

**The University of Texas Southwestern Medical Center at Dallas
Institutional Review Board**

PROJECT SUMMARY

PROJECT TITLE: PROSPR Project 2: Comparative Effectiveness of FIT, Colonoscopy, & Usual Care Screening Strategies

PRINCIPAL INVESTIGATOR: Amit Singal, MD

SPONSOR/FUNDING SOURCE: Population-Based Research Optimizing Screening through Personalized Regimens (PROSPR)

PROSPR CENTER OVERVIEW:

The overall goal of the *Parkland-UT Southwestern PROSPR Center* (IRB #082011-040) is to optimize colon cancer screening through personalized regimens in our integrated safety-net clinical provider network, which serves a large and diverse population of under- and un-insured patients in Dallas. Together, three research projects will assess clinic, system, and organizational factors associated with over-, under- and guideline-based screening among this important population and will compare benefits, harms, and costs of strategies for facilitating optimized screening regimens. Our theme of optimizing colorectal cancer screening in a safety-net clinical provider network brings together several components. Its focus on colorectal cancer (CRC) screening which is important, because CRC is the second cancer killer in the US while being the only major cancer for which optimized screening results in primary prevention. Despite this strong potential benefit, CRC screening remains suboptimal overall, and especially among low-income and minority individuals served by safety-nets. Safety-net networks therefore offer tremendous potential for CRC prevention and control, but numerous factors at the clinics-, system-, and organization-level influence their ability to provide optimized care.

Each of our PROSPR Center's projects is innovative and addresses the continuum of care. Project 1 addresses transitions 1 and 3, employing novel, algorithmically driven tools in clinics to determine personalized optimized screening regimens for individual patients and track whether each has received the indicated guideline-based screening. Project 2 addresses all three transitions through a novel comparative effectiveness study of benefits, risks, and costs of two outreach strategies for promoting screening completion and guideline-appropriate follow-up. Project 3 addresses transitions 2 and 3 by focusing on organizational culture, structure, and protocols, using both quantitative and qualitative methods to elucidate factors influencing completion of effective screening processes. Our projects address research priorities identified through a recent NIH State of the Science Conference, including: implementing interventions proven effective at increasing CRC screening (Projects 1 & 2), conducting research to assess effectiveness of tailoring programs to match characteristics and preferences of target populations (Project 1), implementing systems to ensure follow up of positive CRC screening results (Projects 1, 2 & 3), and conducting studies to determine comparative effectiveness of CRC screening methods in usual practice (Project 2).^{21;22}

Our PROSPR Center's goals are to:

- 1:** *Develop a Parkland-UT Southwestern PROSPR Center to promote coordinated, transdisciplinary research to evaluate and improve the CRC screening process in a large population-based safety-net.*
- 2:** *Conduct three projects that address the continuum of care for CRC screening and address these goals:*

Project 1 - Employ innovative methods for assessing personalized guideline-based screening in the clinic setting to evaluate guideline-based, over- and under-screening;
Project 2 - Compare benefits, harm, and costs of three system-level strategies for inviting patients to screening and promoting guideline-based follow up, with particular focus on completing an effective screening process.
Project 3 - Examine specific organizational factors that contribute to completion of guideline-based screening processes and examine which organizational factors modify relationships between social disadvantage and completion of guideline-based repeat screening and follow up of abnormal test results.

3: *Contribute to a national PROSPR network by actively participating in network activities, including:* (a) collaborating with the National Data Coordinating Center regarding approaches for measuring screening effectiveness, (b) sharing algorithmically driven tools facilitating personalized screening regimes, (c) sharing EMR capabilities with other Epic institutions, and (d) becoming a leader in cancer screening processes in safety-net systems.

While the SPDU will be exclusively responsible for all required PROSPR network data collection, processing and transfer activities, our complementary Shared Research Resources Core (SRRC) will serve as the local “data coordinating center” of our PROSPR center. The SRRC will work with Projects 1-3 to identify patients for recruitment; track study accrual; and manage, process, and analyze all Project data. The SRRC will also help assure consistent data definitions and terminology for harms, benefits, and other common domains across the SPDU and Projects. The SRRC and SPDU will work closely together as much of the required SPDU screening process data will be used by the SRRC to identify eligible patients for Projects 1-3, and ascertain the processes and outcomes of the CRC screening process for study participants. An innovative activity of the SRRC will be to extract from Epic a novel set of electronically derived measures of social disadvantage previously developed by the Parkland Center for Innovation.²⁷ This will empower Projects 1 and 2 to examine the influence of these factors on the in-reach and out-reach programs, as well as provide Project 3 with critical explanatory variables to understand the impact of clinic-level organizational factors on the CRC screening process.

PROJECT 2 PURPOSE:

This study addresses two critical public health questions: (1) What is the most clinically and cost-effective CRC screening strategy from a population perspective in general, and (2) among safety-nets in particular? Innovative features include a centralized process to promote outreach invitation and guideline-appropriate follow up, a focus on a population at high risk for adverse CRC outcomes, and a pragmatic design to maximize generalizability. Study findings will provide great insight into the most clinically and cost-effective ways to provide population screening to groups at highest risk for adverse CRC outcomes. We will conduct a system-level, randomized comparative effectiveness trial of the benefits, harms, and costs of three screening strategies over three years, among 6000 patients age 50-64 years, who are not up-to-date with CRC screening, served by a large safety-net system. The three strategies that will be studied are:

- 1) Fecal immunochemical testing, with annual mailed invitation outreach (including a test kit), and a centralized process to promote participation and complete clinical follow up (FIT)
- 2) Colonoscopy, with annual mailed invitation outreach, and a centralized process to promote participation and complete clinical follow up (Colo)
- 3) Usual Care, with screening initiation and subsequent follow up at discretion of individual providers during clinic visits (Usual Care). Groups 1 and 2 will also receive Usual Care.

The primary measure of benefit will be an outcome measure that summarizes patient-specific effective screening “successes.” The primary measure of harm will be screening non-participation. The primary measure of cost will be cost-per patient effectively screened.

Our Specific Aims are to:

Aim 1. Compare benefits, harms, and costs of a fecal immunochemical test strategy versus a colonoscopy strategy for CRC screening among patients not up-to-date with screening.

- Hypothesis 1a. The rate of patient-specific effective screening “successes” will be higher for the FIT vs. the Colo strategy.
- Hypothesis 1b. The rate of screening non-participation will be lower for the FIT vs. the Colo strategy.
- Hypothesis 1c. The cost per-patient effectively screened will be lower for the FIT vs. the Colo strategy.

Aim 2. Compare benefits, harms, and costs of a) the FIT strategy vs. Usual Care and b) the Colo strategy vs. Usual Care.

- Hypothesis 2a1. The rate of patient-specific screening “successes” will be higher for the FIT strategy vs. Usual Care.
- Hypothesis 2a2. The rate of screening non-participation will be lower for the FIT strategy vs. Usual Care.
- Hypothesis 2a3. The cost per-patient effectively screened will be lower for the FIT strategy vs. Usual Care.
- Hypothesis 2b1. The rate of patient-specific screening “successes” will be higher for the Colo strategy vs. Usual Care.
- Hypothesis 2b2. The rate of screening non-participation will be lower for the Colo strategy vs. Usual Care.
- Hypothesis 2b3. The cost per-patient effectively screened will be lower for the Colo strategy vs. Usual Care.

BACKGROUND:

Colorectal cancer is an important public health problem, but participation in CRC screening is suboptimal, particularly for the uninsured and minorities. Colorectal cancer (CRC) is the 2nd leading cause of cancer death in the US, though CRC mortality can be reduced by effective screening. Observational and randomized controlled studies have shown that stool blood testing, sigmoidoscopy, and colonoscopy can reduce CRC mortality and incidence⁴⁻¹⁵. However, participation in CRC screening remains suboptimal, and is particularly low for the uninsured and minorities¹⁶.

