Appendix Table 1. Mailed FIT Completion by Demographic Characteristics

Characteristics	Total (n=261)	Returned FIT (n=62)
	n (%)	n (%)
Age, years		
50–59	109 (41.8)	22 (20.2)
60–69	120 (46.0)	30 (25.0)
70–75	32 (12.2)	10 (35.5)
Race/Ethnicity		
Black/African American	158 (60.5)	35 (22.1)
White/Caucasian	84 (32.2)	21 (25.0)
Hispanic	9 (3.4)	3 (33.3)
Unknown	10 (3.9)	3 (30.0)
Sex		
Male	254 (97.3)	60 (23.6)
Female	7 (2.7)	2 (29.6)

Note: All comparisons were non-significant with $p>0.05$.

R&D (151)

Research Staff Form

CMCVAMC IRB
Corporal Michael J. Crescenz VA Medical Center Institutional Review Board

APPROVED by CMCVAMC IRB 2
Date: 12/22/15

TITLE OF RESEARCH PROTOCOL: Reducing Colorectal Cancer Death through Mailed Outreach **DATE: 12/16/2015**

MIRB # (if applicable)	PI Name	PI Name	Staff Member Name	Staff Member Name	Staff Member Name
Name	Emily C. Paulson, MD, MSCE	Co-I: Chyke Doubeni, MD, MPH	Shivan Mehta, MD, MBA, MSHP	Adina Lieberman, MPH	Kara Magane, MS
E-Mail Address	Emily.Paulson@va.gov	Chyke.Doubeni@ uphs.upenn.edu	Shivan.mehta@ uphs.upenn.edu	Adina.lieberman@ uphs.upenn.edu	Kara.Magane@ uphs.upenn.edu
VA Phone Number	215-823-5800 x6637	215-823-6333	215-823-6333	215-823-6333	215-823-6333
Non-VA Phone Number		215.662.3349	215-898-9807		
Role and Responsibilities	Oversee the development, implementation, and evaluation of the study	Oversee the development, implementation and evaluation of the study	Assist with implementing and evaluating data	Research Project Manager –implement study protocol	Research Assistant – implement study protocol
% Effort on Study	15%	5%	5%	10%	50%
Is this staff member a VA employee?	☒ YES ☐ NO ☐ WOC	☐ YES ☐ NO ☒ WOC	☐ YES ☐ NO ☒ WOC	☒ YES ☐ NO ☐ WOC	☐ YES ☐ NO ☒ WOC
Does this staff member exercise independent clinical decision making related to the grant/project?	☒ YES ☐ NO	☒ YES ☐ NO	☒ YES ☐ NO	☐ YES ☒ NO	☐ YES ☒ NO
Does this staff member come to the CMCVAMC and see either VA patients or VA patients' private health information?	☒ YES ☐ NO	☒ YES ☐ NO	☒ YES ☐ NO	☒ YES ☐ NO	☒ YES ☐ NO
Does this staff member decide if potential subjects meet inclusion/exclusion criteria?	☒ YES ☐ NO	☒ YES ☐ NO	☒ YES ☐ NO	☐ YES ☒ NO	☐ YES ☒ NO
Does this staff member obtain subjects' informed consent?	☒ YES ☐ NO	☒ YES ☐ NO	☐ YES ☒ NO	☒ YES ☐ NO	☒ YES ☐ NO
Does this staff member document in CPRS?	☒ YES ☐ NO	☒ YES ☐ NO	☒ YES ☐ NO	☐ YES ☒ NO	☐ YES ☒ NO

Submit an additional form if necessary.
Reminder: All research staff must meet or exceed the minimal standards set forth by CMCVAMC IRB. **This form must be updated by the PI and submitted to the IRB for approval before protocol personnel changes can be implemented.**
R&D Revisions: 07/11/2006; 05/31/2007, 08/14/2008; 03/2009

R&D (151)

Research Staff Form | **CMCVAMC IRB**
Corporal Michael J. Crescenz VA Medical Center Institutional Review Board

APPROVED by CMCVAMC IRB 2/
Date: 12/22/15

TITLE OF RESEARCH PROTOCOL: Reducing Colorectal Cancer Death through Mailed Outreach **DATE: 12/16/2015**

MIRB # (if applicable)	Staff Member Name	Staff Member Name	Staff Member Name	Staff Member Name	Staff Member Name
Name	Kenneth Walton	Danielle Bauscher, MSW	Mounika Kanneganti	Christopher B. Roberts	Amanda Walling
E-Mail Address	Kenneth.Walton2@va.gov	Danielle.Bausher@va.gov	mounikak@sas.upenn.edu	Christopher.Roberts5@va.gov	Amanda.walling@va.gov
VA Phone Number	215-823-6333	215-823-6333	215-823-6333	215-823-5800 x 3882	215-823-4631
Non-VA Phone Number					
Role and Responsibilities	Research Assistant – implement study protocol	Research Assistant – implement study protocol	Research Assistant – implement study protocol	Dataset Administrator	Program Analyst
% Effort on Study	15%	15%	10%	>1%	>1%
Is this staff member a VA employee?	☐ YES ☐ NO ☒ WOC	☐ YES ☐ NO ☒ WOC	☐ YES ☐ NO ☒ WOC	☒ YES ☐ NO ☐ WOC	☒ YES ☐ NO ☐ WOC
Does this staff member exercise independent clinical decision making related to the grant/project?	☐ YES ☒ NO	☐ YES ☒ NO	☐ YES ☒ NO	☐ YES ☒ NO	☐ YES ☒ NO
Does this staff member come to the CMCVAMC and see either VA patients or VA patients' private health information?	☒ YES ☐ NO	☒ YES ☐ NO	☒ YES ☐ NO	☒ YES ☐ NO	☒ YES ☐ NO
Does this staff member decide if potential subjects meet inclusion/exclusion criteria?	☐ YES ☒ NO	☐ YES ☒ NO	☐ YES ☒ NO	☐ YES ☒ NO	☐ YES ☒ NO
Does this staff member obtain subjects' informed consent?	☒ YES ☐ NO	☒ YES ☐ NO	☐ YES ☒ NO	☐ YES ☒ NO	☐ YES ☒ NO
Does this staff member document in CPRS?	☐ YES ☒ NO	☐ YES ☒ NO	☐ YES ☒ NO	☐ YES ☒ NO	☐ YES ☒ NO

Submit an additional form if necessary.

Reminder: All research staff must meet or exceed the minimal standards set forth by CMCVAMC IRB. **This form must be updated by the PI and submitted to the IRB for approval before protocol personnel changes can be implemented.**

R&D Revisions: 07/11/2006; 05/31/2007, 08/14/2008; 03/2009

Dear Mr./Mrs. [Last name]

Here is your FIT (Fecal Immunochemical Test) kit for colorectal cancer screening at no cost to you. The FIT kit is a simple, effective way to screen for colorectal cancer and takes less than 5 minutes.

Why is this important?

By completing the FIT screening every year, you are taking an important step toward keeping yourself cancer free.

How do I use the kit?

Place the kit in your bathroom and collect a stool ("poop") sample the next time you have a bowel movement. You only need one sample to complete the screening. Follow the instructions included in the kit and remember to write your name, date of birth, and the date you completed the test on the bottle. **Mail back the kit within 48 hours** in the self-addressed, pre-paid envelope included.

What is next?

There is no need to call to let me know that you completed the test. The lab will send me the results of your FIT screening, and I will let you know the results as soon as I have them. Depending on your results, it may be necessary to come in for further testing.

What if I have questions?

If you have any questions before, during, or after completing the FIT, please contact our screening team at 215-615-4796. Staff are available to help you from 8AM to 5PM on Mondays through Fridays. If you call and nobody is available to answer the phone, please leave a message with your phone number and a time to contact you.

I hope you complete this free and important screening test.

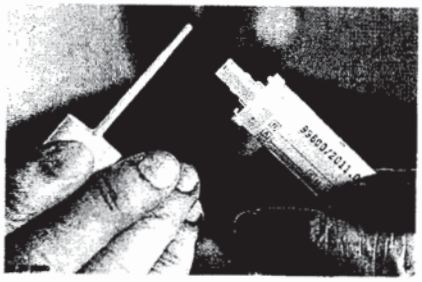
Sincerely,

[[Doctor's Name]] [[Title]]

CMC VA Medical Center

[[Patient first name]] [[last name]]
[[street address]]
[[city]], [[state]] [[ZIP code]]

[[date]]



You will get your screening kit in an envelope within 1 to 2 weeks.

Dear Mr./Ms.[LASTNAME]:

Our records show that you are due for colorectal cancer screening. For your convenience, we will mail you a FIT kit at no cost to you. FIT stands for Fecal Immunochemical Test - a simple, effective way to screen for colorectal cancer. The kit has everything you need to complete your part of the screening in the privacy of your own home.

Colorectal cancer is very curable when found early.

By taking this test every year, you take an important step toward keeping yourself cancer free. Depending on your FIT results, I may need you to come in for further testing.

Completing the FIT takes less than 5 minutes.

The FIT kit will be in your mailbox within 2 weeks at no cost to you. You will need only one stool ("poop") sample, and do not need to do anything to prepare. You will mail the kit back to the VA using a self-addressed, pre-paid envelope. Full instructions are provided in the kit.

Colorectal cancer can run in families.

If this is the case for you, let's talk about the best way for you to be tested and how often.

If you get your colorectal cancer screening tests outside of the VA, or if there is another reason that you no longer need screening, please call our screening team at 215-615-4796 and we will update your records.

Sincerely,

[[Doctor's Name]][[Title]]
CMC VA Medical Center

APPROVED by CMCVAMC IRB 2
Date: 12/22/15

[[Patient first name]] [[last name]]
[[street address]]
[[city]], [[state]] [[ZIP code]]

[[date]]

Dear Mr./Ms.[LASTNAME]:

Our records show that you are due for colorectal cancer screening. Please contact our screening team at 215-615-4796 to schedule an appointment to discuss how you should get screened for colorectal cancer.

Colorectal cancer is very curable when found early.

By getting screened, you take an important step toward keeping yourself cancer free. Depending on the test you receive and the result of that test, I may need you to come in for further testing.

Colorectal cancer can run in families.

If this is the case for you, let's talk about the best way for you to be tested and how often.

If you get your colorectal cancer tests outside of the VA, or if there is another reason that you no longer need screening, please call our office at 215-615-4796 and we will update your records.

Sincerely,

[[Doctor's Name]][[Title]]
CMC VA Medical Center

APPROVED by CMCVAMC IRB 2
Date: 12/22/15

Please fill out the following information so that we can ensure we have the most accurate information in your medical record at the VA.

Below are types of screening for colorectal cancer. For the test(s) that you have received, please check the box and write the date you had the test(s).

☐ I have not received any colorectal cancer screening tests

☐ Stool test[1] Date: _____

☐ Colonoscopy [2] Date: _____

☐ Sigmoidoscopy [3] Date: _____

☐ CT Colonography [4] Date: _____

If you have any questions, please call us at 215-615-4796. Thank you!

Name (print): _____ Date: _____

[1] Stool test, called either FOBT (Fecal Occult Blood Test) or FIT (Fecal Immunochemical Test) are tests where the patient collects 1 to 3 stool or "poop" samples at home and sends them to a lab to be tested for hidden blood.

