Protocol & Statistical Analysis Plan for:

Pragmatic Trial of Behavioral Interventions to Increase Response to Mailed FIT Outreach

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Brief Description

This project aims to evaluate different approaches to increase colorectal cancer screening among primary care patients at Penn Medicine through a centralized screening outreach program. In a pragmatic trial, we will evaluate different approaches to increase response rate to mailed fecal immunochemical test (FIT) kits among eligible patients, including differentiated packaging, sending text reminders, and personalized reminders.

Protocol

Abstract

While colonoscopy procedures are recommended by guidelines for early detection of colorectal cancer, colonoscopy access remains limited due to delays in screening due to the pandemic and capacity issues. In this project, we will evaluate different ways of reaching out to eligible patients to encourage them to participate in colorectal cancer screening using fecal immunochemical testing (FIT). In a mailed FIT outreach campaign, we will compare user friendly packaging, text messaging, and personalized reminders to standard outreach with the goal of increasing colorectal cancer screening uptake.

Study Instruments

N/A

Group Modifications

N/A

Method for Assigning Subjects to Groups

We will randomize patients in a 2 x 2 x 2 factorial design. Eligible patients will be randomized in a 1:1 ratio (stratified by practice) to receive a standard mailing envelope or a Penn Medicine-branded blue box highlighting the importance of screening.

In a factorial design, patients will concurrently be randomized in a 1:1 ratio (stratified by box arm and practice) to receive text messaging in addition to the standard messaging. Text messaging will include a series of messaging about the importance of CRC screening, the recommendation from the PCP, and an opportunity for feedback.

In a factorial design, we will concurrently randomize patients in a 1:1 ratio (stratified by box, text arm and practice) to receive a mailed reminder letter signed by the PCP if they do not respond after 1 month of initial outreach.

Administration of Surveys and/or Process

We plan to start enrollment in April 2022. We will then follow patients for 6 months after initial outreach.

Data Management
Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Source documents are maintained in PennChart. No source documents will be printed or maintained in paper form at the study site. Data from PennChart will be recorded in Penn Medicine's REDCap system. The investigator and study team will have access to PHI within PennChart and REDCap. We will label all PHI within REDCap as identifiable information so that de-identified exports are possible. All reports that include identifiable information will be stored on the Innovation Center secure drive, maintained behind the UPHS firewall. Direct identifiers will be maintained on RedCap until manuscript publication in case additional chart review is needed for confirmation of results. Once data analysis and manuscripts have been published, direct identifiers will be deleted from RedCap and the de-identified database will be stored on the Innovation Center secure drive.

Objectives

Overall objectives

In addition to providing direct outreach to patients in included practices, we have the following aims:

Aim 1: To evaluate if a differentiated box increases uptake of mailed FIT

Aim 2: To evaluate if text messaging could increase uptake for mailed FIT

Aim 3: To evaluate if sending personalized reminders increases uptake

Primary outcome variable(s)

The primary outcome will be the percentage of patients who complete FIT within 4 months of outreach.

Secondary outcome variable(s)

Secondary outcomes will be completion of FIT within 6 months, and completion of any CRC screening within 4 and 6 months. We will also track what percentage of the completed FIT that have positive results and schedule and complete colonoscopy, as well as the results of the procedure (adenoma, advanced adenoma, cancer). We will compare response rates by age, race/ethnicity, insurance, income (by zip code), MyPennMedicine status, and completion of prior CRC screening. We will also compare colorectal cancer screening completion of the patients in the trial to patients in similar practices that were not included in the trial to understand the effect size for outreach compared to no outreach. We will use the same inclusion and exclusion criteria to identify a cohort of patients in the control practices, and compare completion of any colorectal cancer screening method to the trial participants during the trial follow-up period.

Background

The initial and subsequent surges from the COVID-19 pandemic caused many patients to delay evidence-based colorectal cancer (CRC) screening. A major challenge was that many of our CRC screening efforts relied on screening colonoscopy. Many patients deferred screening, and there were also access issues related to scheduling and clinician capacity.

