will be added as soon as such information becomes available.

<u>Projected Enrollment Impact</u>

To facilitate planning, projections on patient and practice enrollment impacts for Aims 3 have been developed. These projections are based on several assumptions.

1. Monthly enrollment rates of 100 or 125 patients as continuation and 5 new practices enrolled per month, consistent with prior data.
2. Two, four and six-month delays in enrollment.

Table 7.

Enrollment suspension length assumption	Enrollment re-start date	Enrollment rate/month	Total number of participants (practices) enrolled by 31JAN2021	Total number of participants enrolled by 31MAR2021
2 months	1-Jun-20	100	3850 (100)	4050
4 months	1-Aug-20	100	3650 (100)	3850
6 months	1-Oct-20	100	3450 (90)	3650
2 months	1-Jun-20	125	4050 (100)	4300
4 months	1-Aug-20	125	3800 (100)	4050
6 months	1-Oct-20	125	3550 (90)	3750

We evaluated other scenarios including being able to increase enrollment to 150 patients per month with delays of two, four and six months and ending enrollment in January 2021 and March 2021.

Impact on Follow-up

The tables below present information on the initiation dates of the 12-month medical record abstraction by PBRN and the information on 12-month patient survey follow up as of March 25, 2020.

Table 8. 12-month Medical Record Abstraction (As of March 19, 2020)	
PBRN Site	**Original ideal date of starting for 12- month medical records abstraction**
A	23MAR2020
B	30MAR2020
C	Unknown
D	Unknown
E	06APR2020
F	No eligible patients until September 2020

Table 9. 12-month Patient Survey – COPD Foundation As of 3/25/2020	
Number Eligible	380
Phone Only	118
Email	256
Mail Only	6
Completed 12 Month Survey	248 (65%)
Web	84
Phone	134
Mail	30
Mailed Surveys	120
Lost to Follow-Up	20

Since all surveys are done by email, telephone call or mailings, there are no planned disruptions of the 12-month follow up patient surveys. All staff triggering email surveys, making telephone calls or preparing mailings are working from home.

Impact on Power

The goal of Aims 3 is to define the impact of CAPTURE information provided to clinicians in identifying and managing patients with respiratory symptoms (CAPTURE+) across a broad range of primary care settings. This Aim depends on the overall number of patients identified who are CAPTURE+, the number of practices enrolled as well as the ability to complete longitudinal follow-up.

Calculations were performed assuming 10 CAPTURE+/practice based on 67 total practices with > 1 CAPTURE+ patients (actual current state) taking into account loss of power due to variable cluster sizes. These data suggest that we are on track for having a well powered study for the primary analysis, even if additional data is difficult to obtain post-COVID crisis.

Table 10. Overall power to detect a difference in rate of meeting primary endpoint in CAPTURE group vs usual care, assuming 5% performance rate in usual care; 67 total practices; 10 CAPTURE+/practice

Improvement over usual care	+7.5%	+10%	+15%	+25%	+50%
ICC=0.05	0.76	0.92	>0.99	>0.99	>0.99
ICC=0.10	0.65	0.84	0.98	>0.99	>0.99
ICC=0.15	0.55	0.76	0.95	>0.99	>0.99

However, we have important secondary analyses that include determining whether care is improved for patients who have spirometrically defined COPD. Based on data accumulated to date, we have a prevalence of roughly 2 spirometrically defined COPD patients per practice. These subsequent calculations demonstrate that based on 2 COPD patients/practice but with otherwise similar assumptions to Table 6, we would not be well powered for small effect sizes. Hence, while we would have important usable data should the study be unable to continue, the returns on investment made to date are far from fully realized. We strongly believe that all attempts should be made to complete the study as planned if we want to have the impact originally intended for this study, namely understanding whether screening benefits undiagnosed patients with COPD

Table 11. Overall power to detect a difference in rate of meeting primary endpoint in CAPTURE group vs usual care, assuming 5% performance rate in usual care; 67 total practices; 2 COPD/practice

Improvement over usual care	+7.5%	+10%	+15%	+25%	+50%
ICC=0.05	<0.50	<0.50	0.69	0.95	>0.99
ICC=0.10	<0.50	<0.50	0.67	0.95	>0.99
ICC=0.15	<0.50	<0.50	0.65	0.94	>0.99

14 Reporting Conventions

P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001". The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or

minimum and maximum will use the same number of decimal places as the original data. Estimated parameters, not on the same scale as raw observations (e.g., regression coefficients) will be reported to 3 significant figures.

14.1 Changes from Protocol-Planned Analyses

The following describes additional analyses that were not described in the protocol (Version 3.0, 26 September 2019) or modifications of protocol-specified analyses. These changes reflect advances in our knowledge since the design of the study in 2018 that were not incorporated as protocol amendments, but were discussed during the formation of the Statistical Analysis Plan. These changes were made prior to the database lock.