[2] Colonoscopy is a procedure that lets a doctor closely look at the inside of your bowels for signs of colon cancer by inserting a small tube into the rectum. Patients are usually given medicine to help them relax and sleep while it's done.

[3] Sigmoidoscopy is a procedure that allows a doctor to look closely at only the lower part of the colon and the rectum. To do this, the doctor inserts a thin (about the thickness of a finger), flexible, hollow, lighted tube into the rectum. The patient usually doesn't need medicine to help them relax.

[4] CT Colonography is a special x-ray of the large intestine, which includes the colon and rectum. To do this, the doctor inserts a well-lubricated tube into the rectum. The patient usually doesn't need medicine to help them relax.

CMCVAMC Specific Protocol Summary Content Requirements for IRB Committee Review	CMCVAMC IRB Corporal Michael J. Crescenz VA Medical Center Institutional Review Board

A. Protocol Title:
   1. **Full Protocol Title**: Reducing Colorectal Cancer Death through Mailed Outreach Screening
   2. **Date of Protocol Summary and Version #**: Version 7 – December 16, 2015

APPROVED by CMCVAMC IRB 2 Date: 1/22/15

B. Principal Investigator's Full Name and Degree: E. Carter Paulson, MD, MSCE

C. Co-Investigator's Full Name and Degree: Chyke A. Doubeni, MD, MPH; Shivan Mehta, MD, MBA

D. Financial Sponsor: This proposal was reviewed at the August 2015 meeting of the HSR&D SMRB. HSR&D intends to fund this proposal upon successful completion of all Just-in-Time requirements. An IRB protocol under review is a condition of funding. However, we wish to conduct the study, even if a favorable funding decision is not received, to assess the feasibility of the screening program, and doing so will enable us to apply for a full HSR&D Merit on the next funding round. We currently have funds from CHERP and the University of Pennsylvania to support pilot data collection on this project.

E. Grant: N/A

F. Protocol Number: PPO 14-369

G. Institution(s) responsible for the project:
   1. For single-site studies - CMCVAMC is the only institution involved. Yes ☒ No ☐
   2. For multi-center studies.
   3. CMCVAMC is the Coordinating Center in which the PI is the lead investigator. Yes ☐ No ☐ N/A ☐
   4. Provide the name of the Coordinating Center. Yes ☐ No ☐ N/A ☐
   5. List the name of the other sites involved.
   6. Provide the FWA numbers for each of the other sites involved.

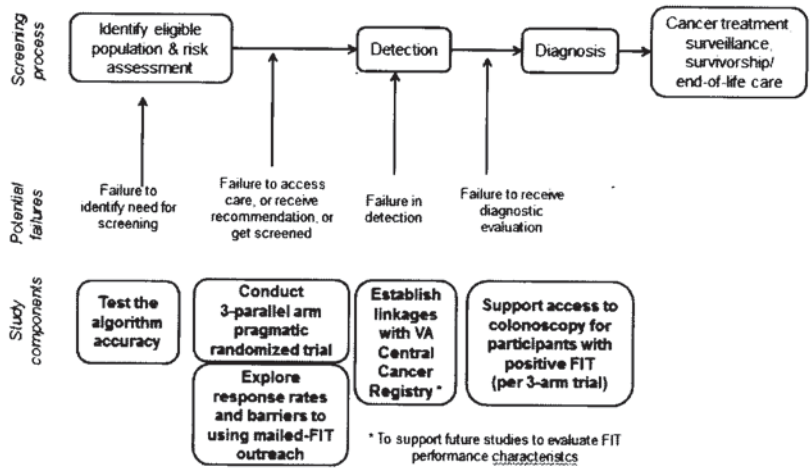
THE FOLLOWING INFORMATION MUST BE CMCVAMC-SPECIFIC, THAT IS, SPECIFIC TO WHAT WILL BE DONE WITH CMCVAMC-RECRUITED VETERANS.

H. **Background and Significance**: Colorectal Cancer (CRC) is the second leading cause of cancer deaths in the United States (US). CRC prevention and control is thus a priority for the VA, which dovetails into the US national objective to reduce CRC mortality to 14.5 per 100,000 persons by 2020. Screening is cost-effective for preventing CRC death. The increasing uptake of screening has been a key contributor to the declining US incidence and mortality rates for CRC over the past three decades. Recently, the National Colorectal Cancer Roundtable launched an initiative to increase CRC screening uptake among eligible adults to 80% by the year 2018. Reports suggest that the VA has already achieved this screening target. However, much of the existing knowledge on CRC screening in the VA has been on veterans who have had recent VA healthcare visits. Thus, the true rate of screening as well as barriers to screening uptake among veterans is not well unknown, and there are potential disparities that remain undiscovered. The U.S. Preventive Services Task Force, as does the Veterans Health Administration (VHA) Directive 2007-004, recommends screening

for CRC in average-risk 50-75-year-old adults using highly sensitive guaiac-based fecal occult blood tests (gFOBT) such as the fecal immunochemical test [FIT] annually, flexible sigmoidoscopy every five years with mid-interval gFOBT or FIT, or optical colonoscopy every 10 years as equally acceptable strategies. CRC screening is underutilized in some populations such as racial minorities, even in the VA, contributing to incidence and mortality disparities. Two of the strongest predictors for receiving CRC screening are having a regular health care visit and a provider's recommendation. This application seeks to create a pilot program of population-based mailed FIT outreach for CRC screening in the VA with the potential for widespread adoption to overcome barriers at patient, provider and systems levels such as the need for a face-to-face encounter. The long-term goal is to optimize access to and use of effective screening among all veterans, particular those hard to reach, by improving the screening process. Thus, the proposed project is specifically geared towards simplying the screening process by changing the default approach to initiating screening by direct mailed outreach.

I. **Purpose of the Project**: This application seeks to establish the foundation to systematically study and improve the delivery and effectiveness of CRC screening in the VA by developing, implementing and disseminating a pilot mailed-FIT screening outreach program that does not rely on having a clinical office visit. As shown in the conceptual framework (Figure 1), we specifically address the need to identify and remediate potential failures to identify and offer screening to eligible veterans through multilevel interventions. We will also create electronic data linkages to, in future studies, enable evaluation of FIT performance characteristics and help close critical evidence gaps for optimizing screening among veterans.

Figure 1: Conceptual framework for optimizing the VA screening process for this pilot project



J. **Describe the Research Questions or Hypotheses**: As this is a pilot study, the focus is to assess feasibility of a population-based screening outreach approach through the development, implementation and dissemination of a mailed FIT outreach program in the CMCVAMC that does not rely on having an office visit. The main study aim is to develop, implement and disseminate a pilot population-based mailed FIT outreach screening program in the Corporal Michael J Crescenz VA Medical Center (CMCVAMC) that does not rely on having an office visit, by conducting a proof-of-concept 3-arm parallel-design pragmatic randomized trial to:

1. Compare the effects of usual care (UC), screening invitation + reminder (invitation-reminder), or screening invitation + mailed FIT kit + reminder (mailed-FIT)
2. Explore whether the FIT completion rate varies by age or race/ethnicity

3. Explore barriers to use of mailed outreach screening for veterans

K. **Primary Outcome Variable(s)**: The primary outcome is the completion rate of FIT within 6 months of baseline.

L. **Secondary Outcome Variable(s)**: Our secondary outcome is the receipt of any CRC screening test within 6 months of baseline.

M. **Study Design and Methods**:

1. **Is this a clinical trial?** ☐YES ☒NO
   a. If yes, what type? Check all that apply.
      ☒ NOT APPLICABLE (Pilot) ☐Phase I ☐Phase II ☐Phase III ☐Phase IV
   b. If yes, this study must be registered on Clinicaltrials.gov.
2. **Design**:
   a. What research methods will be used in the project? Check all that apply.

☒ Surveys/Questionnaires	☒ Interviews	☐ Audio Taping
☐ Behavioral Observations	☒ Chart Reviews	☐ Video Taping
☐ Focus Groups	☒ Randomization	☐ Double-Blind
☐ Control Group	☐ Placebo	☐ Withhold/Delay Treatment
☒ Specimen Collection	☐ Deception	☒ Telephone Survey
☐ Other (Describe)		

   b. *Describe how randomization or other treatment assignment will be made:* We will conduct a 3-arm parallel-design pragmatic randomized trial to compare amongst the effect of usual care (UC), and population-based screening invitation + reminder (invitation-reminder only), or screening invitation + mailed FIT kit + reminder (mailed-FIT). The 3,388 potentially eligible veterans will be block-randomized to one of the three arms.
   c. *For retrospective research studies, provide the "look-back" period. (e.g., December 1, 1999 through December 31, 2008)*: We will identify all potentially eligible veterans via CPRS chart review; eligible veterans include veterans in the southeastern Pennsylvania and Southern New Jersey who, during the funding year, are 50 to 75 years old, have received care in CMCVAMC in the 18-48 months prior to selection for the study but who, have not been seen by primary care in the past 18 months prior to selection, are due for CRC screening, and are asymptomatic
3. **Study Duration**:
   a. *Provide the estimated length of time to enroll all subjects and complete the study*: October 1, 2015 (or as soon as Approved by the IRB) to September 30, 2016.
   b. *Explain the expected duration of subject participation including any follow-up*: This study will primarily test the effect of an outreach mailing, along with reminders, of the FIT to veterans. The outcome will be assessed through Months 3-7. We anticipate mailing the kits through Months 3-5 and will conclude follow-up procedures by Month 11 of the study period.
   c. *Specify the projected date of completion of the proposed study*: The projected date of completion is December 31, 2016.
4. **Drug Information**: NOT APPLICABLE
   a. *Specify if the drug or biological agent is:*
      i. FDA approved:
      ii. Used for off-label purposes
      iii. Not yet FDA approved.

