GECo1 PROTOCOLS AND STANDARD OPERATING PROCEDURES

Effectiveness-Implementation of COPD Case Finding and Self-Management Action Plans in Low and Middle Income Countries: Global Excellence in COPD outcomes (GECo) Study Protocol (*Siddharthan et al. Trials 2019*)

Background

The Global Importance of COPD

Chronic Obstructive Pulmonary Disease (COPD) is "*a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases".*[1] The primary risk factor for COPD in high-income countries (HICs) is tobacco smoke exposure; however, household air pollution (HAP), from burning solid fuels such as wood, dung, agricultural crop waste, and coal for energy, is the primary risk factor for COPD in low- and middle-income countries (LMICs).[2] In addition to chronic progressive symptoms and functional impairment, some individuals with COPD are prone to intermittent deteriorations in respiratory health, or exacerbations, often driven by infection.[3] The global burden of COPD is large and increasing. In 2015, it was estimated that 174 million people worldwide had clinically significant COPD, and an estimated 3.2 million individuals died from the disease, an increase of 11.6% since 1990.[4] COPD will become the third leading cause of death by 2030.[5] Prevalence estimates vary due to different methods of diagnosis; however, the BOLD studies report a prevalence of moderate COPD or higher to be around 10% globally.[1, 6] Exacerbations are a major source of morbidity from COPD, and cause of direct health-care costs in high-income countries.[7]

COPD in LMICs

More than 90% of COPD-related deaths occur in LMICs.[8] The economic cost of illness due to COPD among LMICs was estimated to be $1 trillion in 2010 and is expected to increase to $2.6 trillion by 2030.[9] Indirect costs, including loss of productivity both by individuals affected by COPD and their caregivers, are expected to be important in LMICs.[9] LMICs face unique challenges when facing COPD, including poorly resourced primary care systems and trained workforce shortages, which present challenges with COPD diagnosis and management, especially during exacerbations.[10] The chronic nature of COPD mean people may access multiple health-care providers, including alternative providers.

COPD Case Finding

The gold standard method for diagnosis of COPD is quality-assured, post-bronchodilator spirometry, though COPD represents a range of phenotypes with different symptomatic presentations including shortness of breath, cough and sputum production.[1] In LMICs this is often only available from pulmonary physicians in specialised urban centres, while most of the burden associated with this condition occurs primarily in rural areas.[10] A number of COPD case-finding questionnaires have been validated in HIC settings, which are therefore likely to be more sensitive to tobacco-associated COPD than biomass fuel smoke.[11-13] In 2010, Yawn et al developed and validated a simple 5-item Lung Function Questionnaire (LFQ) and compared this to standard spirometry (area under the curve [AUC] = 0.720) with sensitivity and specificity of 73.2% and 58.2%, respectively).[11] Martinez et al combined peak expiratory flow (PEF) measurements with a case-finding instrument to improve the sensitivity, specificity and area under the curve for detecting COPD (89.7%, 78.1%, 0.795 respectively).[12] Case-finding instruments combined with low-cost peak flow meters could be useful tools for identifying

individuals who should be further screened for COPD in LMIC settings as well, although this has not been previously tested.

Given the high and rising global burden of COPD, better strategies to diagnosis COPD and manage exacerbations are urgently needed for LMICs. In two linked studies (GECo1 and GECo2), we aim to validate a modified COPD case finding questionnaire (with and without PEF) to better identify individuals for further screening for COPD, as well as to develop evidence to support the wider implementation of COPD Action Plans among CHWs, allowing for simple, low-cost models of COPD care in LMICs. This study will enrol individuals in three distinct LMIC regions, namely Nepal, Peru, and Uganda.

Method / Design

Goals The over-arching goal of the GECo studies is to develop simple, cost-effective models of COPD diagnosis and care that can be implemented in LMICs

Objectives

The objectives of the present study are to validate case finding instruments with and without peak flow measurements in three diverse LMIC settings, and to develop evidence supporting the effectiveness, cost-effectiveness, and implementation of a CHW-based strategy to deliver self-management Action Plans for COPD.

Research Questions

Primary Research Questions

1. GECo1: What is the diagnostic accuracy of case-finding for COPD using a questionnaire with and without peak flow measurements, compared to gold-standard spirometry?

Implementation Research Questions

1. GECo1: What is the appropriateness, acceptability, and feasibility of using questionnaires to identify COPD cases from the perspective of local community members, community health workers, local health centre physicians and ministries of health?