There is uncertainty as to whether a strategy of screening based on colonoscopy is more effective than a strategy of screening based on a stool blood test. There is also uncertainty as to the most effective approaches to include within a screening strategy to optimize screening participation and guideline-appropriate follow up. Colonoscopy and stool blood testing (such as with a fecal immunochemical test—FIT) are the two most common screening tests used^{3;17}. Colonoscopy is particularly heavily endorsed by some medical societies and the media^{1;18}. Nonetheless, there is uncertainty as to which test is best as part of a screening strategy. Further, there is uncertainty regarding the most effective approaches for optimizing screening participation and guideline-appropriate follow up^{3;17}. Modeling studies suggest that the benefits and harms of colonoscopy and FIT strategies are similar, but these generally *assume* 100% participation in tests and subsequent clinically appropriate follow up—something *never* achieved in clinical practice^{2;19-21}. Colonoscopy is a more sensitive test for polyps and CRC, but prior work suggests that some patients are unwilling to participate in colonoscopy, and that organizational capacity to perform colonoscopies for all individuals is limited^{17;21;21;22}. Thus, a screening strategy offering colonoscopy may be ultimately ineffective because of both limited participation and colonoscopy capacity. Similarly, though a FIT strategy may be associated with high initial participation, effectiveness of this strategy requires repeat annual testing for patients with normal

tests, and colonoscopy for patients with abnormal tests. However, prior studies have shown suboptimal adherence to annual stool blood testing, as well as follow up colonoscopy after abnormal tests²³⁻³¹. Given such examples of test-specific variability in elements required for effective screening, it remains unclear which screening strategy will be most effective in real world settings. *Discovering the best screening strategy requires a comparative effectiveness trial of screening strategies, with comparisons of specific tests and approaches to optimizing effective test use, and utilization of an outcome that takes into account all challenges to the effectiveness of a given strategy, including test participation and successful guideline-appropriate follow up.*

Safety-net health systems (safety-nets) care for populations, such as the uninsured and minorities, at increased risk for adverse CRC outcomes and ineffective screening. The uninsured have much lower CRC screening rates, higher stage at presentation, and worse overall and stage specific CRC mortality compared to the insured³². African Americans have the highest CRC incidence, youngest age of onset, and most advanced stage at presentation, leading to the highest CRC mortality rates of any group^{33;34}. Hispanics are less likely to be screened, and more likely to be diagnosed with advanced CRC and die from CRC than non-Hispanic Whites³⁵. Further, Spanish language preference is strongly associated with lower colorectal screening rates^{36;37}. *Because safety-nets disproportionately serve the uninsured and minorities³⁸, they have an opportunity to be at the forefront of improving CRC disparities for these and other groups at high risk for adverse CRC outcomes.*

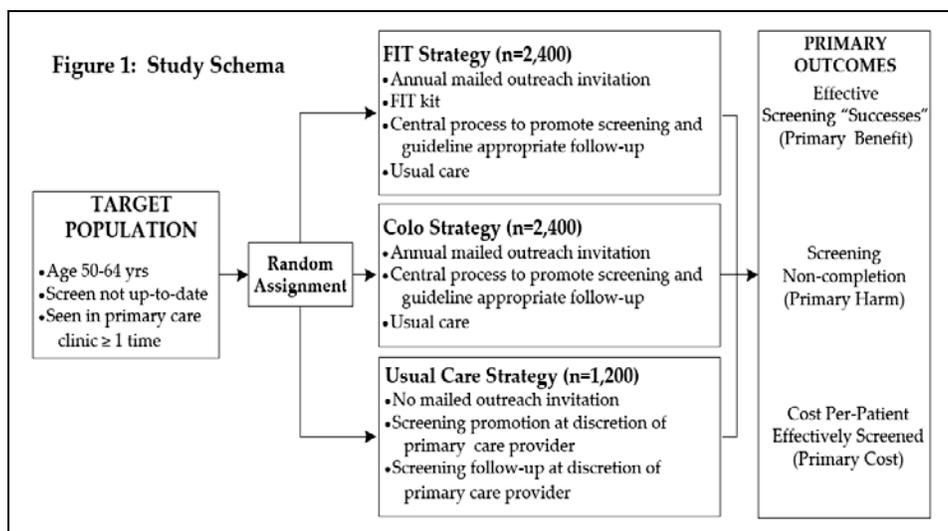
Safety-nets must resolve the uncertainty regarding the most effective population-based screening strategy by comparisons of benefits, harms, and costs of candidate strategies. Safety-nets, because of service to groups at highest risk for ineffective screening outcomes such as lack of screening participation, are responsible for a large population with great screening needs. In our Parkland safety-net, more than 32,000 patients are not up-to-date with CRC screening, and the number at our neighboring safety-net in Fort Worth, TX is 16,000³⁹. Safety-nets must be careful not to offer services they cannot fully deliver. For example, a colonoscopy strategy requires an immense investment in endoscopy lab facilities, providers for colonoscopy services, and infrastructure to prepare and follow up patients post-colonoscopy. Alternatively, a primary FIT-based strategy requires investment in lab facilities to process FIT kits, processes to follow up patients with abnormal FIT with colonoscopy and normal FIT with yearly FIT, and sufficient colonoscopy resources to accommodate abnormal results.

These factors, when considered together with the requirement for safety nets to optimize use of limited resources, mandate that safety nets study the comparative effectiveness—including benefits, harms, and costs—of candidate screening strategies. We will conduct a randomized comparative effectiveness study of three strategies to boost colorectal cancer screening: 1. Mailed invitation to FIT screening, with centralized processes to promote screening completion, 2. Mailed invitation to colonoscopy screening, with centralized processes to promote screening, and 3. Usual medical care.

CONCISE SUMMARY OF PROJECT:

Colorectal cancer (CRC) is the 2nd leading cause of cancer death in the US, though CRC death can be reduced by screening. However, there is uncertainty as to which screening strategy is most clinically and cost-effective from a population perspective where the aim is to optimize completion of the entire screening process continuum. Modeling studies suggest benefits and harms of colonoscopy and stool blood test strategies are similar, but generally assume 100% participation and subsequent clinically appropriate follow up—something never achieved in clinical practice. Comparative effectiveness studies of testing strategies, including comparisons of specific tests and approaches to optimizing effective test use, are necessary. Safety-net health systems care for populations at increased risk for adverse CRC outcomes, such as the uninsured and minorities, and have more limited resources. Therefore, safety-nets

must resolve the uncertainty regarding the most effective screening strategy. We will conduct a system-level, randomized comparative effectiveness trial of the benefits, harms, and costs of 3 screening strategies over 3 years, among 6000 patients age 50-64 years, who are not up-to-date with CRC screening, served by a large safety net health system. The three strategies studied will be: 1) Fecal immunochemical testing, with annual mailed invitation outreach (including a test kit), and a centralized process to promote participation and complete clinical follow up (FIT); 2) Colonoscopy, with annual mailed invitation outreach, and a centralized process to promote participation and complete clinical follow up (Colo); 3) Usual Care, with no mailed invitation outreach, and screening offered at primary care visits. The primary measure of benefit will be an outcome measure that summarizes patient-specific effective screening “successes.” The primary measure of harm will be screening non-participation. The primary measure of cost will be cost per-patient effectively screened. Our specific aims are to: 1) Compare benefits, harms, and costs of a FIT strategy versus a Colo strategy for CRC screening among patients not up-to-date with screening, and 2) Compare benefits, harms, and costs of a) the FIT strategy vs. Usual Care and b) the Colo strategy vs. Usual Care for CRC screening. The study design is summarized by the Study Schema (Figure 1).