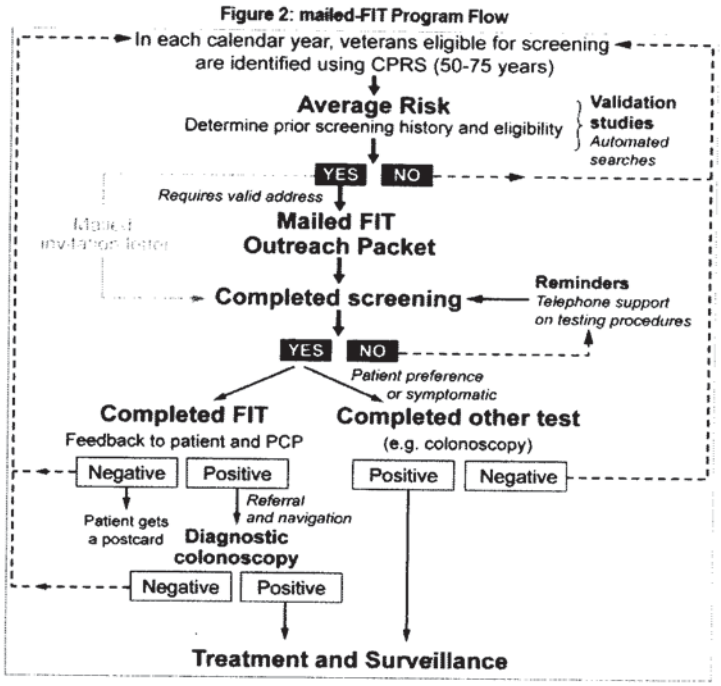
b. *Include the FDA Investigational New Drug (IND) number for all non-FDA approved and off-label drugs, biological agents or nutritional supplements:*
c. *Provide all relevant information about the drug*
d. *Explain any wash-out periods, rescue medications permitted and any type of medications not permitted while enrolled in the study.*
e. *Describe blinding and un-blinding procedures.*
f. *Include the dosage, route of administration, previous use, and the safety and efficacy information on any drug used for research purposes.*
g. *Describe rationale for the dosage in this study.*
h. *Justify why the risks are reasonable in relation to anticipated benefits and/or knowledge.*
i. *Describe where drug preparation will be done.*
j. *All drugs for CMCVAMC subjects must be dispensed through the VA investigational pharmacy.*
k. *Describe where the study treatment will be administered.*
l. *Describe plan for tracking a non-compliant treatment study subject.*
m. *Summarize any pre-clinical data.*
n. *Describe the process for the storage, security, dispensing and return of an investigational drug.*

5. **Investigational Device**: NOT APPLICABLE
   a. The Investigational Device Exemption (IDE) number must be submitted for all *significant risk devices and if an IDE exists for a non-significant device.*
   b. *Significant Risk or Non-significant Risk - If a device is not approved by the FDA, specify whether or not the sponsor has determined this device to be a "significant risk" or "non-significant risk" as defined by the FDA.*
   c. *Provide all relevant information about the device.*
   d. *Describe blinding and un-blinding procedures.*
   e. *Specify if device is:*
      i. *FDA approved*
      ii. *Used for off-label purposes*
      iii. *Not yet FDA approved.*
   f. *Explain if the investigational device will be delivered and/or stored by the Principal Investigator or Pharmacy Services.*
   g. *Describe the process for the storage, security, dispensing and return of an investigational device.*
   h. *For research involving an investigational device, describe the SOP or plan for device control.*
   i. *Address how the device will be stored in such a way that only research staff associated with the protocol will have access to the device.*
   j. *Describe measures that will be put into place to ensure that the device will only be used in participants of this research protocol.*

N. Does this project involve international research? ☐YES ☒NO

O. Study Procedure

1. *Study Procedures*: We will conduct a 3-arm parallel-design randomized trial to compare UC, screening invitation + reminder alone (invitation-reminder), and invitation-reminder + mailed FIT kit (mailed-FIT). The program flow is outlined below and described in the sections below (Figure 2).



2. *Creation of Tracking database*: A database of eligible veterans is critical to the program. We will build on the database currently used by Dr. Dubb (consultant) to monitor FIT at the CMCVAMC. At the start of the pilot program, we will run the electronic query to identify age-eligible veterans who had received medical care at CMCVAMC in the 18-48 months prior to the start of our study and not currently up-to-date on CRC screening in the beginning of 2016. We will develop an approach to update and improve the accuracy of the registry in subsequent calendar years to minimize mailing FIT to veterans who are already up-to-date. Individuals will age into (as they turn 50) or age out of (age >75) the registry. In the future, we will explore the possibility of adding veterans to the registry at earlier ages (i.e., ≥45 years) to expedite outreach as they approach the eligible age.
3. *Mailing the FIT kits*: In the mailed-FIT arm, a screening invitation that includes a PCP-signed pre-notification letter and a screening confirmation card will precede the kits, as practiced in Kaiser Permanente Northern California (we have received permission to adapt their outreach materials – see attached for examples). The FIT kit will be sent about 1 week after the screening invitation. The kit will have specimen collection instructions in English and Spanish using resources developed by the American Cancer Society. We are currently working on procedures to pre-label kits with each participant's unique information.
4. *Validation study of screening history*: We have extensive experience in algorithms to identify CRC screening history in EMR. The advantage in the VA is its integrated delivery structure. However, the screening history in CPRS (a Veterans Health Information Systems and Technology Architecture [VistA] computer application) may be incomplete, because tests received outside the VA may not be recorded in VistA. Thus, we will test the accuracy of electronically determined screening histories. Chart audits and administrative data may underestimate, and patient report may overestimate, screening use. We will conduct formal chart review on the study sample (n=783). At the end of the study, we will also conduct surveys of participants to compare their screening history in VistA with both EMR and patient interview. The screening history questionnaire will be conducted at 6 months from baseline on all participants to ask for information on receipt of CRC screening test, the last test and type (if applicable), and location where the test was performed – interviews at baseline will contaminate the UC arm. We have

80% power to detect 3.8% false negative rates (that is, if 30 were previously screened among 783 subjects). This will allow us to refine our program strategy and improve accuracy of algorithms to determine guideline-concordant screening by identifying patient and registry level predictors that are correlated with false negative rates. We have extensive tools of our own to use for chart audit and patient surveys.

5. Distinguishing asymptomatic participants from those with GI symptoms: We will provide information cards in the invitation letters about CRC symptoms, family history, or other risk factors. Doing this will allow the latter group to be directed to their doctor for evaluation. We will, in future studies, develop procedures to evaluate the effectiveness of this approach.
6. *Valid contact information* is critical to the program, but may be challenging with some veterans. We will assess the extent to which kits are successfully delivered and explore approaches such as returned receipt confirmation. To support annual rescreening and assure that we can contact screen-positive participants, we will obtain updated contact information such as telephone numbers and emergency contacts, as part of the outreach procedures. We will safeguard participant data during and after mailing.
7. *Specimen analysis*: The OC-FIT CHEK is analyzed at the CMCVAMC using OC Sensor DIANA, an auto-analyzer system that provides quantitative results corresponding to the concentration of hemoglobin in the collected sample. Specimens will be analyzed according to manufacturer's instructions to minimize potential degradation of hemoglobin. Results are provided as positive if the hemoglobin concentration is ≥100ng/dL. The machine records (but does not report) the quantitative results of the hemoglobin concentration in the sample, which we will seek to obtain from the laboratory for future studies.
8. *Communication of results and diagnostic work-up for abnormal screen*: Results will be recorded in CPRS and the tracking REDCap database and communicated to the PCP using existing procedures. Patients with a negative result will be informed by mail. Patients who test positive will be notified by mail and phone. We will track results with positive results by phone, as needed, and by monthly CPRS queries and EMR review until diagnostic testing is completed or clinical decision is made not to do diagnostic testing.
9. *Data Linkages*: We will apply for VA Central Cancer Registry (VACCR) linkages on all study patients to enable full evaluation of performance characteristics of FIT for the detection of CRC at the VA, including FIT's performance variations according to selected patient-level and environmental factors. The VACCR aggregates data collected by approximately 120 VAMCs. Our VACCR application will request CRC diagnosis dates, and tumor stage, morphology, histologic behavior characteristics, grade, and location (subsite) using International Disease Classification, Oncology codes. Potential analysis for this exploratory study will examine the sensitivity, specificity, and the predictive value positive of FIT for detection of CRC using detection of CRC within 24 months of result date as the standard. We will also develop an approach to create linkages to National Oceanic and Atmospheric Administration (NOAA) public databases, as we have done in ongoing studies, to enable us to monitor performance characteristics variation according to ambient temperature exposures.
10. *Study Procedures for the Proof-of-Concept Pragmatic Trial*: We will conduct a 3-arm parallel-design pragmatic randomized trial to compare amongst the effect of usual care (UC), and population-based screening invitation + reminder (invitation-reminder only), or screening invitation + mailed FIT kit + reminder (mailed-FIT). The rationale is to determine if mailed invitation with a FIT kit is effective at increasing uptake separately from ongoing practices at the CVMAC and separately from standardized invitation and

reminders. Ongoing evaluation of these approaches will help VA adapt to changes in veterans screening behaviors.

11. *Recruitment*: An estimated 783 eligible patients will be recruited for this trial. We will obtain PCP approval, through discussion at schedule clinical and program meetings with support from Dr. Tzanis, for participation and to confirm the inclusion and exclusion criteria. There are an estimated 3,388 potentially eligible veterans for this pilot. We have obtained a waiver of informed consent from the IRB since this is considered minimal risk to the participants, and obtaining consent would inherently change the intervention.
12. *Randomization*: Patients will be block-randomized to UC, invitation-reminder, or mailed-FIT with guidance from Dr. Richardson to achieve the desired sample size. We will mail all study materials to patients during Months 3-5 of the study in weekly waves of about 50 mailings; with this volume, it is feasible for us to confirm eligibility through chart audits prior to mailing invitations to study participants.
    a. Participants randomized to UC: These patients will continue to receive the current practice at CMCVAMC of offering screening during an office visit. Other interventions will be embedded within this existing program for a pragmatic approach. However, all participants in the trial, including those in UC, will receive follow-up of test results and navigation to diagnostic colonoscopy for positive FIT results.
    b. Participants randomized to screening invitation-reminder: These patients will continue to receive UC. They will in addition receive an invitation letter with all of the information about CRC testing in the mail-FIT arm (except the kit and instructions, see below). The information will include lay-audience description of screening tests such as FIT and colonoscopy and, if appropriate, Cologuard (sigmoidoscopy is not offered at CMCVAMC), and symptoms that should prompt diagnostic work-up such as change in bowel habit with rectal bleeding. The packet will also have a screening confirmation card and instructions to contact the study team if the patient believes he/she is not eligible and to update the contact information on record. The letter will inform patients that a telephone reminder will follow in 4 weeks from invitation letter if screening is not completed (even if they have an appointment scheduled). They will receive three weekly reminders at weeks 4, 5, and 6 from the invitation letter. They will also receive notification of test results and navigation to colonoscopy, if needed. For the purposes of this intervention, Week 1 will be the week the invitation letter was sent (time zero). It is generally unclear whether mail reminders may be more effective at reaching veterans than phone calls because telephone numbers may change or run out of purchased minutes, but addresses may also change or a veteran may be homeless. Thus, we will also explore sending mailed reminders when participants cannot be reached by phone and track the success of each approach used during the study.
    c. Participants randomized to Mailed-FIT will receive a mailed FIT pre-notification letter (plus a screening invitation and screening confirmation card) followed by the kit 1 week later (see section D2d2). Patients will receive a screening confirmation card and instructions to contact the study team if the patient believes he/she is not eligible and to update the contact information on record. They will be informed that a telephone reminder will follow 4 weeks from notification letter if screening is not completed. Patients who do not return their kit after 4 weeks of the date the pre-notification letter was mailed will receive a live telephone reminder (even if they have an appointment scheduled, as with the invitation-reminder arm), followed by 2 additional calls at the end of weeks 5 and 6, if needed.82 For the purposes of this intervention, Week 1 will be the week the pre-notification letter was sent (time zero). We will explore and evaluate the approaches for successfully contacting participants in our study setting.