In September 2020, Penn Medicine identified CRC screening among Black patients as a system-wide goal. Due to issues with endoscopy capacity and limited scope of clinic-based outreach efforts, the Colorectal Cancer Strategy group conducted a sprint in the Spring of 2021 to send mailed fecal immunochemical test (FIT) kits directly to patients based on prior experiences from pilot projects. We sent out approximately 4000 kits to practices with a high proportion of minority patients, and included a user-friendly Penn Medicine-branded box as well as text message navigation, resulting a 25% response rate.

Due to continued endoscopy capacity issues, we would like to conduct a similar outreach campaign, but also rigorously evaluate the effectiveness of the designed box, text messaging, as well as a reminder that might increase uptake. These behavioral interventions require additional resources, so the goal is to determine effectiveness of each approach, which will inform future efforts.

Study Design

We will randomize patients in a 2 x 2 x 2 factorial design. Eligible patients will be randomized in a 1:1 ratio (stratified by practice) to receive a standard mailing envelope or a Penn Medicine-branded blue box highlighting the importance of screening.

In a factorial design, patients will concurrently be randomized in a 1:1 ratio (stratified by box arm and practice) to receive text messaging in addition to the standard messaging. Text messaging will include a series of messaging about the importance of CRC screening, the recommendation from the PCP, and an opportunity for feedback.

In a factorial design, we will concurrently randomize patients in a 1:1 ratio (stratified by box, text arm and practice) to receive a mailed reminder letter signed by the PCP if they do not respond after 1 month of initial outreach.

Study duration

We anticipate 1 month to coordinate with PCSL leadership, identify eligible patients through electronic data extraction, and conduct initial outreach. We will then follow patients for 6 months after initial outreach. We plan to start enrollment in April 2022.

Resources necessary for human research protection

Dr. Shivan Mehta is the PI of this study. He is a gastroenterologist, Associate Chief Innovation Officer at Penn Medicine, and assistant professor of medicine at the Perelman School of Medicine, University of Pennsylvania. All members of the research team have completed CITI human subjects research training. Standard Operating Procedure documents for the project will be accessible to all members of the research team, which will keep research staff informed about the protocol and their related duties.

There are adequate facilities to conduct the research; all research staff have adequate office space on the UPenn campus.

Characteristics of the Study Population

Target population

Patients age 50-74 seen in one of the participating Penn Medicine primary care practices at least once in the past 2 years who are not up to date on colon cancer screening per Health Maintenance, with Penn Labs designated as their preferred lab.

Subjects enrolled by Penn Researchers

5000

Subjects enrolled by Collaborating Researchers

0

Subject Recruitment
5000 patients will be identified through automated data extraction from the electronic health record (EHR). All eligible patients in the included primary care practices will receive outreach through the study.

Accrual

We plan to include approximately 5000 patients from practices determined by Primary Care leadership since there are operational limitations to the processing of the FIT kits that we anticipate will be returned to the laboratory.

Key inclusion criteria

1. Patients ages 50-74 with Penn as preferred lab
2. Followed by Primary Care with a participating Penn Medicine PCP listed and at least one visit in the last 2 years
3. Not up to date on colorectal cancer screening per Health Maintenance (no colonoscopy in the last 10 years, stool testing in the last year, flexible sigmoidoscopy in the last 5 years, FIT-DNA in the last 3 years).

Key exclusion criteria

1. Personal or significant family history of CRC, colonic polyps, hereditary nonpolyposis colorectal cancer syndrome, familial adenomatous polyposis syndrome, other gastrointestinal cancer, gastrointestinal bleeding, iron-deficiency anemia, or inflammatory bowel disease
2. History of total colectomy, dementia or metastatic cancer
3. Currently on hospice or receiving palliative care
4. Uninsured or self-pay patients
5. Currently scheduled for a colonoscopy or sigmoidoscopy

As a pragmatic trial, we will have no other exclusions.

Procedures

Program Planning: Through automated data extraction from Clarity, we will identify eligible patients, along with their contact information and demographics. We will obtain approval from the PCSL and participating practices.

Randomization: We will randomize patients in a 2 x 2 x 2 factorial design. Eligible patients will be randomized in a 1:1 ratio (stratified by practice) to receive a standard mailing envelope or a Penn Medicine-branded blue box highlighting the importance of screening.