STUDY PROCEDURES:

Candidate participants will be identified using Epic and administrative databases by the Shared Research Resources Core (SRRC) (Parkland-UT Southwestern PROSPR Center IRB #082011-040). Eligible patients will be randomly assigned to one of the three screening strategies. SAS procedures will be used for randomization. Patients will be assigned to the three strategies in a 1:2:2 ratio, with:

- 1,200 patients assigned to Usual Care
- 2,400 patients assigned to FIT
- 2,400 patients assigned to Colo

Eligibility will be assessed every 3 months of the first year of enrollment, with ¼ of the target sample for each group assigned each quarter. Thus, each quarter, 400 patients will be assigned to Usual Care, 600 to FIT, and 600 to Colo.

Patients assigned to the FIT screening strategy will receive annual invitation to complete FIT screening for a total of three years. Annual invitation will be stopped if the patient has an abnormal FIT test. Patients assigned to the Colo screening strategy will receive annual invitation to complete colonoscopy screening for a total of three years. Annual invitation will be stopped if the patient has a colonoscopy completed. The frequency of mail and phone contact with patients as part of annual invitations is summarized in Table 1.

Patients assigned to the FIT and Colo strategies will be recruited to participate in screening via mailed invitation. Retention in the screening strategy will be encouraged based on centralized processes to

promote screening completion and guideline-based follow up of abnormal tests (phone call reminders to complete screening, screening team communication of abnormal test results to patient and facilitation of subsequent colonoscopy and required treatment visits) as well as repeat annual invitation to screening until a screening test is abnormal (in the case of the FIT group) or a colonoscopy is completed (in the case of the Colonoscopy group). “Live” reminder phone calls will occur in the 2nd and 3rd week after mailing invitations; up to two attempts in total will be made to reach the patient to encourage and facilitate screening completion. If a patient refuses contact screening invitations and phone calls will stop.

To promote guideline appropriate clinical follow up, the screening team will initiate the specific procedures for each of the following clinical scenarios (summarized in Table 1):

- a) Normal FIT. Patients with a normal FIT result will be mailed a letter that reports the normal result and recommends repeat FIT screening annually. The normal FIT result will also be routed via the EMR to the patient’s primary provider.
- b) Canceled FIT. Patients with a canceled FIT result (e.g., specimen too old, specimen label incomplete, and specimen unsatisfactory for testing) will be contacted by telephone, informed why the FIT could not be processed, and encouraged to repeat the test. Interested patients will receive another invitation to FIT screening, with kit included. Patients may receive up to three FIT kits annually.
- c) Normal Colonoscopy or polyps at colonoscopy. Patients with a normal colonoscopy or polyps detected at colonoscopy will be mailed a letter that reports these results, along with the recommendations documented by the patient’s colonoscopist. The patient’s primary provider will be sent the post-colonoscopy results and recommendations through the EMR system.
- d) Abnormal FIT. Patients with an abnormal FIT will be called within one week to be told of their abnormal result and to schedule a diagnostic colonoscopy. This decision will be based on use of a succinct, structured phone triage. Attempts will be made to reach the patient by phone daily for 4 weeks. The patient will also be sent a mailed result report that includes recommendation to call and schedule a colonoscopy. If a patient with an abnormal FIT is reached for phone triage, but cannot be scheduled for colonoscopy due to underlying medical comorbidities, the patient’s primary care provider will be notified per usual care. If a patient with an abnormal FIT cannot be reached for phone triage after 5-10 attempts over a 2 week period or if a patient declines diagnostic colonoscopy the nurse practitioner will create a telephone encounter in the patient’s electronic medical record (see below). The patient’s primary provider will be informed of any abnormal FIT result through the EMR system in order to enlist him/her in encouraging the patient to complete a colonoscopy if the patient is seen in clinic.
 - a. Telephone encounter note for abnormal FIT patients who cannot be contacted: Patient recruited to participate in colorectal cancer screening via mailed invitation (IRB # STU 102011-069). PROSPR Occult Blood Fecal FIT was abnormal. Parkland-UT Southwestern colorectal cancer screening center was unable to contact the patient to schedule diagnostic colonoscopy after 5-10 attempts over a two week period.
 - b. Telephone encounter note for abnormal FIT patients who decline diagnostic colonoscopy: Patient recruited to participate in colorectal cancer screening via mailed invitation (IRB # STU 102011-069). PROSPR Occult Blood Fecal FIT was abnormal. Parkland-UT Southwestern colorectal cancer screening center contacted the patient who declined diagnostic colonoscopy at this time.
- e) CRC detected. Standard practice post CRC detection at Parkland is treatment referral at the time of colonoscopic diagnosis. However, for patients for whom diagnosis is made after biopsy review, or for whom no first treatment visit was scheduled, the screening team will conduct several actions to promote first treatment visit consultation. The patient will be called daily to schedule a treatment visit consultation for 7 days. Additionally a mailed letter will be sent to the

patient informing him/her of the diagnosis and need to schedule follow up. Further, the patient’s primary provider will be notified through the EMR system of the CRC diagnosis and need for follow up.

Outreach invitation letters for the FIT and Colo strategies will be developed in English and Spanish with experts in health communication (Skinner), and our Clinical and Translational Science Initiative’s language validation core. The goal will be clarity for patients with low literacy. The letter will be on Parkland letterhead, note patient’s age-based risk for CRC, and invite the patient to complete screening.

Table 1. Summary of annual central processes to promote screening completion and guideline-appropriate follow up for FIT and Colo strategies.		
FIT Strategy	Colo Strategy	
Outreach		Timing within invitation quarter
Mailed invitation to FIT screening, with kit included	Mailed invitation to Colonoscopy	First day of strategy
Reminders		
“Live” phone calls to promote FIT completion	“Live” phone call to promote Colonoscopy scheduling	Weeks 2 and 3 of strategy
“Live” phone calls to remind patients scheduled for a diagnostic colonoscopy	“Live” phone calls to remind patients scheduled for a screening colonoscopy	10 and 2 days before appointment
Guideline Appropriate Follow up Based on Clinical Findings		Timing relative to clinical result
<i>CRC Detected</i>		
Phone call to patient to schedule 1 st treatment visit		Daily attempts x 7 days within one week
Mailed result to patient		Within one week
EMR result to primary provider		
1 st treatment consultation visit		Within two weeks
<i>Normal FIT</i>	<i>Normal Colonoscopy or Polyps at Colonoscopy</i>	
Mailed result and follow up recommendation to patient		Within one week
EMR result and follow up recommendation to primary provider		
<i>Abnormal FIT</i>		
Phone call to patient to report result and schedule a diagnostic Colonoscopy	n/a	Within one week
Mailed result to patient	n/a	
EMR result to primary provider	n/a	
Colonoscopy	n/a	Within 12 weeks of result

The FIT screening strategy is comprised by:

- Mailed outreach invitation to complete FIT, including a test kit. The invitation kit will include a 1-sample FIT, including simplified instructions on how to perform the test, as well as a return mailer with prepaid postage. Kits will be provided by Polymedco. Diet/medication restriction will not be required. Kits will be returned to the Parkland clinical laboratory and processed per manufacturer recommendations. Hemoglobin of 100 ng/mL will be set as the abnormal threshold per approved standard recommended by Polymedco and the FDA.
- “Live” phone call reminders to encourage screening completion. Participants will receive two “live” phone reminders from project staff 2 to 3 weeks after the invitation. All communications will use standard English or Spanish scripts.
- Centralized processes to promote guideline-based follow up, including reminder calls 10 and 2 days before patients’ diagnostic colonoscopy appointment. Colonoscopy preparation, instructions,

and an appointment reminder will be mailed following the 10-day reminder. Patients with an initial normal FIT will receive recommendation to repeat FIT annually, and annual repeat invitation including an FIT kit. Patients with abnormal FIT will be reflexively called by the screening team to report the result within 1 week of the result and facilitate direct scheduling of a diagnostic colonoscopy. Pre-colonoscopy clinical review will be conducted by a Parkland Clinical Access Coordinator. The goal will be to schedule colonoscopies within 12 weeks of the abnormal FIT. If a CRC is detected, patients who do not have a first treatment consultation visit scheduled immediately after detection will be reflexively called to schedule this visit. These calls will be made daily for up to one week. The goal will be to have a first treatment consultation visit within 2 weeks of CRC diagnosis. All results and recommendations will also be sent to the patient via mail and to the patient's primary provider via the EMR email within 1 week of the result.