13. *Study Population*: The study population will be all veterans in the southeastern Pennsylvania and Southern New Jersey area who, during the study period, are 50 to 75 years old, have received care in CMCVAMC in the 18-48 months prior to selection for the study but who have not been seen by primary care in the past 18 months prior to selection, are due for CRC screening, and are asymptomatic for CRC.
14. *Setting*: This study will be conducted at CMCVAMC in southeastern Pennsylvania and Southern New Jersey.
15. *Exclusion*: We will exclude tests of patients with known gastrointestinal symptoms such as bleeding, unexplained weight loss, or change in bowel habits, family history of CRC, inflammatory bowel disease (IBD), or colectomy using International Classification of Disease (9th and 10th edition) diagnostic code or by self-report (Figure 2). We will exclude patients with evidence of prior colonoscopy within 10 years, sigmoidoscopy within 5 years, and FOBT/FIT in the same calendar year. There is a pool of at least 3,388 veterans to draw from for our study based on screening eligible population at the CMCVAMC.
16. *Test results*: Data on the date, and result of FIT performed will be obtained from CPRS/Regional Data Warehouse.
17. *Measurement of Outcome*: The primary outcome measure in all analyses is the completion rate of FIT within 6 months of the mailing of the screening invitation. Absence of screening completion data in CPRS will be recorded as failure to complete screening. We will also evaluate a secondary outcome measure of receipt of any CRC screening test in the 6-month period after enrollment into the study. Our rationale as articulated in Gupta et al.,39 is that the 'best test is the one that gets done'. Thus, the numerator for such an alternative definition will include those who received a colonoscopy for any indication. Since the screening process for a positive tests is completed only after diagnostic testing, we will define a third outcome as receipt of screening plus timely diagnostic testing (within 90 days) when positive. We will also collect data on a number of other outcomes, including the proportion of non-responders who responded to reminders, positivity rate, completion of diagnostic colonoscopy. We will measure several of those factors to be considered as covariates in some analyses as shown in Table 1, recognizing that some of these variables will be exploratory, as we will not have an adequate sample size to obtain meaningfully precise estimates.
    a. *Analysis plan on primary outcome measures to compare the effects of UC, invitation-reminder, and mailed-FIT)*: We will use Chi-squared statistic to test the null hypothesis that the completion rates between the mailed-FIT and UC and between mailed-FIT and invitation-reminder are equal using an "intention-to-treat" approach, based on a 2-sided alpha of 0.05. We do not anticipate loss to follow up or missing outcome data because outcomes will be tracked in integrated electronic medical record systems. We will examine the distribution of test types to assess the ability to analyze an 'any CRC screening test' outcome, and the other pre-specified secondary outcome measures.
    b. *Exploratory analysis of FIT completion rate by age or race/ethnicity*: We will assess the association of age and of race/ethnicity with the FIT completion rate (dependent variable) among all study participants using logistic regression. Our rationale is that a VA study found that screening use differed by age and was lower among persons of black race. We will model fit completion by race/ethnicity (African Americans vs. others), age (50-64 vs. 65+), and race/ethnicity*intervention and age*intervention interaction terms, to explore the overall effect of race/ethnicity and age, and possible effect modification. This analysis will allow us to understand if specific groups need to be targeted when a program is fully implemented and if larger sample sizes will be needed. We will use both univariate and multivariable logistic regression analyses (2-

sided alpha of 0.05). The primary approach will be 'intention-to-treat' analysis and additional analyses will be restricted to those with valid addresses.

c. *Exploratory analyses of mailed outreach screening barriers*: A valid participant contact information is key to a successful outreach. Thus, we will track and assess the proportion of participants whose mail was returned due to bad addresses. We will seek to verify addresses and assess our ability to contact study veterans by phone by calling non-responders. Once tumor registry linkage is established, we will seek to explore the number of cases of CRC diagnosis in CMCVAMC patients and assess the FIT positivity rates and explore the relation with CRC diagnosis using 2 X 2 contingency tables as described section D2d8, using 1 or 2 years between FIT result dates and CRC diagnosis ascertainment.

d. *Sample size and power estimates for primary outcome measures*: Gupta et al. found that, among underserved patients in Dallas, 40% of those assigned to mailed-FIT completed screening compared to 12% in UC.38 In our power and sample size analysis, we assumed 15% screening rate in UC alone, 25% with invitation-reminders, and 40% with mailed-FIT. With those assumptions, a total sample size of 500 (250 per arm) will give 80% power for UC vs. screening invitation-reminder, and 152 patients per arm will give a power of 80% for the screening invitation-reminder vs. mailed-FIT. Accounting for the possibility that up to 20% of participants could be ineligible post-randomization, we will identify about 783 patients for this trial.

18. **Explain if and how the follow-up of subjects will occur**. All participants, including those in UC, will be tracked electronically in VistA. We will select randomized patients in batches each week, so that even those in UC will have a set reference date for tracking outcomes. We will set a minimum of 6 months from time zero to determine completion of screening after invitation or pre-notification letter, but our goal is to track outcomes electronically over a minimum of 12 months from the invitation date, depending on funding availability. All returned kits will be analyzed as described in section D2d6. Study staff will send the patient a letter with the results (and education about future testing) and record the data into the tracking REDCap database with guidance from Dr. Dubb (Figure 2). Participants who test positive (estimated 4-6%, or 31-47 patients) will receive a letter and phone call from trained staff to explain the findings and assist in scheduling a colonoscopy within 30 days in collaboration with the CMCVAMC gastroenterology division.

19. **Describe where, how and who will be conducting study procedures**. The study will be conducted under the auspices of CHERP using trained research assistants. The PI will oversee all research activities in collaboration with Drs. Richardson and Doubeni who are Co-Investigators on this study. Drs. Dubb and Tzanis will serve as consultants. All study activities will be logged into secure REDCap databases at the CMCVAMC. The trained research assistants will contact patients by phone if they do not return the test kits or complete screening in a timely manner. Also, some participants needing assistance in completing the kit will be contacted to support them in completing the test. In addition, a research assistant will call patients with a positive result to inform and guide them on scheduling a colonoscopy.

    a. *If a survey study, specify the estimated amount of time that subjects will need to complete the questionnaires/tools*. At the end of the study, we will conduct surveys of participants to compare their screening history in VistA with both EMR and patient interview. The screening history questionnaire will be conducted at 6 months from baseline on all participants to ask for information on receipt of CRC screening test, the last test and type (if applicable), and location where the test was performed - interviews at baseline will contaminate the UC arm. These surveys take 10-20 minutes.

b. *If a blood draw, specify the amount of blood to be drawn in milliliters and in teaspoonfuls or tablespoonfuls and specify how often and where the blood will be drawn.* Not Applicable

20. Data Collection (Include all questionnaires and survey tools with the submission)

a. *Provide the mode of data collection, e.g. telephone, in-person, questionnaire, interviews*: At the end of the study, we will conduct surveys of participants to compare their screening history in VistA with both EMR and patient interview. The screening history questionnaire will be conducted at 6 months from baseline on all participants to ask for information on receipt of CRC screening test, the last test and type (if applicable), and location where the test was performed. The survey instrument is included in the submission.

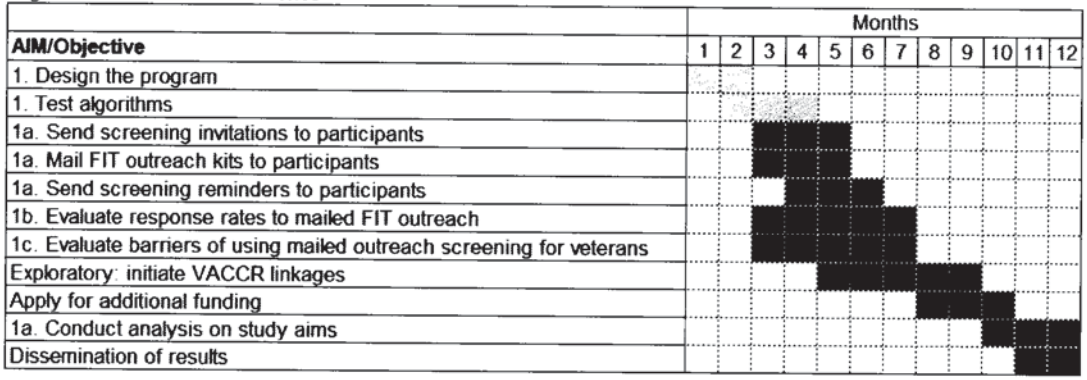
b. *Provide the precise plan for how data is to be collected or acquired*: See section 12 for a complete outline of how data is collected. Data collection will be performed by research assistants under the supervision of the PI in collaboration with Dr. Doubeni. The Dataset Manager and/or the Statistical Analyst will perform analysis on the study with guidance from the PI and Drs. Richardson and Doubeni. The research data obtained will be stripped of all identifiers prior to analysis at the CHERP.

c. *Exact location where data will be collected*: Data will collected at the CMCVAMC Primary Care Clinic. Data entry will take place at:
Center for Health Equity Research & Promotion
Philadelphia VA Medical Center Annex
3900 Woodland Avenue, Room 236, Cubicle #9
Philadelphia PA 19104

d. *The "title" of individual(s) collecting the data and analyzing the data, e.g. principal investigator, research coordinator*:
   i. E. Carter Paulson, MD, MSCE, Principal Investigator
   ii. Chyke A. Doubeni, MD, MPH, Co-Investigator
   iii. Shivan Mehta, MD, MBA, Co-Investigator
   iv. Christopher Roberts, MPH, Data Set Manager
   v. Statistical Analyst (TBD)

e. Provide a time line for each aspect of the study. The timeline is shown in the Figure below

Figure 3: Timeline and milestones



21. **Chart/Records/Data Review (retrospective and/or prospective)**:

a. Provide the planned or approximate number of charts/records/data to be accessed
   i. CMCVAMC: 783
   ii. Other site: NOT APPLICABLE

b. Does this protocol employ an Honest Broker? ☐YES ☒NO
   i. If yes, provide name of individual.

ii. If no, explain who will access the charts/records. The PI, co-Investigators and the Research Assistants will access the charts.
iii. Describe from what database charts/records/data will be accessed. Charts will be accessed through CMCVAMC CPRS/VistA

22. **Future Use of Data and Re-Contact, if applicable**.
    a. If any of the participant's data are going to be retained after the study for future research, the following information must be provided to the participant:
        i. *Where will the data be stored*? The data will be stored in the CMCVAMC clinical REDCap databases. Analytic Datasets will be stored in VA databases at CHERP. All analytic data will be stripped of identifiers. All data analyses will be performed/stored on Center for Health Equity Research and Promotion's (CHERP's) secure analytic servers. CHERP has a 64-bit Windows 7 virtual server running 30 gigabytes of RAM, and 2.2 terabytes of disk space located on a redundant array of independent disks. This virtual server resides on a 64-bit Dell PowerEdge physical machine running four Intel Xeon X5460 3.15GHz 64-bit dual microprocessors (for a total of eight processors) and 32 gigabytes of RAM. The servers reside behind the VA firewall and are entirely compliant with Federal Information Security Management Act (FISMA) standards.
        ii. *Who will have access to the data*? The PI, Co-Investigators, Statistician, Dataset Manager/Analyst, and Research Assistants
    b. *If the subject is going to be re-contacted in the future about participating in future research, this must be specified. Describe the circumstances under which the participant would be re-contacted whether within the VA or outside the VA.* We will re-contact patients in future studies to assess the response to annual invitation to screen. If subjects will receive aggregate study results at the end of the study, the informed consent document must contain this information. Not applicable. Results will be provided to patients during the course of the study as happens in routine medical care