In a factorial design, patients will concurrently be randomized in a 1:1 ratio (stratified by box arm and practice) to receive text messaging in addition to the standard messaging. Text messaging will include a series of messaging about the importance of CRC screening, the recommendation from the PCP, and an opportunity for feedback.

In a factorial design, we will concurrently randomize patients in a 1:1 ratio (stratified by box, text arm and practice) to receive a mailed reminder letter signed by the PCP if they do not respond after 1 month of initial outreach.

Centralized Outreach. After identifying the patients, we will work with physician leads for the practices to bulk order FIT kits for all eligible patients in their respective clinics, with the PCP listed as the authorizing provider. In April, we will mail 5000 FIT kits: 2500 standard envelopes containing a letter describing the importance of CRC screening, the patient's eligibility for FIT, a FIT kit, and information about how to complete and return the test; and 2500 blue Penn Medicine branded boxes with additional user-friendly messaging and images to encourage patients to complete the test and return in a reasonable time frame.

A file containing eligible patients name, MRN, and contact information will be transferred to a Penn Medicine approved vendor (Paradigm Digital Color), who has agreed to comply with security measures identified by UPHS IS as appropriate for the transfer and protection of this data. Digital Color will not store any patient data once the appropriate files have been produced.

Those randomized to the texting arm will receive outreach with a series of text message reminders that incorporate principles from behavioral science using the Way to Health platform.

Among those who are randomized to receive reminder outreach, we will mail a reminder letter signed by the PCP if FIT completion is not reported by one month from initial outreach.

All FIT results will be routed to the authorizing provider (PCP) and all patients will be notified of their results. The PCP will assist with care coordination and follow-up for patients with FIT positive results.

Analysis Plan

We plan to include approximately 5000 patients determined by Primary Care leadership since there are operational limitations to the processing of the FIT kits that we anticipate will be returned to the laboratory. Our power calculations are based on the number of estimated eligible patients and meaningful differences to justify implementation of the interventions.

We estimate an 18% response rate in the simple outreach arm (no box, no text message, no reminder), based on a prior outreach and findings from other outreach activities. We anticipate an additive effect from each intervention with an effect size of 4 percentage points for each enhancement, based on prior work and other studies. For the box mailing comparison, we therefore anticipate an aggregate response rate of 22% in the no box arm (with half the patients receiving text messaging and half receiving reminders in a factorial design). See Figure 1. An equal allocation of 2,500 in each arm will provide over 90% power to detect a 4 percentage point increase in response rate in the box order arm using the chi-squared test of proportions and intention-to-treat protocol, and considering a two-sided P value less than 0.05 as statistically significant [STATA: power twoprop .22 .26, n(5000) a(.05)]. This increase is clinically meaningful and would justify investment by a health system in the materials and packaging of the box after it is implemented.

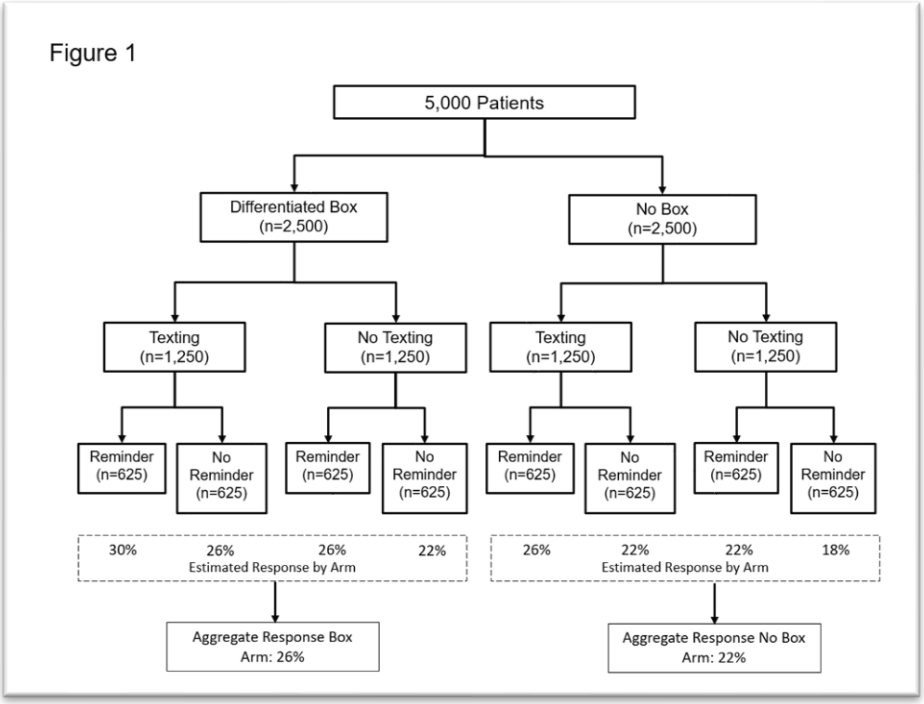
We estimate a 22% response rate in the no text messaging arm, based on prior work. Similar to the box comparison, half the patients will receive the box and half will be assigned to receive a reminder in a factorial design. The eligible population of 5,000 would provide over 90% power to detect an increase in response rate of 4 percentage points in the text message arm compared to no text message [STATA: power twoprop .22 .26, n(5000) a(.05)]. This increase would justify investment in the text messaging technology and implementation.