The Colo screening strategy is comprised by:

- Mailed outreach invitation to complete a colonoscopy. The invitation will include a number to call to schedule a colonoscopy. At time of contact, patients will be triaged by project staff with a structured screening questionnaire to either 1) "direct book" colonoscopy or 2) pre-colonoscopy clinical review conducted by a Parkland Clinical Access Coordinator.
- "Live" phone call reminders to encourage screening completion. Participants will receive two "live" phone call reminders from project staff 2 to 3 weeks after the mailed invitation. All communications will use standard English or Spanish scripts.
- Centralized processes to promote guideline-based follow up, including reminder calls 10 and 2 days before patients' screening colonoscopy appointment. Colonoscopy preparation, instructions, and an appointment reminder will be mailed following the 10-day reminder. Patients with a normal colonoscopy or polyps detected will receive findings and recommendations for repeat testing via mail from the colonoscopist. Findings and recommendations will be taken from the colonoscopists' procedure reports and communications to patients and providers. If no post-procedure communication is identified within 3 weeks of the pathology report, we will prompt colonoscopists via email (up to two attempts in total will be made). Notably, during the course of the study, recommendations and communications for post-polypectomy patients will become standardized based on completion of Aim 2 of Project 1. As part of that PROSPR effort, we will design and implement an Epic-based SmartForm decision support tool that will help colonoscopists generate and communicate guideline-based recommendations after post-polypectomy to patients and referring providers. If a CRC is detected, patients who do not have a first treatment consultation visit scheduled immediately after detection will be reflexively called to schedule this visit. These calls will be made daily for up to one week. The goal will be to have a first treatment consultation visit within 2 weeks of CRC diagnosis. All results and recommendations will also be sent to the patient via mail and to the primary provider via EMR email within 1 week.

Usual Care is currently comprised by:

- No outreach mailed invitations.
- Ordering of colonoscopy or FIT for screening at the discretion of the primary provider. All orders in usual care are placed in the EMR. FIT kits are distributed at point of care and returned to clinic for processing at a central lab. Referrals for colonoscopy are handled by the GI clinic/lab staff.
- Follow up of abnormal tests and results reporting to the patient at the discretion of primary and specialty providers. Currently, primary providers and their staff report abnormal FITs to patients and order colonoscopy follow up based on individual practice. If a CRC is diagnosed, either the primary provider or colonoscopist orders first treatment consultation with a surgeon or cancer specialist. A patient navigator in the oncology clinic facilitates cancer staging tests and treatment consultation visits.

Invitation and procedure timing: One-quarter of patients assigned to the FIT and Colo strategies will be invited every 3 months to facilitate workflow. Annual repeat invitations will occur one year from the initial invitation. For example, a patient invited to complete FIT in the second quarter of the first year of study follow up will receive her second invitation to complete a FIT in the second quarter of the second year of follow up. Patients in the FIT strategy will continue to receive annual invitations unless they have an abnormal FIT result. Patients in the Colo strategy will continue to receive annual invitations unless they complete a colonoscopy (Table 1).

STATISTICAL ANALYSES:

Primary comparisons of screening strategies will be based the intention to screen principle. All outcomes will be adjudicated within 3 years of randomization. All outcomes will be adjudicated by the SRRC using screening process and outcomes data in Epic.

Aim 1. Compare benefits, harms, and costs of a FIT strategy versus a Colo strategy for CRC screening among patients not up-to-date with screening.

- *Hypothesis 1a. The rate of patient-specific effective screening “successes” will be higher for the FIT vs. the Colo strategy.* “Successes” will be adjudicated based on stringent “all or nothing” criteria⁵¹. For example, a patient who completes an initial FIT that is normal, but does not subsequently complete an FIT annually for two years will be counted as an effective screening failure. Patients assigned to the FIT or Colo strategy who cross over and receive alternate screening as a result of usual care will be adjudicated as having a screening “success” so long as they meet an endpoint listed in Table 2. Indeed, we anticipate that in some cases the mailed invitation outreach will result in patient discussions with primary providers who deliver Usual Care that will lead to screening that is not concurrent with the initial strategy to which the patient was randomized. For example, a patient receiving the FIT strategy may visit with a doctor, have a colonoscopy ordered for screening, and complete a colonoscopy that is normal, and be counted as a FIT strategy screening “success.” FIT and Colo strategies will be compared using a chi-square test of proportions (2-sided $p < .05$).
- *Hypothesis 1b. The rate of screening non-participation will be lower for the FIT vs. the Colo strategy.* Non-participation will be adjudicated based on absence of any FIT, sigmoidoscopy, or colonoscopy within the 3 year follow up period. FIT and Colo strategies will be compared using a chi-square test of proportions (2-sided $p < .05$).

Aim 2. Compare benefits, harms, and costs of a) the FIT strategy vs. Usual Care and b) the Colo strategy vs. Usual Care.

- *Hypothesis 2a1. The rate of patient-specific screening “successes” will be higher for the FIT strategy vs. Usual Care.*
- *Hypothesis 2a2. The rate of screening non-participation will be lower for the FIT strategy vs. Usual Care.*
- *Hypothesis 2b1. The rate of patient-specific screening “successes” will be higher for the Colo strategy vs. Usual Care.*
- *Hypothesis 2b2. The rate of screening non-participation will be lower for the Colo strategy vs. Usual Care.*

For comparisons of the FIT strategy vs. Usual Care, and the Colo strategy vs. Usual care on the outcomes of screening success and screening non-participation under Hypotheses 2a1, 2a2, 2b1, and 2b2, pairwise comparisons will be performed using a chi-squared test of proportions, with 2-sided $p < 0.05$ considered statistically significant.

Table 2. Definition of Effective Screening “Successes”
Invited to colonoscopy, responded to invite, determined to be too sick to scope by phone triage and clinical review. This is deemed a success because over screening is avoided.
Screening colonoscopy completed, no cancer detected.
Screening colonoscopy completed, cancer detected, first cancer treatment consultation visit completed.
FIT screening completed, test normal, and FIT repeated annually for 2 years.
FIT screening completed, test abnormal, failed phone triage and clinical review, primary care provider notified per usual care.
FIT screening completed, test abnormal, colonoscopy completed, no cancer detected.
FIT screening completed, test abnormal, colonoscopy completed, cancer detected, first cancer treatment consultation visit completed.

Sample size estimation for the primary comparison of the FIT vs. the Colo strategy. Our primary sample size estimates were based on the primary effectiveness outcome: proportion of patients achieving one of the effective screening “successes” (Table 2). In order to conduct sample size estimates, we estimated the strategy-specific proportion of patients expected to meet one of the effective screening success endpoints. For example, under the Colo strategy, one success endpoint is: Screening colonoscopy completed, no cancer detected. To estimate the predicted number of patients reaching this endpoint, we used the following formula: *Expected Participation Rate Colonoscopy X Expected Prevalence of Patients with No CRC X Expected Rate of Colonoscopy to Cecum with Adequate Bowel Preparation*. We then added this proportion to our estimate of the proportion of patients reaching the other effective screening success endpoint expected for the Colo strategy: Screening colonoscopy completed, CRC detected, first treatment consultation visit completed. This was estimated using the formula: *Expected Participation Rate Colonoscopy X Expected Prevalence of Patients with CRC X Sensitivity of Colonoscopy for CRC X Expected Rate of Colonoscopy to Cecum with Adequate Bowel Preparation X Expected Rate of Completion of 1st Treatment Consultation Visit*. Formulae used for each of the effective screening endpoints are summarized in Table 3. The assumptions required for the value of each term in the formulae were based on available medical literature and our prior work, and are summarized by Table 4.