23. **Specimen Collection**:
    a. *Give the source of all specimens and whether they were collected for research, treatment or diagnosis:* Stool sample (from a bowel movement) is collected for stool-based colorectal cancer testing. This is collected for diagnosis of colorectal cancer.
    b. *State where specimens will be stored, secured and when discarded.* Disposition of the specimens will be at the discretion of the CMCVAMC laboratory; Room 3b123
    c. *Explain how destruction of samples will be substantiated.* Not applicable because the specimen collection is part of routine care

P. Genetic Testing:

1. **Explain if the study is looking for an association between a genetic marker and a specific disease or condition, but at this point it is not clear if the genetic marker has predictive value**. Not Applicable
    a. The uncertainty regarding the predictive value of the genetic marker is such that studies in this category will not involve participant counseling.
    b. Describe if the study is based on the premise that a link between a genetic marker and a specific disease or condition is such that the marker is clinically useful in predicting the development of that specific disease or condition.
    c. Will the subject be notified of the results and the provision for genetic counseling? ☐ Yes ☐ No ☐ N/A
    d. If yes, explain further.
    e. If biological specimens are used in this protocol, please respond to the following questions by checking the appropriate box:

	YES	NO	N/A
Does the project involve genetic testing?	☐	☐	☐
Will specimens be kept for future, unspecified use?	☐	☐	☐
Will samples be made anonymous to maintain confidentiality? *(Instructions: Note: If there is a link, it is not anonymous. Coding is not anonymous.*	☐	☐	☐
Will specimens be destroyed after the project-specific use is completed?	☐	☐	☐
Will specimens be sold in the future?	☐	☐	☐
Will subjects be paid for their specimens now or in the future?	☐	☐	☐
Will subjects be informed of the results of the specimen testing?	☐	☐	☐
Are there any implications for family members based on specimen testing results? (If yes, they may be participants.)	☐	☐	☐
Will subjects be informed of results obtained from their DNA?	☐	☐	☐

f. Will specimens be de-identified? ☐YES ☐NO ☐ N/A
   i. If yes, please describe the procedures to be used.
   ii. Include at what point in the process the specimens will be de-identified.
g. Describe what measures will be taken to minimize the following risks from breaches of confidentiality and privacy resulting from participating in This aspect of the research project:
   i. physical
   ii. psychological
   iii. financial
   iv. social
   v. legal harm

Q. Banking of Collected Specimens:
1. **Will collected specimens be banked?** ☐YES ☒NO ☐N/A
   a. ***IF BANKING SPECIMENS, IT MUST BE AT AN APPROVED VA REPOSITORY.*** *(For additional information, refer to VHA Handbook 1200.12, Use of Data and Data Repositories in VHA Research - March 9, 2009.)*
   b. *If yes, specify the location where specimens will be banked.*
      i. If the location is a non-VA site, has the mandatory approval from the Chief Officer of Research and Development (CRADO) been obtained through submission of a tissue banking application (VA Form 10-0436 - Off-site Application for an Off-site Tissue Banking Waiver)? ☐YES ☐NO ☒N/A
      ii. If applicable, attach a copy of the VA Form 10-0436
   c. *Explain how destruction of banked samples will be substantiated.*

R. Subject Recruitment (characteristics of the study population)
1. **Provide the planned or targeted enrollment at:**
   a. CMCVAMC - 783
   b. Other sites - Not applicable
   c. Not applicable; chart review or use of previously collected data - ☐
2. **Screening and/or Eligibility Requirements**
   a. *Describe and provide justification for:*

i. Inclusion criteria: The pragmatic trial will include veterans in southeastern Pennsylvania and Southern New Jersey who, during the funding year, are 50 to 75 years old, have received care in CMC in the 18-48 months prior to selection for the study but who have not been seen by primary care in the past 18 months prior to selection, are due for screening, and are asymptomatic for CRC. This includes the period during which 3-sample testing was being regularly used at the CMCVAMC.

ii. Exclusion criteria: Have any known gastrointestinal symptoms such as bleeding, unexplained weight loss, or change in bowel habits, family history of CRC, inflammatory bowel disease (IBD), or colectomy using International Classification of Disease (9th and 10th edition) diagnostic code or by self-report. We will also exclude veterans with evidence of prior colonoscopy within 10 years, sigmoidoscopy within 5 years, and FOBT/FIT in the same calendar year. The information used to exclude patients will be derived from the electronic queries or chart audits.

b. *List all screening and/or eligibility requirements.*

i. Men and women veterans age 50-75 on the date of screening for eligibility
ii. Received care in the CMCVAMC in the 18-48 months prior to selection for the study but who have not been seen by primary care in the past 18 months prior to selection
iii. Are due for screening
iv. are asymptomatic for CRC
v. Have no evidence of colonoscopy in the prior 10 years, sigmoidoscopy in the prior 5 years, and FOBT/FIT in the same calendar year.
vi. Have no history of any known gastrointestinal symptoms such as bleeding, unexplained weight loss, or change in bowel habits, family history of CRC, inflammatory bowel disease (IBD), or colectomy

(The information used to exclude patients will be derived from the electronic queries or chart audits.)

c. *Explain any special test or evaluations potential subjects may have to undergo before they are actually determined to be eligible for the study.* Some patients may undergo a telephone interview to determine if they have received screening for colorectal cancer outside the VHA yet undocumented in VistA

d. Not Applicable; subjects not recruited; chart review. ☐

3. **If applicable, indicate what populations will be targeted for recruitment as participants.** Check all that apply.

Males	☒
Females	☒
Inpatients	☐
Outpatients	☒
VA Employees	☐
Non-English Speaking**	☐
Veteran Family members***	☐
Non-Veterans***	☐
Other (Specify)	☐
Not Applicable, chart review	☐

a. **For non-English speaking subjects - If an investigator proposes to use a participant population that does not speak or read English, a copy of the translated document, as well as the English version, needs to be forwarded to the IRB for approval. Translator certification is also required.

b. ***If non-veterans will be recruited for this study, explain why sufficient veterans are not available to participate in the project [VHA Handbook 1200.5, paragraph 16a]. Veteran's spouses/partners, caregivers, etc. are considered non-veterans for the purposes of this study.

c. ***Has approval to recruit non-veterans been received from the ACOS/R&D and Medical Center Director?
   i. ☐ Not Applicable
   ii. ☐ Pending *(Non-veteran forms should be used. IRB office will obtain approval from ACOS/R&D and Medical Center Director.)*

4. **Does this project target a specific race or ethnic group as participants?**
☐YES ☒ NO
   i. If yes, check all that apply.

Race	
American Indian or Alaskan Native	☐
Asian	☐
Black or African American	☐
Native Hawaiian or other Pacific Islander	☐
Black, not of Hispanic origin	☐
White, not of Hispanic origin	☐
Other	☐

Ethnicity	
Hispanic or Latino	☐
Not Hispanic or Latino	☐
Other	☐

   b. Provide justification why this/these group(s) was/were chosen.

5. **What is the age range of participants?** Check all that apply.

Children (Under 18) Requires Waiver from CRADO (VHA Directive 2001-028, Research Involving Children)	☐
Young Adults (18-21)	☐
Adults (22-65)	☒
Seniors (Over 65)	☒
Over 89	☐
Not Applicable, chart review	☐

6. **Are there specific reasons why certain populations (i.e., age, gender or ethnic groups) are excluded as participants?** ☒YES ☐NO ☐N/A
   a. *If yes, specify reasons.* We are studying a population that is eligible for routine screening for colorectal cancer, which according to current guidelines are ages 50-75 years. Therefore, veterans who are younger than 50 years or older than 75 years will not be included in our study.

7. **Does the project require enrollment of the following classes of participants?**

	YES	NO
Employees	☐	☒
Individuals with impaired decision making capability	☐	☒
Pregnant women	☐	☒
Economically and/or educationally disadvantaged persons	☐	☒
Prisoners	☐	☒
Illiterate, limited, or no English language proficiency	☐	☒
Terminally ill patients	☐	☒

   a. *If applicable, what is the justification for including any of the above classes of participants in the project?* None of these groups will be specifically targeted for inclusion into the study. The study is of community-dwelling veterans. Employees who are veterans may be included. For women who are 50 years or older who are

generally postmenopausal. Thus, it is unlikely for a pregnant to be included in the study.

b. *If the project requires enrolling any of the above classes of participants describe any project-specific measures or special considerations, steps, or safeguards to ensure that these individuals are adequately protected.* Not applicable. See above.

8. **Describe the exact plan how subjects will be identified and recruited for the study**. Patient selection for the study will be based on the criteria described in above sections. To summarize, we will run the electronic query to identify age-eligible veterans who had received medical care at CMCVAMC in the 18-48 months prior to the start of our study and not currently up-to-date on CRC screening in the beginning of 2016. We will obtain PCP approval, through discussion at scheduled clinical and program meetings with support from Dr. Tzanis, for participation and to confirm the inclusion and exclusion criteria. There are an estimated 3,388 potentially eligible veterans for this pilot, and we plan to randomize 783 patients.
   a. *Discuss methods, e.g., referrals from physician offices, clinics, programs, or through advertisements and brochures.* We will obtain PCP approval, through discussion at scheduled clinical and program meetings with support from Dr. Tzanis, for participation and to confirm the inclusion and exclusion criteria.
   b. *If using a clinic, be specific about who will identify the potential subject and how that information will be transmitted to the research staff.* Not applicable
   c. *If snowball method will be used, discuss the process and how the first individuals will be recruited.* Not applicable
   d. *Describe how information will be disseminated to subjects, e.g. handouts, brochures, flyers and advertisements (include all recruitment materials with this submission).* The information to be sent to subjects will be included as part of the outreach kit

9. **Informed Consent**
   a. *Informed Consent will not be sought.* ☐
   b. *Written informed consent from participants (VA Form 10-1086 is attached).* ☒ Note: We are submitting the Oral Informed Consent Form instead of Written Form10-1086.
   c. *Written informed consent from participants' legally authorized representative (LAR) as required by VA policy and/or applicable state laws (VA Form 10-1086 is attached).* ☐
   d. *Request Waiver of Documentation of Informed Consent* ☒
   e. *List the title of the key personnel involved in the following activities*:
      i. Person Obtaining Consent
         (a)) Research Assistants
            (i) Type of training received to perform this process: Research Assistant will be trained in the study procedures and have appropriate VA appointment including required VA information security training and have Human Subjects certification
      ii. *Pre-Recruitment Screening (the use of medical records and other data bases to determine populations and individuals eligible for the study).* We will use the medical records to prescreen patients for eligibility for the study based on the criteria described above
      iii. *Recruitment Process (the process in which individuals are contacted and first introduced to the study and to the possibility of participating as subjects):* Not applicable
      iv. *Informed Consent Process (the process by which recruited subjects are fully informed about participating in the study and then formally give their voluntary consent for participating),* We waiver of informed consent above.

v. *Screening of Recruited Subjects (those activities in the protocol in which a final determination of eligibility of prospective subjects is made during the early phases of the study, using laboratory data, inclusion and exclusion criteria, and other person-specific information),* The final decision on eligibility will be based on review of EMR/CPRS.