Study Design Overview

GECo1: For the ***Case-finding study*** (GECo1) will test the diagnostic accuracy of case-finding instruments in LMIC settings. To achieve the aim we will enrol a representative community sample of up to 10,500 adults 40 years of age and above in Nepal, Peru, and Uganda (**Figure 1**). We will apply two modified questionnaires with and without PEF measurements and compare performance of this testing to spirometry, which will be conducted in the field according to the American Thoracic Society/European Respiratory Society standards using Easy-on-Air spirometers (ndd, Zurich, Switzerland). The primary endpoint is area under the ROC curve. We will report the sensitivity, specificity and receiver operating curve characteristics of case finding instrument with and without PEF compared to standard spirometry.

Settings

The study settings represent three distinct geographic and economic regions in Asia, Latin America, and Sub-Saharan Africa. Inclusion of these countries will allow us to assess varying degrees of urbanisation, environmental exposures (i.e. tobacco and biomass fuel smoke), and varying implementation contexts.

Nepal is a low-income country located in Southeast Asia with a total population of 26.5 million, of which 82% is rural. Nepal's GDP is £49 billion, with 25% of the population living below the national poverty line. The current ratio of physicians per person are 1:1,742. The current minimum wage is Rs 9,700 per month (£66). The study site is in Bhaktapur, eight miles east of Kathmandu. The majority of the estimated 80,000 inhabitants of Bhaktapur municipality are either craftsman or businessmen, while many migrants come to work in the outskirts at brick or carpet factories. CHWs, called female community health volunteers (FCHVs), are volunteers coordinated by the Bhaktapur municipality to promote community-based healthcare, health education and referrals. FCHVs are trained by their District Public Health Office, under the Ministry of Health to serve within their respective communities, mainly on family planning, vaccination and nutrition programs. There are approximately 90 FCHVs active in the municipality of Bhaktapur and over 52,000 throughout Nepal.

Peru is an upper-middle income country located in South America with a population of 30.5 million, 10 million of whom live in the capital (Lima), and 78.6% of whom live in urban areas. Peru's GDP is £145 billion, and 26% of the population lives below the national poverty line. The current ratio of physicians per person are 1:1,116. The minimum wage in Peru is 850 soles per month (£186). We will conduct this study in Pampas de San Juan de Miraflores, a peri-urban community in southern Lima, Peru's capital. CHWs or "agentes comunitarios" include community members who volunteer to support health education programs and campaigns at their corresponding health center. The size of CHW networks and specific duties and responsibilities can vary considerably depending on the region, district, or health center.

Uganda is a low-income country located in East Africa with a total population of 37 million, and a large rural population (>80%). Uganda's GDP is £19 billion with 19.5% living below the national poverty line. The study will be carried out in the Nakeseke District of Uganda. Most of the inhabitants (75%) are subsistence farmers and over 60% of them live on less than 45,000 shillings (£9) per month. The current ratio of physicians and nurses per person are 1:25,000 and 1:5,000, respectively, making Nakeseke one of the most under resourced health districts in Uganda. CHWs called Village Health Teams (VHT) are selected in each village by the Uganda Ministry of Health. They provide formal referral services to local health centres and assist with community-based follow up. The VHT consist of community members who volunteer for the position and are trained by the Uganda Ministry of Health.

Study Populations

We will enrol an age- and Sex-stratified random sample of full-time residents of the proposed study areas in Nepal, Peru, and Uganda using existing census data. Inclusion criteria are: aged ≥40 years; capable of performing spirometry; and being a full-time resident of the community. Full-time residence will be defined as having lived in the study area for more than 6 months. Exclusion criteria are: self-reported pregnancy; having active pulmonary tuberculosis or being on medications for pulmonary tuberculosis; unable to do spirometry because they had eye surgery, thoracic surgery, abdominal surgery, or myocardial infarction in 3 months prior to study visit or a blood pressure >180/100 mmHg. For the self-management component of the trial, we will enrol individuals who were identified to have Grade B-D COPD.[1]

Procedures Case Finding Phase (GeCO 1)

Data collection

Demographic questionnaires will be applied to obtain socioeconomic information, exposure history to cigarettes and household air pollution, medical history and family history of

respiratory illness. Data will be collected by field trained field workers at each site and will be electronically entered into REDCap using tablets with GPS capability (Asus Z380M ZenPad, Taipei, Tawain).[25]

Lung Function Questionnaire (LFQ).
We will administer an instrument context-adapted from the original LFQ, which has been validated in high-income countries, and apply it to LMIC settings.[11] The LFQ assesses five items, age, smoking history, wheeze, dyspnoea and phlegm. The modified questionnaire will include additional items including exposure to biomass fuel and will be administered by field workers. (See Online Supplement).