Using the formulae for estimating strategy-specific rates of effective screening successes (Table 3), and the assumptions in Table 4, we calculated summary estimates of the primary outcome: proportion of patients reaching effective screening successes. The predicted rate is 8.6% for Usual Care, 13.5% for the Colo strategy, and 16.6% for the FIT strategy. These outcome estimates are far lower than prior reported outcome rates of CRC intervention studies because the typical primary outcome rate of such studies is the screening participation rate, not the much more stringent, difficult to achieve outcome of proportion of patients completing an effective screening “success” endpoint. Indeed, for randomized studies of interventions to improve screening participation rates, outcome rates of over 25% have been typically reported. Further, it should be noted that in our study, estimates are based on a population which is already known to be not up-to-date with screening, and which may be a particularly refractory population expected to have low rates of conversion to being screen up-to-date or completing an effective screening endpoint. For the primary comparison of the FIT vs. the Colo strategy, assuming $\alpha=0.05$, a sample size of 2,152 patients per group is required to have 80% power to detect a statistically significant difference. In order to take into account potential loss to follow up from the health system of 10%, we will further increase the sample size to take this into account to 2,400 patients. **Thus, our estimated total sample size for the primary comparison of FIT vs. Colo strategy is 2,400 patients for the FIT group, and 2,400 patients for the Colo group.**

Table 3. Formulae used to estimate rates of strategy-specific effective screening success endpoints	
Definition of Effective Screening Endpoint “Successes”	Formulae for Predicted Rate Used for Sample Size Estimation
Colo Strategy*	
Screening colonoscopy completed, no cancer detected	Expected Participation Rate Colonoscopy X Expected Prevalence of Patients with No CRC X Expected Rate of Colonoscopy to Cecum with Adequate Bowel Preparation
Screening colonoscopy completed, cancer detected, first cancer treatment visit completed	Expected Participation Rate Colonoscopy X Expected Prevalence of Patients with CRC X Sensitivity of Colonoscopy for CRC X Expected Rate of Colonoscopy to Cecum with Adequate Bowel Preparation X Expected Rate of Completion of First Treatment Consultation Visit
FIT Strategy*	
FIT screening completed, test normal, and FIT repeated annually for 2 years	Expected Participation rate FIT X Expected Rate of Normal FIT X Expected Rate of Repeat FIT
FIT screening completed, test abnormal, colonoscopy completed, no cancer detected	Expected Participation Rate FIT X Expected Rate of Falsely Abnormal FIT X Expected Rate of Colonoscopy Completion after Abnormal FIT X Expected Rate of Colonoscopy to Cecum with Adequate Bowel Preparation
FIT screening completed, test abnormal, colonoscopy completed, cancer detected, first cancer treatment visit completed	Expected Participation Rate FIT X Expected Prevalence of Patients with CRC X Sensitivity of FIT for CRC X Expected Rate of Colonoscopy Completion after Abnormal FIT X Expected Rate of Colonoscopy to Cecum with Adequate Bowel Preparation X Expected Rate of Completion of First Treatment Consultation Visit
*For each strategy, the predicted rates of each “success” were estimated, and then summed to come up with the overall predicted strategy-specific proportion of patients achieving effective screening “successes”	

We considered several factors for sample size selection for primary comparisons of the FIT strategy vs. Usual Care, and the Colo strategy vs. Usual Care on the outcome of proportion of patients with effective screening successes. Given that 2,400 patients will be assigned to the FIT strategy, and 2,400 to the Colo strategy, assuming alpha=0.05, 170 patients are required to be assigned to Usual Care for the FIT vs. Usual Care, and Colo vs. Usual Care comparisons to have at least 80% power to detect the differences predicted above. However, we decided to assign a sample size of 1200 patients to the Usual Care Strategy for the following reasons. First, the cost of including more patients in the Usual Care strategy is minimal. This is because no interventions are planned for this group, and because outcome adjudication will be done using EMR data. Much of the data required for all patients in this project’s analyses are the same as the data that the Screening Process Documentation Unit will have to submit for all Parkland patients as part of PROSPR mandated Documentation Unit activities. Second, we expect some variation in Usual Care practices across the primary care clinics within the Parkland system. Specifically, individual physicians and clinics may have processes in place that may lead to higher than system average rates of effective screening. *We therefore decided to include 1200 patients in the Usual Care arm, resulting in a final randomization ratio of 1:2:2 for Usual Care, FIT, and Colo.*

We conducted a post-hoc power calculation using Bonferroni correction to allay potential concerns about Type 1 error. With sample sizes of 2,400 patients in FIT outreach and 2,400 patients colonoscopy outreach and a potential loss-to-follow up of 10%, we had 67% power to detect a difference in the screening process completion proportions of 13.5% and 16.6% between the two intervention groups using a chi-square test at a two-sided significance level of 0.017 with Bonferroni correction. If we assumed no loss-to-follow up, we would have 72% power to detect this difference at a significance level of 0.017. With a sample size of 2100 patients assigned to usual care, assumed screening process completion rate of 8.6%, and 10% potential loss to follow-up, we had >95% power to detect differences of between both outreach intervention groups and usual care using a chi-square test at a two-sided significance level of 0.017. Thus overall, given that power to detect the target differences was substantial, even requiring Bonferroni correction for the key comparisons, chances of a type 1 error are low. Further, examination of the 95% confidence intervals for

differences in screening process completion for FIT vs. colonoscopy outreach, and each outreach arm versus usual care, suggest that repetition of the trial would be predicted to result in clinically meaningful, and qualitatively similar differences. Notably, the range of differences between the lower and upper confidence interval bounds around estimates of intervention group differences for the outcome of screening process completion is narrow (under 6%) for all comparisons.

Achieving our target sample size of 6000 patients is entirely feasible. Our preliminary data indicate over 32,000 patients age 50-64 years are seen one or more times within a year, and that over 17,000 also are covered by the Parkland Health Plus medical assistance program for the uninsured. Of these, 38.8% (95%CI, 38.0-39.5) are screen up to date, thus over 10,500 patients are likely to be screen eligible, and the vast majority is expected to meet our simple inclusion/exclusion criteria.

Table 4. Key assumptions for sample size calculations	FIT Strategy	Colo Strategy	Usual Care: FIT	Usual Care: Colonoscopy
Sensitivity for CRC ²⁰	.75	.95	.75	.95
Expected Participation Rate* ^{53;57;58}	.32	.15	.2	.10
Expected Colonoscopy Completion Rate After Abnormal FIT ²³⁻²⁵	.75	n/a	.5	n/a
Expected Rate of Completion of First Treatment Consultation Visit If CRC Diagnosed*	.95	.95	.95	.95
Expected Rate of Abnormal FIT† ^{59;60}	0.1	n/a	0.1	n/a
Expected Proportion of Patients with Normal FIT Completing Annual FIT X 2 ^{30;31}	.50	n/a	0.4	n/a
Expected Prevalence of CRC for Individuals Age 50-64 Years ⁶¹	0.001	0.001	0.001	0.001
Expected Rate of Colonoscopy to Cecum with Adequate Bowel Preparation**	0.9	0.9	0.9	0.9
*Estimated based on prior analyses for Usual Care **Estimated †Also based on prior feasibility RCT data				

To evaluate the consistency and magnitude of outcomes for all primary hypotheses, we will conduct pre-specified, subgroup analyses on the following baseline (pre-randomization) characteristics: gender, race, ethnicity, socioeconomic status, insurance status, comorbidity rates, and frequency of outpatient visits. These factors were chosen because all have been associated with rates of screening completion, and may predict effective screening “successes”^{16;39}. Simple subgroup stratified analyses will be complemented with multiple logistic regression analyses using the proportion of patients effectively screened as the dependent variable, and baseline demographic characteristics and intervention group assignments as independent variables to determine independent predictors of effective screening. Similar analyses will be performed for the outcomes of screening non-participation and cost per-patient effectively screened. Comorbidity will be estimated using the Charleson comorbidity index.