vi. *Include the breakdown of each individual's responsibilities:*
   (a) *Principal Investigator*, Supervision
   (b) *Co-Principal Investigator*, Supervision and selection of sample
   (c) *Research Assistants*, Determining eligibility through CPRS audits and, obtaining oral informed consent, and conducting phone interviews
   (d) Additional research staff by title, Dataset Manager/Analyst will select a list of potentially eligible patients from CPRS

f. *Will informed consent be obtained from potential subjects prior to determining eligibility?* ☐YES ☒NO ☐N/A
   i. *If no, provide justification and a HIPAA Waiver of Individual Authorization for Disclosure of Protected Health Information.* It will not be feasible to obtain informed consent on over 3,000 patients prior to determining eligibility. The study involves procedures that are used in routine clincal care

g. *Define when a subject is enrolled into the study, e.g. after the subject signs the informed consent or after randomized to treatment.* Once a subject is randomized, they are considered enrolled on the study.

h. Describe:
   i. *The process when informed consent will be obtained and protecting patients' privacy.* not applicable, waiver of informed consent obtained
   ii. *Any waiting period between informing the prospective participant and obtaining consent.* not applicable, see above
   iii. *Steps taken to minimize the possibility of coercion or undue influence.* No compensation is provided.

i. Provide the language
   i. *Used by those obtaining consent* not applicable
   ii. *Understood by the prospective participant or the legally authorized representative* English or Spanish

j. Provide location where informed consent will be obtained. not applicable

10. Waiver or Alteration of Informed Consent Requirements/Waiver of Requirement to Obtain Documentation of Informed Consent

a. Are you requesting a waiver or alteration of informed consent? (Check all that apply)
   i. No ☐
   ii. Yes; provide justification. ☒ This research involves no more than minimal risk. The procedures to be used involve methods that are currently the standard of care for delivering colorectal cancer screening in the VA and in a variety of other settings. Thus, the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. The study offers a net benefit in increasing the reach of screening to veterans. We will also enhance the current practices of screening by informing patients by phone of test results with a dedicated staff. Therefore, a waiver will not adversely affect the rights and welfare of the subjects. The research cannot be practically carried out without the waiver. In this pragmatic study, we are seeking to determine optimal approaches to deliver colorectal cancer screening. Getting consent will inherently make the research infeasible and alter the design because individuals who consent to participate will likely represent those willing to return the kits. We will therefore

not be able to learn from those unwilling to participate in screening, a priority for the VA. This will lead to a serious selection bias and lead to a fatal flaw in the study. The bias occurs because only subjects interested in colorectal cancer screening will likely consent. This will undermine our ability to test the hypotheses. We are interested in the proportion of individuals who respond to the invitation to screen. Subjects will receive additional pertinent information about the study. For instance, all selected subjects will receive information about CRC screening including the testing options (see attached for examples). This pilot program is designed to effectiveness of mailed FIT outreach to increase the use of screening in the VA, compared to the current usual care.

b. Yes; for recruitment purposes only. ☐
   i. An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:
      (a) ☒ 1. The research involves no more than minimal risk to the subjects;
      (b) ☒ 2. The waiver or alteration will not adversely affect the rights and welfare of the subjects;
      (c) ☒ 3. The research could not practicably be carried out without the waiver or alteration; and
      (d) ☒ 4. Whenever appropriate, the subjects will be provided with additional pertinent information after participation
      (e) ☐ 5. The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine:
         (i) Public benefit or service programs;
         (ii) Procedures for obtaining benefits or services under those programs;
         (iii) Possible changes in or alternatives to those programs or procedures; or
         (iv) Possible changes in methods or levels of payment for benefits or services under those programs.

c. Are you requesting a waiver to obtain documentation of informed consent?
   i. No ☐
   ii. Yes; provide justification. ☒
      (a) An IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds either:
         (i) ☐ 1. That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or
         (ii) ☒ 2. That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.
         (iii) *NOTE: In cases in which the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research.*

S. Compensation *(The amount of compensation may not constitute an undue inducement to participate in the research.)*
   1. Summarize any financial compensation that will be offered to subjects. There is no financial or other compensation provided for participation in the study

2. Provide the schedule for compensation. No compensation is provided
   a. Per study visit or session. None
   b. Total amount for entire participation. None
3. Explain how compensation will be provided via cash, voucher, gift card, etc. Not applicable
4. If financial compensation will be prorated, explain the process. Not applicable
5. Not Applicable - ☒

T. Withdrawal/Early Withdrawal

1. **Describe how and when a subject may withdraw from the study**. Those included in the pragmatic trial will be asked to contact the office to report their eligibility status. It is not uncommon in screening programs for some subjects to opt out of screening. The usual approach is to place such subjects on a 'do not contact' list for the specific program. We will adopt this approach for the proposed program. Subjects contacted 6 months after baseline can withdraw from participation by stopping the survey questions at any time.
2. **Provide procedures for the orderly termination of participation by the participant and if any consequences would result from early withdrawal from the study.** There are no consequences associated with withdrawal from the study. Subjects will be advised when called that they can withdraw from the study at any time.
3. **Explain if survival data is required.** If so, clarify how data will be obtained. Not required
4. Not Applicable; subjects not recruited; chart review. ☐

U. Risk/Benefit Assessment

1. Potential Study Risks

a. Describe and assess all of the following risks that may be associated with the research:
   i. *Physical* There is no risk of physical harm to participants
   ii. *Psychological* There is minimal risk of psychological harm resulting from receiving a positive screening result. This may create anxiety about diagnosis with cancer. We are addressing this by training the Research Assistants to facilitate timely scheduling of diagnostic colonoscopy. The Research Assistants will also be trained to elicit any concerns the patient may have and encourage the patient to schedule the appointment. We will also track patients with positive results to ensure that diagnostic testing is performed and coordinate our efforts with primary care doctors to ensure that diagnostic work up is addressed by the primary care doctor.
   iii. *Social* There is minimal to no risk of social harm from this study
   iv. *Economic* There is minimal to no risk of economic harm. Early detection of CRC may provide economic benefit from the averted cost and morbidity of late-stage cancer treatment.
   v. *Monetary* None
   vi. *Legal* None
   vii. *Loss of confidentiality.* There is a small risk of loss of confidentiality if PHI or study materials are inadvertently disclosed or stolen. In discussing with the CMCVAMC Lab Director, using an order number may be sufficient for the purposes of identifying the patient. We will explore this option, but also ensure that our procedures are JCAHO-compliant.
   viii. *Assess the likelihood and seriousness of such risks.* This is addressed under each section above.
   ix. Other

b. *Specify what steps will be taken to minimize these risks.* We address the small and minimal risk of psychological distress by helping to schedule a colonoscopy in the earliest available timeslot. We will reduce the risk of loss of confidentiality by following VA information security procedure for data safety. We will use VA procedure to mail kits to patients. The crosswalk file containing patient study identification numbers will be kept in a secure location in password-protected drives, and only trained authorized personnel will be allowed access to the patient data. Permissions of research staff on the project will be reviewed periodically to ensure that are consistent with each individual's job description. There is also the risk of loss of confidentiality while the test is being mailed to patients. However, our methods are routinely used in clinical settings including the VHA and we will use VA approved mailing methods.

c. *If methods of research create potential risks, describe other methods, if any, that were considered and why they will not be used.* Our methods represent minimal risk to patients, the study itself will be conducted within the existing CMCVAMC CRC screening program

d. *If chart review, breach of confidentiality is always a concern. Specify what steps will be taken to minimize these risks.* As outlined above, we will adhere strictly to VA privacy policy and all research staff will have appropriate VA appointment and receive VA Privacy and Information Security Awareness training; all data will be stored in secure password-protected drives with access granted to authorize staff. Identifiable data will not be allowed to be removed from the VA and only de-identified data will be stored in research files at CHERP, CMCVAMC Center Annex (3900 Woodland Drive) Suite 202, file room 235 Philadelphia, PA 19104.

2. Potential Study Benefits

a. *Assess the potential benefits to be gained by the individual subject, as well as benefits that may accrue to society in general as a result of the planned work.* CRC is potentially preventable through screening and the VA recommends the use of the FIT, which is inexpensive and has high sensitivity and specificity for detecting cancers early, and hence decreases the risk of CRC death. This is particularly important for minority populations who are at higher risk for the disease but may be less likely to be screened. This study provides a simple and inexpensive way to screen individuals in a way that is non-invasive and may appear less threatening to individuals than colonoscopy. Our proposed approach can reach individuals who are less likely to have regular medical visits and thus may be at risk for developing later-stage cancers if undetected, unlike current strategies. Thus, there is substantial potential benefit from the project and the risks to participants are minimal.

b. *If the subject does not receive any direct benefit, then it must be stated here and in the consent form.* Early cancer detection will be highly beneficial to patients

3. Alternate Procedures

a. *Describe the alternatives available to the subject outside the research context.* Subjects can receive screening for colorectal cancer outside this program. Subjects' ability to do so will not be restricted by the study.

b. *If none, state that the alternative is not to take part in this research study at all.* Not applicable

V. Data and Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC) (All Phase III studies are required to have a DSMB. *However, the IRB has the right to require a DSMB with any study.)*

1. Will an independent DSMB or DMC oversee the project? ☐YES ☐NO ☒N/A

a. If yes, please provide contact information for the DSMB or DMC or Coordinating Center Representative and attach a copy of the charter.
   i. Name: Phone Number:
   ii. Title: E-mail:

2. If a DSMB or DMC will not monitor this study, who will monitor this study? Check all that apply.
   a. ☒ Principal Investigator
   b. ☐ Sponsor
   c. ☐ VA Cooperative Studies Program
   d. ☐ Safety monitoring committee

W. Data Monitoring (*Monitoring plans describe how a monitor, independent of the study team, regularly inspects study records to ensure the study is adhering to the study protocol and applicable research regulations and CMCVAMC requirements. Monitoring plans do not necessarily require the use of an independent Data and Safety Monitoring Board (DSMB). Such independent boards are usually reserved for high-risk phase I studies, or large, multi-center phase III trials. Federally funded studies may require the use of an independent DSMB.)*

1. **Describe the data monitoring plan**. (All protocols must have a data monitoring plan appropriate for the potential risks and the complexity of the study.) The PI in collaboration with the co-Investigators will monitor the study's data. We will review the progress of the study quarterly to evaluate adherence to policy and overall progress. We will review the overall progress of the study, ascertain how many subjects are identified/recruited, ascertain response rates, and assess the ability to reach patients. Because this is NOT a study that involves an investigational drug or device, there will be no DSMB. However, we will make every effort to ensure the safety of all data collected. There is precedence for use of EMR in clinical and observational studies. Thus, procedures for protecting patient data have become enhanced. The PI will provide oversight for all data collection and analysis procedures. Research staff will have human subject's certification through the Collaborative Institutional Training Initiative (CITI) and will be responsible for maintaining and updating a tracking REDCap database of screen-eligible individuals. Research staff will also have appropriate VA appointments such as a WOC and be required to complete VA Privacy and Information Security Awareness training and included in the IRB protocol before beginning study activities. The PI and a database manager will regularly monitor the database. In addition, research staff will assist in conducting regular data checks to ensure the accuracy of the data collected. Only authorized staff will be provided access via password to study databases. Additional oversight will be provided through the IRB at the VA. Any adverse events, e.g. evidence of severe psychological distress as a result of news of a positive test result, will be immediately reported to study investigators and to the IRB within 24 hours of its occurrence in accordance with IRB guidelines and VA rules.
2. **Describe how protocol deviations, adverse events, serious adverse events, breaches of confidentiality, unanticipated adverse device effect (UADE), and unanticipated or unexpected problems will be reported to the CMCVAMC IRB and sponsor.** *(Refer to the CMCVAMC IRB Standard Operating Procedure (SOP) Manual for reporting guidelines.)* Any breach of confidentiality, unanticipated problems, or protocol deviations will be reported to the IRB within 1 hour of it becoming known to the PI, and appropriate actions as directed by the IRB including additional staff training will be undertaken.
   a. *Describe the management of information obtain that might be relevant to participant protections such as:*

i. *Unanticipated problems involving risks to subjects or others:* Any unanticipated problems such as psychological problems in a subject will be reported to the IRB within 1 hour and if necessary, patients will be referred to the appropriate clinical services.
ii. *Interim results:* This is a 1-year study. Screening for CRC using FIT is recommended once every year. Thus, there will be no need for interim analysis. If however our results show that screening using the outreach approach is more effective than with current usual practice, the procedures under study is likely to be adopted for routine clinical practice.
iii. *Protocol modifications:* When needed, we will seek modification of the protocol to make such changes as increase the number of study subjects, add a new procedure, or to add or remove staff.