14.2 New SARS-COV-2 Inspired Analyses

The SARS-COV-2 pandemic has affected patient and practice enrollment and will potentially affect practice patterns moving forward. As part of the next protocol revision, the CAPTURE study plans to collect additional SARS-COV-2 inspired patient and practice information. This is a placeholder to update analyses once the next version of the protocol is complete. Of particular note will be analyses of additional data collected in response to SARS-COV-2 and analyses studying trends of 12-month outcomes that account for calendar time of collection

Protocol: N/A

SAP: 10.2.1 Secondary analyses of primary outcome

Additional sensitivity analyses will be conducted to assess the influence of the SARS-COV-2 pandemic on primary and secondary analyses. For the purpose of these analyses, we assume that participants who have completed their 12-month visit by March 1, 2020 provided baseline and 12-month follow-up measures that were unaffected by SARS-COV-2. We define an indicator variable SARS-COV-2=0 if a participant's baseline and 12-month follow-up measures were unaffected by SARS-COV-2 or SARS-COV-2=1 if participant's baseline or 12-month follow-up measures were affected by SARS-COV-2.

Protocol: N/A

SAP:10.2.2 Efficacy analyses of secondary outcomes

15 References

1. Gosset, W.S. [Student, pseud.] 1908. The probable error of a mean. Biometrika 6: 1-25.
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4. PMID: 2336267 Liang, K.-Y. and Zeger, S.L. (1986) Longitudinal data analysis using generalized linear models. Biometrika, 73, 13-22.
5. Laird, N. M. and Ware, J. H. Random-effects models for longitudinal data, Biometrics , 38, 963-974 (1982)
6. Laird, N. M. and Ware, J. H. Random-effects models for longitudinal data, Biometrics , 38, 963-974 (1982)

16 Listing of Tables, Listings and Figures

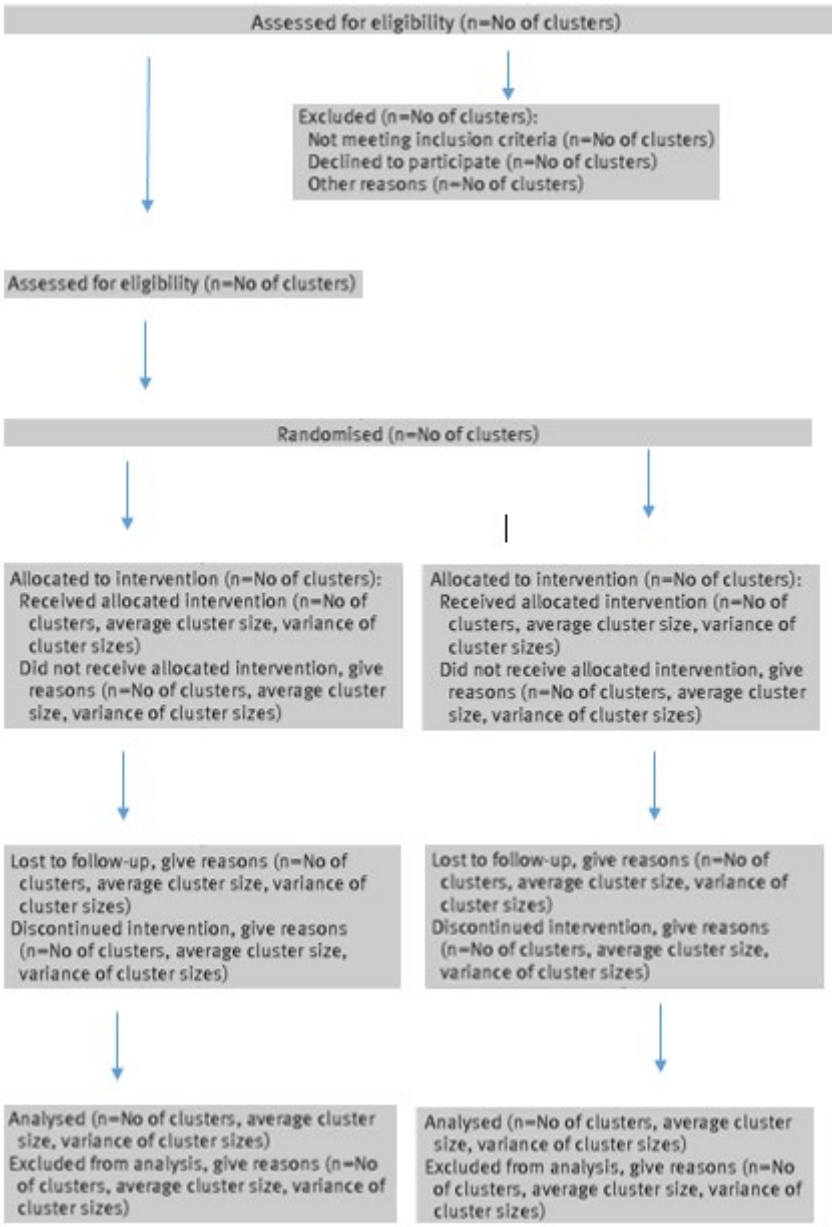

Figure. 12