CAPTURE
CAPTURE is a simple 5-item questionnaire which together with PEF, has been shown to be a viable approach for COPD case identification in the US in primary care settings.[12] CAPTURE with PEF can identify COPD patients who would benefit from currently available therapy and require further diagnostic evaluation, and we will use this validated instrument and apply it to LMIC. CAPTURE assesses five items, environmental exposure, sensitivity to air quality/weather, how breathing interferes with physical activities, comparing health with peers, and exacerbations.

MRC Dyspnea Scale and COPD Assessment Test (CAT)
At the case-finding visit, participants will be asked to complete the modified Medical Research Council Dyspnea Score (mMRC) and the COPD Assessment Test (CAT), which have been translated into relevant local languages and previously validated. The mMRC categorises self-perceived disability among those with COPD on a 5-item scale. The CAT is designed to measure the impact of COPD on a person's well-being and daily life and is measured with 8 items on a 40-point scale and will be administered to those with COPD on spirometry.

Anthropometry and Spirometry
All participants will have blood pressure, weight and standing height, and spirometry performed**.** Anthropometric measurements will be recorded in triplicate and the median measurements will be used for analysis. Systolic and diastolic blood pressure measurements on the second and third measurements will be averaged to calculate blood pressure; the first measurement will be ignored to avoid potential white-coat hypertension.

Trained study fieldworkers will conduct spirometry using a flow-based portable spirometer to measure pulmonary function and will record forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), the percentage of FVC exhaled in the first second (FEV_1/FVC), and flow-volume curves. We will obtain at least three acceptable maneuvers in accordance with ATS/ERS guidelines.[26] We will use the Global Lung Function Initiative mixed ethnic population reference for calculation of percent-predicted values or Z-scores.[27] We will test for reversibility (increase in FEV_1 of $\geq$12% and increase in FEV_1 $\geq$200 mL) with 2 puffs from a salbutamol inhaler (90 mcg/puff) via a spacer. A COPD diagnosis will be defined as post-bronchodilator FEV_1/FVC below the lower limit of normal for that population following ATS/ERS standardized guidelines.[26]

Spirometry Quality Control
All spirometry will be read by two independent reviewers locally who have been trained in spirometry per ATS/ERS guidelines.[27] Spirometry that is deemed not acceptable or reproducible will be repeated up to one additional time. If there is discrepancy in local reviewers over reads, the spirogram in question will be reviewed centrally. Additionally, 10%

or all curves will be independently reviewed centrally for site-specific quality control. Spirometry will be graded according to ATS/ERS classification and only high quality spirometry will be included for analysis and trial recruitment.[28]

Sample Size and Data Analysis

Sample size: The sample size required to estimate the ROC area within 1.5% (based on a 95% confidence interval), assuming an anticipated sensitivity of 90% and specificity of 60%, and assuming 11% of those screened will have COPD is 9,669 participants.[2, 29] To ensure an adequate sample size is subsequently available for GECo2, we will recruit a total of up to 10,500 subjects (3,500 at each site).

Analysis: By site and overall we will summarise the characteristics of those consenting to the study including demographics, exposure history to tobacco and/or household air pollution, anthropometric measurements, spirometry measurements (FEV_1, FVC and FEV_1/FVC ratio) and lung function scores (mLFQ, Capture, mMRC dyspnea scores).

Using a receiver operating characteristic (ROC) area analysis, we will examine diagnostic accuracy of the questionnaire scores in identifying cases of COPD (compared to spirometry). Curves will be obtained for the mLFQ and CAPTURE questionnaires alone and then each with addition of the PEF scores. Logistic regression models will be used to obtain the ROC curve and area (AUC), with 95% confidence interval. Estimates will be weighted based on census information from each site to better reflect the population. A comparison between the ROC areas will be made by site.

Management

The core team (TS, SP, SQ, NR, WC, JH) report to a Trial Steering Committee that includes representation from the Funder, and other stakeholders. Independent members (including the Chair) are drawn from our International Advisory Board. The TSC meets six monthly. There is an independent DSMB with one planned interim analysis examining safety data, reporting directly to the TSC. Our other team-members run the Health Economics (MS, AM, MKC), Implementation Research (SP, AC, SM) and Data (JB) cores. Each site has a dedicated member of the core team to provide initial support and assistance. Data will be analysed biweekly by the data core to assess for missingness and outliers.