In secondary analyses, we will compare the frequency and rates of screen-detected CRC, advanced adenoma, and CRC mortality for the three strategies (FIT vs. Colo, FIT vs. Usual Care, and Colo vs. Usual Care). These are rare outcomes, so power on these is limited.

In secondary analyses, will compare rates of completion of the steps that are required for effective screening between the three strategies. We have deliberately chosen a stringent, “all or nothing” primary outcome of effective screening success. We will also perform secondary analyses to compare the FIT and Colo strategies, as well as FIT vs. Usual Care, and Colo vs. Usual Care, based on the “partial credit” measure of proportion of steps in the screening continuum completed

Cost Assessment Plan. We will conduct cost assessment from the healthcare system perspective of Parkland, with the primary goal of determining the cost per patient effectively screened, for each of the three screening strategies. Effectively screened will be defined by meeting one of the screening

“success” endpoints (see Table 2). Follow up time for cost-assessment will start at randomization and end either when a patient reaches an effective screening “success” endpoint, or at the end of the three year-follow up time. In the primary cost analysis, costs will specifically include:

- **For the FIT strategy**, costs of mailed outreach invitation and centralized processes to promote screening completion and guideline based follow up. In detail, this will be comprised by costs of identifying screen non-up-to-date patients, invitation letters, FIT kits with return mailer and prepaid postage, test processing, result letters for normal and abnormal tests, and activities to promote screening completion and guideline appropriate follow up, including reminder phone calls, phone calls to direct book a diagnostic colonoscopy and pre-colonoscopy clinical review, follow up test scheduling, colonoscopy costs, and first treatment consultation visits for patients with CRC.
- **For the Colo Strategy**, costs of mailed outreach invitation and centralized processes to promote screening completion and guideline based follow up. In detail, this will be comprised by costs of identifying screen non-up-to-date patients, invitation letters, colonoscopy tests, bowel preparations, result letters for normal and abnormal tests, and activities to promote screening completion and guideline appropriate follow up, including reminder phone calls, phone calls to direct book colonoscopy with pre-colonoscopy clinical review as needed, follow up test scheduling, and first treatment consultation visits for patients with CRC.
- **For the Usual Care strategy**, costs of any FIT kits distributed, FIT kits processed, colonoscopies completed for purposes of screening or follow up of abnormal FIT, bowel preparations, pre-colonoscopy clinical review and pre-op visits at the Ambulatory Surgical Center, and first treatment consultation visits for patients with CRC.

We will employ well-established methods for all economic analyses, including sensitivity analyses, and use robust measures to gather the inputs required for cost assessments. Standard national cost-effectiveness guidelines will be followed^{62;63}. In the sensitivity analysis, we will consider the costs of screening that exclude FIT processing and colonoscopy costs to examine cost per patient screened of the centralized processes to promote screening completion and clinical follow up. We will also perform sensitivity analyses to investigate the robustness of the findings to different assumptions including: 1) variation in time costs for the two interventions; and 2) variations in the assumptions made on the discount and inflation rates. We will carry out one-way sensitivity analyses (i.e., examining effect on outcomes by varying one parameter at a time), multivariate sensitivity analyses (i.e., examining effect on outcomes by varying several parameters simultaneously using Tornado diagrams) and probabilistic sensitivity analyses (i.e. simulations based on the likelihood of parameters’ values occurring)^{62;63}. Strategy costs in each group consist of time costs and material costs. Time costs will be obtained from time logs completed by intervention staff (recording time spent in strategy related activities) and staff wages and benefits. Material costs (for example cost of letters and of FIT kits mailed) will be obtained from invoices and budgets, and claims data when appropriate. Costs of medical services, specifically for hospital-health system inputs, will be obtained from the Parkland system. Medical costs will be measured by the Parkland cost accounting system (Lawson version 9.03). All costs will be standardized to 2013 dollars using the Consumer Price Index for Hospital and Related Services, with costs and outcomes discounted at 3%⁶⁴.

Statistical analyses for cost assessment.

- *Hypothesis 1c. Costs, including the cost-per patient effectively screened, will be lower for the FIT vs. Colo strategy.*

- *Hypothesis 2a3. The cost per-patient effectively screened will be lower for the FIT strategy vs. Usual Care.*
- *Hypothesis 2b3. The cost per-patient effectively screened will be lower for the Colo strategy vs. Usual Care.*

The primary cost outcome is the strategy cost per-patient effectively screened. Incremental cost-effectiveness ratios (ICER) will be computed as incremental outcome (number of patients meeting one of the effective screening “successes” in the FIT group minus number of patients meeting the same outcome in the Colo group) divided by the incremental cost (total strategy-specific costs in the FIT group minus total strategy-specific costs in the Colo group). Bootstrapping will be used to obtain 95% confidence intervals for the ICER^{65;66}. For comparisons of the FIT strategy vs. Usual Care, and the Colo strategy vs. Usual Care, on the outcome of cost per-patient effectively screened, ICERs will be calculated in a similar fashion.

CRITERIA FOR INCLUSION OF SUBJECTS:

The target study population includes 6000 patients (names and contact information selected from the Parkland-UT Southwestern PROSPR Center database IRB #082011-040) who are not up-to-date with CRC screening, age 50-64 years, seen one or more times at a Parkland primary care clinic, and participants in Parkland’s medical assistance program for the uninsured, Parkland Health Plus (Parkland Health Plus insurance and ≥ 1 primary care visit within one year (Index Year)). Patients who obtain coverage through the Affordable Care Act’s Health Insurance Marketplace after randomization will not be removed from the study. Information regarding prior CRC screening will be based on Epic codes and EMR-derived diagnosis and procedure codes (CPT, ICD-9, HCPCS, LOINC) for colonoscopy, sigmoidoscopy, or stool blood testing⁴⁸. Both English and Spanish speakers will be eligible for participation. No racial or ethnic group will be excluded from participation.

CRITERIA FOR EXCLUSION OF SUBJECTS:

Patients will be excluded if they are up-to-date with CRC screening, defined by: a) Colonoscopy in the last 10 years, b) Sigmoidoscopy in the last 5 years, or c) Stool blood test (FIT) in the last year. Patients with a prior history of CRC, inflammatory bowel disease, or colon polyps, or who do not have an address or phone number on file will be excluded. Incarcerated individuals will also be excluded.

SOURCES OF RESEARCH MATERIAL:

The Research materials are: 6000 subjects’ names and contact information selected from the Parkland-UT Southwestern PROSPR Center database (IRB #082011-040) who have been seen one or more times at the PHHS primary care clinic and PHHS electronic medical records to review CPT codes related to CRC screening, visits and tests.

RECRUITMENT OF SUBJECTS:

Recruitment will occur with the following steps:

1. EMR data will be used to identify individuals aged 50 to 64, with at least one primary care visit in the last year.
2. Study inclusion and exclusion criteria will be applied to this dataset.
3. A random sample of 6000 individuals meeting study inclusion criteria will be identified.
4. The 6000 patients randomly selected will be randomly assigned to one of three groups in a 1:2:2 ratio: a) Usual Care, b) FIT strategy, c) Colo strategy.
5. Individuals randomized to usual medical care will not be directly contacted at any point of the trial; study data and outcomes will be abstracted from the EMR data.
6. Individuals initially randomized to colonoscopy based screening will receive the following:
 - a. Mailed invitation to complete colonoscopy
 - b. “Live” reminder phone calls

- c. Centralized processes to promote screening completion and guideline appropriate follow up
7. Individuals initially randomized to fecal immunochemical testing based screening will receive the following:
 - a. Mailed invitation to complete a FIT, with a test kit
 - b. “Live” reminder phone calls
 - c. Centralized processes to promote screening completion and guideline-appropriate follow up

Process for obtaining informed consent, and justification for waiver of informed consent:

1. A waiver of consent will be sought for identifying patients aged 50 to 64 who meet study inclusion criteria from the EMR data.
2. A waiver of consent will be sought for random selection of 6000 participants for study inclusion, and for randomization of these participants into one of three strategies.
3. A waiver of consent will be sought for collection of study data for individuals randomized to usual medical care from EMR data, as well as for the FIT and Colo strategies.