3. If applicable, define the plan for subjects if research shows results such as:

a. *Depression* There is a minimal risk of subjects developing or reporting depression as a result of our study. However, if it occurs, the research assistants will be trained as part of our standard operating procedures to refer the patient for mental health services at the CMCVAMC.
b. *Suicide* There is minimal to no risk of suicide occurring as a result of the study.
c. *Abuse* There is minimal to no risk of abuse being detected during the course of this study.

4. Statistical Analysis

a. *Include statistical power calculations and the assumptions made in making these calculations.* Gupta et al. found that, among underserved patients in Dallas, 40% of those assigned to mailed-FIT completed screening compared to 12% in UC. In our power and sample size analysis, we assumed 15% screening rate in UC alone, 25% with invitation- reminders, and 40% with mailed FIT. With those assumptions, a total sample size of 500 (250 per arm) will give 80% power for UC vs. screening invitation-reminder, and 152 patients per arm will give a power of 80% for the screening invitation-reminder vs. mailed-FIT. Accounting for the possibility that up to 20% of participants could be ineligible post-randomization, we will recruit about 783patients for the pragmatic trial.
b. *Define plans for data and statistical analysis, including key elements of the statistical plan, stopping rules and endpoints.* We will use Chi-squared statistic to test the null hypothesis that the completion rates between the mailed-FIT and UC and between mailed-FIT and invitation-reminder are equal using an "intention-to-treat" approach. All tests will be based on a 2-sided alpha of 0.05. We will examine the distribution of test types to assess whether there are large enough numbers of patients receiving tests other than FIT to warrant examining "receipt of any CRC screening test" as an outcome. We will assess the association of age and race/ethnicity with the completion of mailed FIT (dependent variable) among recipients of the mailed FIT test using logistic regression. We will focus primarily on age categorized as 50-64 vs. 65+ and race/ethnicity as predictors, controlling for socio-demographic covariates such as marital status and other factors such as sex. Our rationale is that a VA study found that screening use differed by age and was lower among persons of black race, which is consistent with our own experience. This analysis will allow us to understand if there are patient groups that may need specific targeted outreach when the program is fully implemented, and if larger sample sizes will be needed. We will use both univariate and multivariable logistic regression analyses (2-sided alpha of 0.05) to examine associations of patient characteristics and sociodemographic measures with the outcome of FIT completion. The primary approach will be 'intention-to-treat' analysis and additional analyses will be restricted

to those with valid addresses. In future studies, we will be able to investigate the relation of other factors such as socioeconomic status and place of residence on completion rate of mailed kits, as well as seasonality effects. A valid participant address is needed to conduct outreach to patients. Thus, it is important to characterize the proportion of invitees whose mail was returned due to bad addresses or were unreachable. We will seek to verify addresses of returned mail by calling participants. We will also generate a report of the screening practices and potential variation in rates of screening across the VA, and relate those to the patterns of testing and screening rates and screening outcomes in the VA.

X. **Privacy and Confidentiality** *(Privacy refers to persons and to their interest in controlling the access of others to themselves.) (Confidentiality refers to protecting information from unauthorized disclosure or intelligible interception.) (Investigator should contact the Privacy Officer for additional details.)*

1. Indicate the type of data that will be received by the Principal Investigator. Check all that apply.
   a. ☐ De-identified – Without any identifiers that could link the data to a specific participant. (Contact Privacy Officer for assistance. *If data is coded, it is not considered de-identified.)*
   b. ☒ Identified – Linked to a specific participant by identifiers sufficient to identify participants. (See HIPAA and Common Rule Criteria for list of identifiers.)
   c. ☒ Coded – Linked to a specific subject by a code rather than a direct identifier. If coded is checked, specify:
      i. *Explain who will maintain the link or code.* The code for identifying study subjects will be kept by the analyst/programmer and the PI
      ii. *Describe who will have access to the link or code.* Only the PI, Drs. Doubeni, Richardson, and the Dataset Manager/Analyst will have access to the code. All other staff will be granted access only when needed to identify specific research subject for purposes of obtaining data or cleaning data.
      iii. *Provide exact details for how the data is coded.* The study data will contain identifiers. However, analytic data will be stripped of all identifiers. Each subject will be identified using an encrypted unique identification number. The code or crosswalk file will be stored by the PI and the Dataset Manager/Analyst in a secure password-protected location.
2. **Does the project require the use of existing Protected Health Information (PHI) from a database, medical records, or research records?** ☒YES ☐NO ☐N/A
   a. If yes,
      i. *Specify the source of the existing PHI Clinical records in CPRS.* We will also use the screening database used by Dr. Abraham Dubb.
      ii. Indicate the specific data elements/identifiers (e.g., name, address, phone numbers, etc.) on the below table.
   b. If the study uses an existing database/data warehouse,
      i. *Provide a description of the database/data warehouse.* The study will use VistA/CPRS supplemented by a clinical screening REDCap database used by Dr. Dubb to identify patients and their screening history
      ii. *Make clear who is responsible for maintaining it.* The REDCap database will be maintained by the Dataset Manager/Analyst with guidance from the PI in consultation with Dr. Abraham Dubb
      iii. *Cite any relevant Standard Operating Procedures (SOP) for the database/data warehouse.* These are existing VA standard databases
      iv. *Provide a copy of the SOP.* These are existing VA standard databases
3. **Will PHI be collected prior to obtaining informed consent?** ☒YES ☐NO ☐N/A

a. If yes, complete and provide a HIPAA Waiver of Individual Authorization for Disclosure of Protected Health Information with this submission.

4. HIPAA Identifiers - Indicate the PHI that will be collected from project participants directly or indirectly.
   a. ☒ Name
   b. ☒ All geographic subdivisions smaller than a State, including street address, city, county, precinct, zip code, and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly available data from the Bureau of the Census
   c. ☒ All elements of dates (except year) for dates directly related to an individual, and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older.
      i. ☒ Birth Date ☐ Date of Death
      ii. ☐ Discharge date ☐ Admission date
      iii. ☒ Appointment Dates ☒ Other Dates (e.g. lab tests, x-rays, MRI, etc.)
   d. ☒ Telephone numbers
   e. ☐ Fax numbers
   f. ☐ Electronic mail addresses ☒ Social Security Number
   g. ☒ Medical record numbers
   h. ☐ Health plan beneficiary numbers
   i. ☐ Account Numbers
   j. ☐ Certificate/license numbers
   k. ☐ Vehicle identifiers and serial numbers, including license plate numbers
   l. ☐ Device identifiers and serial numbers
   m. ☐ Web universal resource locators (URLS)
   n. ☐ Internet protocol (IP) address numbers
   o. ☐ Biometric identifiers, including fingerprints, voiceprints, audio recordings
   p. ☐ Full-face photographic images and any comparable images
   q. ☐ Any other unique identifying number, characteristic, or code
   r. ☐ Personal and Family History
   s. ☐ History and Physical Examination ☐ Progress Notes
   t. ☐ Discharge Summary(ies) ☐ Photographs, videotapes, other images
   u. ☐ X-Ray ☐ HIV (testing or infectious disease) records
   v. ☐ Diagnostic/Laboratory tests ☐ Sickle cell anemia
   w. ☐ Drug Abuse Information ☐ Behavioral Health notes
   x. ☐ Alcoholism or Alcohol Use ☐ Operative Reports
   y. ☐ Billing records ☐ Medication List
   z. ☐ Health Summary Reports ☐ Anatomic Pathology Report
   aa. ☐ Other Records:

5. **Will participants be contacted from existing PHI?** ☒YES ☐NO ☐N/A
   a. If yes, clearly explain how participants will be contacted (NOTE: this would be the same information as listed under section R.8 identification and recruitment of subjects). Patient selection for the study will be based on the criteria described in above sections. To summarize, we will run the electronic query to identify age-eligible veterans who had received medical care at CMCVAMC in the 18-48 months prior to the start of our study and not currently up-to-date on CRC screening in the beginning of 2016. We will obtain PCP approval, through discussion at scheduled clinical and program meetings with support from Dr. Tzanis, for participation and to

confirm the inclusion and exclusion criteria. There are an estimated 3,388 potentially eligible veterans for this pilot, and we plan to randomize 783 patients.

6. *Provide the titles of the exact individuals who will have access to the collected data.* Principal Investigator, Co-Investigator, Statistician, Dataset Manager/Analyst, Research Assistants
   a. *Explain why these individual will have access to this data.* These individuals need access to the data for purposes of collecting, analyzing, interpreting, and disseminating the results

Y. Information Security (*Contact the Information Security Officer for additional assistance regarding confidentiality (storage/security) of research data.)*

1. **Provide the precise plan how data is to be collected or acquired (repeat the same information as listed under "Data Collection" section of this form.** Patients will be block-randomized to UC, invitation-reminder, or mailed-FIT with guidance from Dr. Richardson to achieve the desired sample size. We will mail all study materials to patients during Months 3-5 of the study in weekly waves of about 50 mailings; with this volume, it is feasible for us to confirm eligibility through chart audits prior to mailing invitations to study participants.
   a. Participants randomized to UC: These patients will continue to receive the current practice at CMCVAMC of offering screening during an office visit. Other interventions will be embedded within this existing program for a pragmatic approach. However, all participants in the trial, including those in UC, will receive follow-up of test results and navigation to diagnostic colonoscopy for positive FIT results.
   b. Participants randomized to screening invitation-reminder: These patients will continue to receive UC. They will in addition receive an invitation letter with all of the information about CRC testing in the mail-FIT arm (except the kit and instructions, see below). The information will include lay-audience description of screening tests such as FIT and colonoscopy and, if appropriate, Cologuard (sigmoidoscopy is not offered at CMCVAMC), and symptoms that should prompt diagnostic work-up such as change in bowel habit with rectal bleeding. The packet will also have a screening confirmation card and have instructions to contact the study team if the patient believes he/she is not eligible and to update the contact information on record. The letter will inform patients that a telephone reminder will follow in 4 weeks from invitation letter if screening is not completed (even if they have an appointment scheduled). They will receive three weekly reminders at weeks 4, 5, and 6 from the invitation letter. They will also receive notification of test results and navigation to colonoscopy, if needed. For the purposes of this intervention, Week 1 will be the week the invitation letter was sent (time zero). It is generally unclear whether mail reminders may be more effective at reaching veterans than phone calls because telephone numbers may change or run out of purchased minutes, but addresses may also change or a veteran may be homeless. Thus, we will also explore sending mailed reminders when participants cannot be reached by phone and track the success of each approach used during the study.
   c. Participants randomized to Mailed-FIT will receive a mailed FIT pre-notification letter (plus a screening invitation and screening confirmation card) followed by the kit 1 week later (see section D2d2). Patients will receive instructions to contact the study team if the patient believes he/she is not eligible and to update the contact information on record. They will be informed that a telephone reminder will follow 4 weeks from notification letter if screening is not completed. Patients who do not return their kit after 4 weeks of the date the pre-notification letter was mailed will receive a live telephone reminder (even if they have an appointment scheduled, as with the invitation-reminder arm), followed by 2 additional calls at the end of weeks 5

and 6, if needed.82 For the purposes of this intervention, Week 1 will be the week the pre-notification letter was sent (time zero). We will explore and evaluate the approaches for successfully contacting participants in our study setting.

d. Unless otherwise specified, data collection will be performed by a research assistant under the supervision of the PI in collaboration with Dr. Doubeni.
e. The Dataset Manager/Analyst will perform analysis on the study with guidance from the PI and Drs. Richardson and Doubeni.
f. The research data obtained will be stripped of all identifiers prior to analysis at the CHERP.