For the personalized mailed reminder comparison, we estimate a 22% response rate in the no reminder arm that includes 2.500 patients. This will provide over 90% power to detect an increase in response rate of 4 percentage points in the personalized mailed reminder arm compared to no mailed reminder. [STATA: power twoprop .22 .26, n(5000) a(.05)]. This increase would justify investment in the resources to mail reminder letters.

For the main comparisons, we will use the chi-squared test of proportions to calculate difference and 95% confidence intervals, along with P-value. We will also conduct analyses for the secondary outcomes of FIT completion at 6 months, and any CRC screening at 4 and 6 months. We will also compare colorectal cancer screening completion of the patients in the trial to patients in similar practices that were not included in the trial to understand the effect size for outreach compared to no outreach. We will use the same inclusion and exclusion criteria to identify a cohort of patients in the control practices, and compare completion of any colorectal cancer screening method to the trial participants during the trial follow-up period.

For the exploratory subgroup analyses, we will fit multivariable logistic models with treatment group, sex, age, race, ethnicity, household median income, patient portal status, and one treatment by covariate interaction at a time. We will conduct likelihood ratio tests to examine significance of the interaction term in each model. We will report the estimated log odds ratio along with a 95% confidence interval for each interaction, which quantifies the differential effect of treatment between subgroups (relative to a reference group for categorical covariates), adjusting for all other covariates in the model. We will report p-values both unadjusted and adjusted for multiple comparisons using the Holm procedure.

Figure 1



Data Confidentiality

Paper-based records will be kept in a secure location and only be accessible to personnel involved in the study. Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords. Wherever feasible, identifiers will be removed from study-related information.

Subject Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). All PHI will be maintained on UPHS servers. Source documents are maintained in PennChart. No source documents will be printed or maintained in paper form at the study site. Data from PennChart will be recorded in Penn Medicine's REDCap system. The investigator and study team (which includes the research coordinator, and research assistants) will have access to PHI within PennChart and REDCap. We will label all PHI within REDCap as identifiable information so that de-identified exports are possible. All reports that include identifiable information will be stored on the Innovation Center secure drive, maintained behind the UPHS firewall. Digital Color will not store any patient data once the appropriate files have been produced.

Subject Privacy

Because this study involves sending a FIT test to patients which will include PHI such as name, etc., research and print vendor staff will be required to check the addresses listed for the patient to ensure mismatches are not made. A file including these data elements will be transferred to a Penn Medicine approved vendor (Paradigm Digital Color), who has agreed to comply with security measures identified by UPHS IS as appropriate for the transfer and protection of this data. Digital Color will print one custom printed label combo sheet with patient name, address, barcode, and test-kit label. One box/envelope will be assembled at a time using one custom label sheet. Once the kit and the box has been fully assembled it will be labeled using the address and barcode from the same custom label sheet, sealed and shrinkwrapped prior to assembling the next. Reminder letters will be generated using a similar file and mail merge to complete patient information in specified fields, then included in a window envelope so no matching between names and address on envelopes and letters will be required. Digital Color will not store any patient data once the appropriate files have been produced.