Justification for waiver of written/informed consent:

- **Minimal risk is anticipated.** Both fecal immunochemical testing and colonoscopy are accepted standards of care for screening for CRC screening. No experimental screening procedures are planned. Indeed it is only the method of invitation to screening, and processes to promote screening completion and guideline-appropriate follow up that are under study. Further all individuals, regardless of the screening group to which they are randomized, are free to engage in usual medical care, which would include opportunities to partake in CRC screening.
- **The waiver would not adversely affect the rights and welfare of the subjects.** Individuals randomized to programmatic invitation to screening are not being invited to experimental therapies or screening tests. Absence of consent is not anticipated to infringe on the participant’s autonomy, as all individuals randomized may chose to participate or not participate in screening⁸⁵. Moreover, individuals invited to a specific modality such as FIT can call the study coordination team and express interest in an alternate screening test; at that point they will be referred to their primary physician to complete screening. The intervention does not interfere with usual medical care, which would otherwise include opportunities for participation in CRC screening. The interventions are not anticipated to decrease the rate of screening as compared to usual medical care. Further, the health system could have introduced one or more of the interventions proposed without research. The main component of this study that constitutes research is the systematic measurement of study outcomes such as effective screening “successes” among individuals randomized to one of the three groups.⁸⁵
- **Study cannot be practically conducting without waiver.** To do a study of interventions that examines effective CRC screening, and require that only those with prior informed consent participate would markedly bias the study trial results, and greatly limit generalizability, as individuals who consent to be a part of the intervention, and then are randomized, are likely to already be motivated to participate in CRC screening. Further, if informed consent is required, it will be unclear whether non-responders to the study intervention did not respond because of inadequacy of the intervention, or because of non-interest in participating in research. In sum, there is no way to answer the study question without a waiver of informed consent.
- **The subjects will be provided with additional information after participation.** We will publicize results of the study, with specific mailings to all participants informing them of the knowledge gained.

POTENTIAL RISKS:

1. Loss of confidentiality of personal health information. Outreach invitation letters for the FIT and Colo strategies will include patient name and address. The likelihood of this complication is low, as substantial steps will be taken to ensure the safety of personal health data. The seriousness to subjects is moderate to severe.
2. Psychological harm of screening invitation. Psychological harms, such as anxiety, depression, and adverse reactions to negative or positive tests have been suggested as a concern for population based screening.^{72;73} Positive tests may occur in the form of a positive fecal immunochemical test (up to 10% of responders), cancer diagnosis (no more than 1%^{10;74-79} among responders to colonoscopy screening, and 25%⁸⁰ among responders to fecal immunochemical testing with positive tests), and advanced polyp diagnosis (approximately 5%^{10;74-79} among responders to colonoscopy screening, and no more than 30%⁸⁰ among responders to fecal immunochemical testing with positive tests). While data regarding psychological harm from colonoscopy based screening are not available, data from a large trial of stool based screening suggest no statistically significant increase in psychological harms such as anxiety after a positive stool blood test, depression, or suicide among individuals invited to stool based screening as compared with controls not offered screening⁸¹. Overall, the seriousness of psychological harm is judged to be moderate, but the likelihood of psychological harm is projected to be low.
3. Physical harm-colonoscopy. Colonoscopy has a known complication rate of 3 per 1000, including bleeding, perforation, and heart or lung complications¹⁹, and a mortality rate of 1 per 14,000⁸². However, in modeling studies of CRC screening with colonoscopy, the life-years gained from colonoscopy based screening relative to no screening has been estimated to be substantial, estimated at 230 life-years gained²⁰. Thus, the seriousness of colonoscopy complications if one were to occur is moderate to severe, the likelihood of occurrence is low, and the balance of benefits of colonoscopy versus risks appears favorable. The colonoscopy associated risks for patients randomized to this study will be expected to be identical to the risks patients not enrolled in the study would experience as part of standard medical care at Parkland.
4. Physical harm-fecal immunochemical testing. Harms associated with stool occult blood screening for CRC are generally limited to risks conferred by colonoscopy performed in follow up of positive stool tests. Approximately 10% of individuals will have positive stool tests and require colonoscopy, and be exposed to the risks outlined under “physical harm-colonoscopy” above. In modeling studies, of CRC screening with fecal immunochemical testing for occult blood the life-years gained from fecal immunochemical testing based screening relative to no screening has been estimated to be substantial, estimated at 227 life-years gained²⁰. Further, in a large randomized trial that closely evaluated physical risks associated with mass-scale fecal occult blood testing, the rate of physical harm was low⁷³. Thus, the seriousness of complications associated with fecal immunochemical testing if one occurs is moderate to severe, but the likelihood of occurrence is low, and the balance of benefits associated with fecal immunochemical testing versus risks appears favorable.
5. Financial harm--screening. There will be no financial cost associated with completion of the fecal immunochemical test to subjects invited for fecal immunochemical testing, as the tests will be provided free of charge, with return postage included, and no cost for processing of the test. For participants who respond to invitation for screening colonoscopy, or require colonoscopy for follow up of a positive fecal immunochemical test, monetary co-pay or co-insurance may be required by the Parkland Health Plus medical assistance program or other insurance plans (such as, insurance through the Affordable Care Act). A copay for colonoscopy completion of up to \$50.00 is anticipated. Thus, the seriousness of financial harms associated with screening is limited, and the likelihood of some financial cost is moderate.
6. Financial harm—treatment of cancer or unresectable polyps. Through the course of the trial, it is conceivable that patients may be diagnosed with CRC and/or polyps not amenable to

colonoscopic removal. Financial costs to treatment of cancer will reflect those incurred as a course of usual medical care for those with health insurance. Thus, participants diagnosed with CRC may incur co-pays and co-insurance for cancer care. Parkland is committed to providing all patients requiring cancer and/or polyp care identified through the intervention arms of the study with appropriate medical care. Overall, the seriousness of financial harms associated with treatment of cancer is minimal to moderate, and the likelihood of some financial cost is low, mainly because the prevalence of cancer is expected to be low.

SPECIAL PRECAUTIONS:

Minimization of psychological harm of screening invitation. All individuals invited to participate in screening will be provided with a number they may call to make inquiries regarding CRC screening and the study. Individuals who respond to invitation for FIT will be informed of their test results within 1 week of test completion. Individuals who are found to have a positive fecal occult blood test will be scheduled for colonoscopy procedures within 12 weeks to minimize anxiety associated with a positive test. Individuals responding to invitation for colonoscopy screening will be provided with colonoscopy results immediately following completion of endoscopy and be given a written report. Those diagnosed with colorectal polyps or cancer based on pathology review will receive results via mail, as well as clinically indicated follow up.

Minimization of physical harm-colonoscopy and fecal immunochemical testing. All colonoscopies will be performed or directly supervised on a one to one basis by colonoscopists with extensive experience (at least 200 colonoscopy procedures per year), as a greater annual volume of colonoscopic procedures per year has been associated with lower likelihood of colonoscopy complications. In accordance with a national quality assurance guideline, all colonoscopists will be required to note a) whether or not the cecum was reached and which landmarks were used to determine cecal intubation, b) adequacy of the bowel preparation, c) number, size, and location of all polyps identified, d) adequacy of removal of all polyps identified, and e) time spent examining the colon mucosa on withdrawal⁸⁶. Harms associated with stool occult blood screening for CRC are generally limited to risks conferred by colonoscopy performed in follow up of positive stool tests. Therefore, the steps taken to minimize harm from colonoscopy outlined above address minimization of harm from fecal immunochemical testing.