2. **Provide a listing of the exact research data that will be stored, including but not limited to signed, original informed consent and HIPAA authorization forms, case report forms, etc.**

The data to be collected are listed below in the table

Measures	Definition and elements
Socio-demographics	Age, sex, race/ethnicity, education/SES/geocode, marital status
Contact information	Address, phone, next of kin, emergency contact, whether address is invalid
Access/Healthcare utilization	PCP (name/type), usual place of care, visit history, transportation
Eligibility for outreach	Eligible (Y/N), ineligibility reason and duration (permanently ineligible due to age, colectomy, IBD, CRC history, etc., or year when becomes eligible again
Risk factors/symptoms	Height/weight, family history, etc., GI symptoms
Screening history	Prior colonoscopy/sigmoidoscopy/FOBT/barium enema date and reason
Mailed introductory letter	Notified to expect the kit/general information about screening and CRC symptoms
Mailed kit	Dates FIT was mailed, date received
Reminders	Dates of reminders to return kit with a flag for those ineligible
Refusals	Date and reasons for refusal
Test collection	Date sample was collected by patient
Date test received and tested	Date kit was received and date tested (goal is within 72 hours)
Received some other screening	Received colonoscopy or other test instead of returning FIT, and results
FIT result/notification	Result (positive, negative, or incomplete), patient and provider notification dates and methods (mail, phone, electronic), and entry into EMR
Diagnostic testing	Receipt of colonoscopy for positive FIT, and results
Detected lesions	Number and types of lesions detected
Ambient temperatures	Ambient temperature on collection and receipt date from NOAA databases
Cancer registry (linkage only)	Date, stage, morphology, behavior, grade, & location

3. **/ndicate how project's research data (original and all copies) will be stored and provide corresponding security systems.** All data will be stored in secure network drive \\vhaphicherpnas\shares2 at the CMCVAMC/VHA. The location will be password-protected and will be only accessible to the PI, analysts and other authorized research team members. A master copy will be stored and copies created for analytical purposes.

Paper copies will be stored at the CMCVAMC CHERP: Center Annex Suite 202, File Room 235, 3900 Woodland Drive, Philadelphia, PA 19104 All data storage procedures will be conducted in accordance with VA privacy policies

4. **CMCVAMC, provide exact location where research data (original and all copies) will be stored and secured.** Identifiable data will remain behind firewalls at the CMCVAMV. De-identified research data will be stored in the VA Informatics and Computing Infrastructure [VINCI] server workspace under the auspices of the Center for Health Equity Research and Promotion (CHERP), Center Annex (3900 Woodland Avenue Philadelphia, PA 19104) Suite 202 Cubicle #9.
5. **Explain how data is to be transported or transmitted from one location to another.** Data will not be transmitted, but rather stored in network drives that are accessible from within the VA, both at the main campus and at CHERP at the Philadelphia VA Medical Center Annex
   a. Informed Consent discloses PHI transported or transmitted off-site. ☐YES ☒NO ☐N/A
   b. HIPAA Authorization discloses entities to which PHI will be transported or transmitted. ☐YES ☒NO ☐N/A
      i. List all entities or individuals outside CMCVAMC to whom data is to be disclosed, and the justification for such disclosure and the authority.
   c. If yes, list the exact data that will be transmitted. Not applicable
   d. If yes, explain how data will be protected during transmission outside of CMCVAMC. Not applicable
   e. Off-site, provide exact location Not applicable (If off-site, attach at least one of the following.)
      i. Data Use/Transfer Agreement ☐YES ☐NO ☒N/A
      ii. Off-Site Storage/Transfer of Research Data ☐YES ☐NO ☒N/A
      iii. Memorandum of Understanding ☐YES ☐NO ☒N/A
      iv. (Note: VA data disclosed to a non-VA investigator at an academic affiliate for research purposes needs to be approved by the Under Secretary of Health or designee.)
6. **List who is to have access to the data and how they are to access it (anyone who has access to the data is responsible for its security).**
   a. Paulson, E. Carter
   b. Doubeni, Chyke
   c. Richardson, Diane M.
   d. Dataset Manager/Analyst
   e. Research Assistants
   f.
7. **Describe who is to have access and be responsible for the security of the information** (e.g., the Coordinating Center, the statistician, and PI who has ultimate responsibility). The PI, dataset manager/analyst, statistician (Diane M. Richardson), Dr. Doubeni
8. **Provide mechanisms used to account for the information.** The PI and dataset manager/analyst will control who has access to the data. They will assign permissions on the shared folder. Regular reviews will be conducted to ensure that appropriate permissions remain in place.
9. **Give security measures that must be in place to protect individually identifiable information if collected or used.** The use of identifiable information will follow VA privacy policies. We will seek guidance from the privacy officer when needed to develop these policies. Identifiable information will be used only for the approved purposes.

10. **How and to whom a suspected or confirmed loss of VA information is to be reported.** Any suspected or confirmed loss of information will be reported by phone and letter to the IRB chair and VA privacy officer within 1 hour.
11. **Identify any circumstances that may warrant special safeguards to protect the rights and welfare of subjects who are likely to be vulnerable including, but not limited to, those subjects who may be susceptible to coercion or undue influence, and describe appropriate actions to provide such safeguards.** This study does not involve vulnerable populations. All subjects will receive the same information and/intervention based on the study arm each subject is assigned to.
12. **Electronic PHI will be stored on the following:**
    a. CMCVAMC desktop computer with password protection and/or encryption. ☐YES ☒NO ☐N/A
        i. If yes, identify where the desktop is located.
    b. CMCVAMC secure server. ☒YES ☐NO ☐N/A
        i. If yes, identify the CMCVAMC server. VA Informatics and Computing Infrastructure [VINCI] server workspace. Exact server address will be named and added to an amended protocol for IRB review prior to the start of research.
        ii. External drive that is password protected and/or encrypted. ☐YES ☒NO ☐ N/A
            (a) If yes, identify the external drive.
    c. Off-Site server ☐YES ☒NO ☐N/A (If off-site, attach at least one of the following.)
        i. Provide exact location and the name of the off-site server.
        ii. Data Use/Transfer Agreement ☐YES ☐NO ☐N/A
        iii. Off-Site Storage/Transfer of Research Data ☐YES ☐NO ☐N/A
        iv. Memorandum of Understanding ☐YES ☐NO ☐N/A
13. **Explain how data is to be transported or transmitted from one location to another.** Not applicable
14. **Informed Consent discloses PHI transported or transmitted off-site.** ☐YES ☒NO ☐N/A
15. **HIPAA Authorization discloses entities to which PHI will be transported or transmitted.** ☐YES ☒NO ☐N/A
16. **List all entities or individuals outside CMCVAMC to whom data is to be disclosed, and the justification for such disclosure and the authority.** Not applicable
17. **Clarify what protection exists for a database.** The servers reside behind the VA firewall and are entirely compliant with Federal Information Security Management Act (FISMA) standards.
    a. Data is stored:
        i. With identifiers - ☐YES ☒NO
        ii. Coded - ☒YES ☐NO
        iii. De-Identified - ☒YES ☐NO
        iv. Provide the exact list of identifiers that will be stored. Encrypted study identification numbers
18. **Describe the plan for protecting research data from improper use or disclosure.** All research data will be stored in password-protected secure drives in which there are user-level access control provided.
    a. The Investigator must notify the Information Security Officer, Privacy Officer, and IRB. Associate Chief of Staff for Research and Research Compliance Officer within one hour of the improper use or disclosure.
19. **Is there a plan to apply for a Certificate of Confidentiality?** ☐YES ☒NO ☐N/A
    a. If yes, provide a copy of the certificate with this application or to the IRB Office as soon as received.

20. Record Retention:

a. The required records, including the investigator's research records, must be retained until disposition instructions are approved by the National Archives and Records Administration and are published in VHA's Records Control Schedule (RCS 10-1). VHA Handbook 1200.05 §26.h
b. Until a schedule for local research records is published, ALL records including identifiers must be retained." ORO/ORD Guidance on Informed Consent Form Modifications Addressing VA Record Retention Requirements (July 23, 2009)
c. If there are additional procedures for record retention, explain further.

Z. Qualification of the Investigators:

1. Provide a description of the qualifications of each Investigator/Co-Investigator and their specific role in the study.

a. E. Carter Paulson, MD, MSCE is the PI of the project. She is an Assistant Professor in the Perelman School of Medicine at the University of Pennsylvania (UPenn) and a member of the Department of General Surgery at CMCVAMC with clinical practice in colorectal surgery. She is a clinical epidemiologist whose research focuses on processes of care and outcomes on CRC, including at the VA.
b. Chyke A. Doubeni, MD, FRCS, MPH (Co-Investigator) is board-certified in both general preventive medicine/public health and family medicine, is Chair of the Department of Family Medicine and Community Health in the Perelman School of Medicine at Upenn, full member of the Abramson Cancer Center at Penn, and is multiple PI and chair of the CRC working group of the PROSPR (Prospective Research Optimizing Screening through Personalized Regimens) Research Center at Kaiser Permanente. His research focuses on health disparities, the effectiveness of screening, and improving the screening process for CRC.
c. Diane M. Richardson, PhD (Co-Investigator/Statistician) is Co-Chief of the Biostatistics and Informatics Core, Core Investigator and Lead Biostatistician at the VA Center for Health Equity Research and Promotion, PI for a VA comparative effectiveness study of influenza vaccination, and a statistical collaborator and Co-investigator for several studies evaluating healthcare quality and disparities in outcomes. She has expertise in analyses of longitudinal and multilevel data, and design and analysis of RCTs.

2. **If applicable, the Principal Investigator must identify a qualified clinician to be responsible for all study related healthcare decisions.** Drs. George Tzanis and Abraham Dubb
3. **PI should submit a current, dated CV with each new initial review.**