Data Disclosure

Completed fecal immunochemical testing (FIT) results will be disclosed to the participant's provider for continuity of care.

Protected Health Information/Data Protection

- Name
- Street address, city, county, precinct, zip code, and equivalent geocodes
- All elements of dates (except year) for dates directly related to an individual and all ages over 89
- Telephone and fax numbers
- Medical record numbers

Consent

1. Consent Process

Overview

Waiver of consent for this study will be requested. Please see below.

Children and Adolescents

Not applicable.

Adult Subjects Not Competent to Give Consent

Waiver of consent is being requested.

2. Waiver of Consent

Waiver or Alteration of Informed Consent*

Waiver or alteration of required elements of consent.

Minimal Risk*

This study involves no more than minimal risk to subjects. Fecal immunochemical testing (FIT) is clinically available and routinely utilized to screen patients for colorectal cancer. The outreach methods in each arm are all offered during routine clinical care either at Penn Medicine or other health systems across the country. The only research related activity is the randomization of subjects to different outreach strategies that would typically occur in routine practice.

Impact on Subject Rights and Welfare*

Subjects' rights and welfare will not be adversely affected by the waiver of authorization and consent. All subjects will have the opportunity to voluntarily participate in colorectal cancer screening. This outreach program is supported as clinical care by PCSL leadership.

Waiver Essential to Research*

We believe that we would not be able to practically conduct the research without waiver of consent. If we had to obtain either written or verbal consent ahead of time, it would substantially limit our study population and it may alter their participation in the intervention. Thus, we would only learn about the response rate for patients who we were able to speak to for consent. This would limit the generalizability to practice. Simply waiving documentation of consent (and thus including a consent letter that does not require a subject signature) is not sufficient in this scenario. We believe that including a consent letter in the mailings could potentially bias subjects to not participate in a clinically available and indicated screening test, and it could alter their participation. Obtaining waiver of consent would allow us to avoid the potential selection/volunteer bias for inclusion of patients particularly interested in screening that can occur when consent is required. Since our main objective is to understand the potential influence varying outreach strategies on subject behavior, we believe that obtaining consent would compromise our primary objective. Additionally, we have received waiver of consent for similar studies related to population health screening outreach (Hepatitis C Screening Outreach (#831526), COVID Vaccine Texting Outreach (#848696), and Mammogram Outreach (#849863)).

Additional Information to Subjects

Subjects who are screened will be provided with appropriate information about screening results as is routine clinical practice.

Written Statement of Research*

No

Risk / Benefit

Potential Study Risks

The risks associated with this study are no more than minimal. There is the potential risk of breach of confidentiality. We will minimize this risk by using de-identified information whenever possible and by maintaining all identifiable information on a secure drive and/or in a HIPAA-compliant system (e.g. REDCap). There is also the risk of psychological harm associated with being screened for colorectal cancer. We will minimize this risk by communicating the results of the screening test to the subject in a timely fashion and facilitating the scheduling of treatment evaluation if the screening test is positive (as is usual practice for screening outreach programs).

Potential Study Benefits

If a participant completes colorectal cancer screening, which is standard clinical care, the subjects will potentially benefit from participation by increasing the chances of curing colorectal cancer at an early stage. Information learned from this study may benefit society through a better understanding of how to effectively increase overall participation rates in colorectal cancer screening which could in turn reduce the morbidity and mortality of the diagnosis.

Data and Safety Monitoring

Safety will be overseen by the PI and the study team. In the case of possible events, the PI or designee will review the study charts to evaluate events at each subject interaction to ensure the grade, relationship to the study procedure, expectedness, and the course of action for each subject is documented.

Risk / Benefit Assessment

The risks associated with this study are no more than minimal. Better knowledge of how to increase colorectal cancer screening rates could potentially address one of the major barriers of accessing care, i.e. having patients come in for clinical office visits. For these reasons and those outlined in the above benefits section, the investigators believe that the risks of participating in the study are outweighed by the potential benefits of participating in the study.