- Procedure for responding to physical harm from colonoscopy. The study participant will immediately be informed of the physical harm, and appropriate medical and surgical interventions will be facilitated. The IRB and NIH will be informed in case of this event.

Minimization of financial harm—screening. There will be no financial cost associated with completion of the fecal immunochemical test to subjects invited for fecal immunochemical testing, as the tests will be provided free of charge, with return postage included, and no cost for processing of the test. For participants who respond to invitation for screening colonoscopy, or require colonoscopy for follow up of a positive fecal immunochemical test, monetary co-pay may be required.

- Procedure for responding to psychological harm from screening. The study participant who experiences psychological harm will be informed by the study primary investigator (Amit Singal, MD) in case of this event. Appropriate referrals for medical and/or psychological care will be facilitated. The IRB and NIH will be informed in case of this event.

Minimization of financial harm—treatment of cancer or unresectable polyps. Financial costs to treatment of cancer will reflect those incurred as a course of usual medical care for those with health insurance. Thus, participants diagnosed with CRC may incur co-pays and co-insurance for cancer care. Parkland has committed to identifying resources to allow for cancer care or surgical resection of polyps un-amenable to colonoscopic resection.

Data and Safety monitoring plan. The principle monitoring entity will be the Primary Investigator, Amit Singal, MD, with daily monitoring. The Institutional Review Boards at University of Texas Southwestern Medical Center and Parkland Health and Hospital System will monitor the trial on an annual basis, and on an ad hoc basis in the case of adverse event report to the one or more of the IRBs. Serious adverse events will be reported to the principle investigator immediately and to both the UT Southwestern and Parkland Health and Hospital System immediately (within 1 business day). Safety and efficacy data will be evaluated formally at the end of the study period, within 3 years from the beginning of the study; no interim safety or efficacy analyses are planned as the risks associated with the study are similar to those a participant would undergo in the course of usual medical care.

The protocol will be stopped for any of the following reasons:

- Unanticipated serious adverse event such as loss of confidentiality (the protocol will be temporarily stopped and if deemed appropriate the protocol will resume after all reports have been completed)
- Occurrence of more than one colonoscopy associated complication such as bleeding or perforation
- Request by Institutional Review Board
- Unanticipated event deemed appropriate indication for stopping the trial by the Principal investigator.

Plans for assuring data accuracy, data security, and protocol compliance include:

- Access to study data only by designated study personnel
- Study data will be kept in a locked room, on a password protected computer, with password protected file. All paper case-report forms will be destroyed after data entry, and kept in a locked room within a locked filing cabinet until data entry and subsequent destruction
- Daily backup of study data to a central, firewalled, password protected server at University of Texas Southwestern Medical Center
- Daily monitoring of protocol compliance through conversations between the principle investigator and research assistants

The mechanisms for reporting unanticipated problems will include:

- Report of the unanticipated problem to the Institutional Review Boards at University of Texas Southwestern Medical Center and Parkland Health and Hospital System immediately (within 1 business day).
- Report of the unanticipated problem to the National Institutes of Health within 10 business days.

Continuing Review will be performed by the IRB on an annual basis, or more frequently, if required.

As part of the Continuing Review submission to the IRB:

- On the IRB Form for continuing review, items referencing unexpected and serious adverse events and DSMB activities will be completed appropriately with a comment to describe the event(s) according to IRB template instructions.
- The Progress Report will be completed according to IRB template instructions and include the principal investigator's a summary of unexpected and serious adverse events and protocol deviations with an analysis of the safety profile of the research.
- If not already done, protocol documents (e.g. protocol, project summary) that require changes based on changes to the risk profile of the research or DSMB recommendations will be submitted as a Modification with the Continuing Review according to IRB instructions.

- A declaration of on-going operational feasibility. If the enrollment rate in the previous year is not sufficient to reasonably reach planned enrollment, a plan should be offered to assure completion of the study.

PROCEDURES TO MAINTAIN CONFIDENTIALITY:

All study data will be kept on within password protected data management programs, on password protected computers, and backed up daily. No non-study personnel will have access to study data. Any data abstraction forms used for data collection such as for chart review will be kept in a locked filing cabinet within a locked room within an office at UT Southwestern Medical Center until data is entered into the database. These paper records will be destroyed after data entry through shredding. At the end of the study, after analyses are complete, all study data will be de-identified, and the identifying key will be destroyed. We anticipate that our procedures to minimize risk of confidentiality will be highly effective.

- **Procedure for responding to loss of confidentiality.** The study participant who experiences loss of confidentiality will be informed by the study primary investigator (Amit Singal, MD) in writing and by phone of the loss of confidentiality. The IRB and NIH will be informed in case of this event. The protocol will be temporarily stopped and if deemed appropriate the protocol will resume after all reports have been completed.

POTENTIAL BENEFITS:

Benefits anticipated as a result of the proposed research include:

- Understanding of which strategy is most clinically and cost-effective for optimizing effective CRC screening. This information will be used to inform local medical care efforts at Parkland, and national policy efforts to improve CRC screening and reduce mortality from CRC, and is thus most relevant to others.
- Understanding whether the type of test offered for screening may influence the rate of effective screening. This information will be used to inform local medical care efforts at Parkland, and national policy efforts to improve CRC screening. Specifically, it may help inform decisions as to whether one screening strategy should be favored for population-based screening over another. Further, as resources available to support CRC screening may be limited, study findings may help guide whether investments in infrastructure for primary colonoscopy based screening or primary stool occult blood test based screening may be favorable. These aspects are most relevant to others.
- Completion of CRC screening for study subjects who are randomized to invitation for screening and respond to invitation. Screening for CRC is believed to reduce mortality from CRC based on randomized controlled trials of stool occult blood testing, case control studies of colonoscopy, and modeling studies²⁰. This aspect of the study is most relevant to the human subjects.

The risks associated to the research subjects are reasonable in relation to the anticipated benefits to research participants and others for the following reasons:

- Participants randomized to the control group will continue to receive usual medical care, and opportunities for screening through the course of usual medical care
- Participants randomized to the intervention groups will be invited to participate in screening in two fully acceptable, standard of care procedures for CRC screening. Thus, while the approach to invitation to screening, and whether type of screening offered affects response to invitation to screening are under study, the screening procedures themselves (colonoscopy and fecal immunochemical testing) are accepted standards for CRC screening and are non-experimental. Indeed, through the course of usual medical care, study participants might otherwise have been recommended one of these screening tests.

- Participants randomized to the intervention group will be free to also engage in usual medical care, and obtain screening outside of study procedures.

Overall, individuals randomized in our study will at minimum receive the usual medical care they would have received were there to be no research study. Further, those randomized to intervention are being offered an additional opportunity to complete a widely accepted, standard of care screening procedure. No experimental procedures or therapies are included. The potential benefits of the study to the human subjects are limited to those who undergo randomization to an intervention arm, as these individuals will have additional opportunities to engage in CRC screening, and will have the process of completing screening encouraged and facilitated.

Importance of knowledge to be gained: The public health implications of our study results to the general population may be substantial. If implementation of centralized processes to promote screening participation and guideline appropriate follow up is effective compared to Usual Care, this approach may be a model for implementing preventive care in large integrated health systems. If the type of screening offered impacts effective screening success rates substantially, then this key information may guide choice of screening test for a national screening program. Study findings may have substantial influence on public health and health policy. In sum, the benefits, both to the human subjects and to others outweigh the risks to which the human subjects are exposed.

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