Economic Evaluation

This analysis will primarily aim to evaluate the cost-effectiveness of a multi-faceted intervention centered on a self-management strategy for COPD exacerbations within the effectiveness-implementation trial. However, in an attempt to integrate implementation science concepts with decision analysis, we will also incorporate health system factors relating to service provision in the analysis for each of the three settings and explore equity implications. The main analysis will compare the health-related costs and benefits of the COPD Action Plan plus education with the health-related costs and benefits of default standard care, as observed within the trial. Costs will be calculated using the reported levels of resource use and multiplying these estimates by the unit costs for each resource. The EQ-5D results will provide estimates of the effectiveness in terms of QALYs. QALY tariffs will be taken from the country itself, when available, or from another relevant source (e.g. adjacent country or international average). Cost-effectiveness ratios will be reported as the additional cost per QALY gained; however, these will also be reported as additional cost per hospitalisation and exacerbation averted to provide a clear picture of the value of the intervention. As COPD is expected to affect the labour status and productivity of working-age people and their caregivers, we will

additionally explore the broader productivity benefits. The main cost-effectiveness analysis will further include a sensitivity analysis that accounts for the performance of the case-finding questionnaire and which extends to the short-term costs using assumptions and evidence of future costs not captured within the GECo study.

To explore equity in the cost-effectiveness analysis, we will assess whether there are population and individual characteristics that enable some sub-groups to gain more from the intervention than others. With the benefit of intense follow-up and monitoring at multiple time periods, we will be able to explore whether the intervention provides equity benefits over the course of implementation. Equity will be assessed according by examining differences in the effectiveness of the intervention according to socioeconomic sub-groups. Within the trial, different health system factors, or "constraints", may hinder access, utilisation or service provision and affect the cost-effectiveness of the COPD Action Plan. Examples of constraints include: access to drugs for the management of exacerbations and access to emergency care for severe complications, which work through factors such as health insurance coverage or distance to health facilities. We will also identify constraints through the implementation science outcomes related to acceptability and feasibility. For this reason, the second part of this work will explore how constraints interact with the value of the COPD Action Plan, in the health system in each setting.

The results from these analyses will be:

1) Establish whether the intervention is cost-effective and to what degree it provides labour and productivity benefits, thus informing decisions for investment and scale-up.
2) Identify important equity concerns so that any trade-offs between maximising health and maximising fairness when scaling up the intervention are made explicit, and
3) Identify the important health system constraints that future implementation efforts should consider in order to maximise COPD Action Plan value.

Implementation Outcomes

Acceptability. We will conduct key informant in-depth interviews to evaluate acceptability of the intervention from the perspectives of local community members, CHWs, local healthcare professionals, and ministries of health over the course of the trial. We will also ask individuals with COPD to evaluate satisfaction with individual components of the intervention in improving quality of life and ability to manage their COPD quarterly.

Feasibility. We will solicit perspectives from the key groups mentioned above regarding the feasibility of the intervention during planned in-depth interviews and focus group discussions quarterly. In addition, we will record and evaluate overuse of rescue packs, which can result in antibiotic resistance and thus limit feasibility of use in these settings. We will also ask CHWs to maintain a log of all visits, contacts from participants, and lengths of these interactions throughout the follow-up period.

Ethics

Approvals: The trial has been reviewed and approved by the University College London Research Ethics Committee (9661/001), Johns Hopkins School of Medicine (IRB00139901), Uganda National Council for Science and Technology, Makerere School of Medicine (SOMREC 2017-096), Nepal Health Research Council (136/2017) and A.B. PRIMSA (CE2147.17). Additionally the trials have been registered with ClinicalTrials.gov (GECo1: NCT03359915, and GECo2: NCT03365713).

Community Consultation: Community leaders were identified and approached to obtain permission to deliver the interventions and conduct the evaluation surveys. Orientation meetings were held to explain the project aims, and community leaders will be invited to observe the randomisation process at the start of the trial.

Role of Funder

This study is funded by the UK MRC (Medical Research Council) under a Global Alliance for Chronic Disease (GACD) call. Peer review of the original grant application contributed to the final design of the study. A representative of the Funder is in attendance at the Trial Steering Committee. The Funder otherwise has no role in the conduct or analysis of the study.

Dissemination

The results of the study will be submitted for publication in peer-review journals, and for presentation at international meetings. We anticipate two primary manuscripts reporting GECo1 and GECo2, and papers reporting subsidiary analyses. Results will be presented locally at each of our sites. Results will be used to formulate policy documents to inform future provision of care for people living with COPD. The GECo studies are active on Twitter (@COPDGECo), and there is a trials website (https://www.globalncd.org/geco-trial) providing updates on progress.