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Colonoscopy vs. Fecal Immunochemical Test in Reducing Mortality From Colorectal Cancer (CONFIRM): Rationale for Study Design

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RATIONALE: **Colorectal cancer (CRC) is preventable through screening, with colonoscopy and fecal occult blood testing comprising the two most commonly used screening tests. Given the differences in complexity, risk, and cost, it is important to understand these tests' comparative effectiveness.**

STUDY DESIGN: **The CONFIRM Study is a large, pragmatic, multicenter, randomized, parallel group trial to compare screening with colonoscopy vs. the annual fecal immunochemical test (FIT) in 50,000 average risk individuals. CONFIRM examines whether screening colonoscopy will be superior to a FIT-based screening program in the prevention of CRC mortality measured over 10 years. Eligible individuals 50–75 years of age and due for CRC screening are recruited from 46 Veterans Affairs (VA) medical centers. Participants are randomized to either colonoscopy or annual FIT. Results of colonoscopy are managed as per usual care and study participants are assessed for complications. Participants testing FIT positive are referred for colonoscopy. Participants are surveyed annually to determine if they have undergone colonoscopy or been diagnosed with CRC. The primary endpoint is CRC mortality. The secondary endpoints are (1) CRC incidence (2) complications of screening colonoscopy, and (3) the association between colonoscopists' characteristics and neoplasia detection, complications and post-colonoscopy CRC. CONFIRM leverages several key characteristics of the VA's integrated healthcare system, including a shared medical record with national databases, electronic CRC screening reminders, and a robust national research infrastructure with experience in conducting large-scale clinical trials. When completed, CONFIRM will be the largest intervention trial conducted within the VA (ClinicalTrials.gov identifier: NCT01239082).**

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/ajg

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INTRODUCTION

Colorectal cancer (CRC) remains the second most common cause of cancer death in the United States (1) despite a decline in both CRC mortality and incidence over the last 40 years (2). Over half of the decline is estimated to be due to CRC screening (3,4). There is strong consensus among experts regarding the value of CRC screening, but the best screening strategy is unclear. Both the US Multi-Society Task Force (5) and the US Preventive Services Task Force (6) endorse a panel of screening test options that include annual high-sensitivity fecal occult blood testing (HS-FOBT, including the fecal immunochemical test (FIT)), flexible sigmoidoscopy, colonoscopy, CT colonography, and stool-based FIT-DNA testing, though varying levels of evidence support each test. Of these recommended modalities, HS-FOBT and colonoscopy are by far the most commonly used both inside the Veterans Health Administration (VA) (7) and in the broader US population (8). These two screening approaches vary markedly in cost, convenience, and risk, but their effectiveness has not been directly compared with respect to important clinical outcomes. This paper describes the methods and rationale for the design of VA Cooperative Study #577- Colonoscopy vs. Fecal Immunochemical Test in Reducing Mortality from Colorectal Cancer (CONFIRM), a comparative effectiveness study now underway.

STUDY OVERVIEW AND RATIONALE FOR KEY DESIGN ELEMENTS

The CONFIRM trial is being conducted in 46 VA medical centers across the United States and Puerto Rico (**Figure 1**). CONFIRM is a large, pragmatic, randomized, controlled, superiority trial designed to compare the effectiveness of screening colonoscopy and annual FIT screening in an average CRC risk population with a primary endpoint of CRC mortality after, at minimum, 10 years of follow up. The secondary endpoints are to compare the effectiveness of the two strategies with respect to CRC incidence, to evaluate the safety of colonoscopy, and to evaluate the association between colonoscopists' characteristics and colonoscopy outcomes including neoplasia detection, complications, and post-colonoscopy CRC.

The initial study protocol was approved for funding by the Department of Veterans Affairs Cooperative Studies Program Study (VA CSP) in June 2010. With a recruitment goal of 50,000 participants, it will be the largest intervention trial ever funded by VA when completed. Study recruitment began at pilot sites on 22 May 2012. Recruitment is expected to be complete in late 2017, with follow-up complete by late 2027. The rationale for key study design elements is available in the **Supplementary text**.

Study population and recruitment

Study population. Asymptomatic, average-risk adults between the age of 50 and 75 years who are due for screening (e.g., no colonoscopy in the past 9.5 years, no FIT in the past 10 months) were eligible for enrollment (**Table 1**). Exclusion criteria included conditions requiring colonoscopy for screening, surveillance, or diagnostic purposes. Individuals who were up-to-date with CRC screening became eligible when sufficient time elapsed to meet the entry criteria. Individuals unlikely to benefit from screening due to significant comorbidity and those with prior colectomy were also excluded.

Recruitment. Multiple approaches were used to identify potential study participants, and potentially eligible Veterans were contacted through one of several mechanisms to assess their eligibility and interest in trial participation. These mechanisms included direct referrals from clinicians, advertisements, and direct solicitation for enrollment to Veterans who appeared to be eligible. Study members educated clinical staff about CONFIRM and offered multiple methods of referral. Electronic consultation processes were developed and, at some centers, the electronic CRC screening reminder was also modified to prompt consultation. Automated reports were developed to identify potentially eligible Veterans from the electronic health record (e.g., using age, prior screening records, and comorbidity), allowing the research staff to prompt providers to consider referrals. Various invitation letters were used to directly recruit participants, each offering the Veteran the ability to "opt out" of further contact. As prior studies have shown that a recommendation from one's personal physician is a strong predictor of screening adherence (9–11), the preferred letter was signed by the Veterans primary care provider. Other letters were signed by the local Chief of Primary Care, Chief of Gastroenterology, and/or local study investigators. At some study sites, referrals for endoscopic CRC screening were reviewed for candidacy for CONFIRM participation. Local study personnel were encouraged to educate Veterans about the trial at various health education classes. Other recruitment materials (e.g., posters, flyers, electronic bulletin board advertisements, buttons, and brochures) were displayed or distributed within the participating VA medical centers. Eligible individuals were enrolled either in person or over the telephone once they provided written informed consent and Health Insurance Portability and Accountability Act authorization. Information about reasons for ineligibility or reasons for declining to participate was collected through a dedicated case report form from individuals who were approached about CONFIRM but did not subsequently participate.

To assist with study recruitment, CONFIRM leveraged the CSP Network of Dedicated Enrollment Sites (NODES) program. This program funds experienced NODES managers who support recruitment efforts at CONFIRM sites, including troubleshooting of issues and training in best practices for recruitment (12).

Baseline assessment and randomization

Enrolled participants were asked to complete a baseline CRC risk factor survey, including demographics, medication use (e.g., aspirin, statins), habits (e.g., tobacco, alcohol, and exercise), prior CRC screening, and family history of CRC (see **Supplementary** for data collection forms). Female participants were also queried about hormonal exposure.

After completing the baseline assessment, participants were randomized to either colonoscopy or annual FIT screening using a centralized Electronic Data Capture website. Randomization

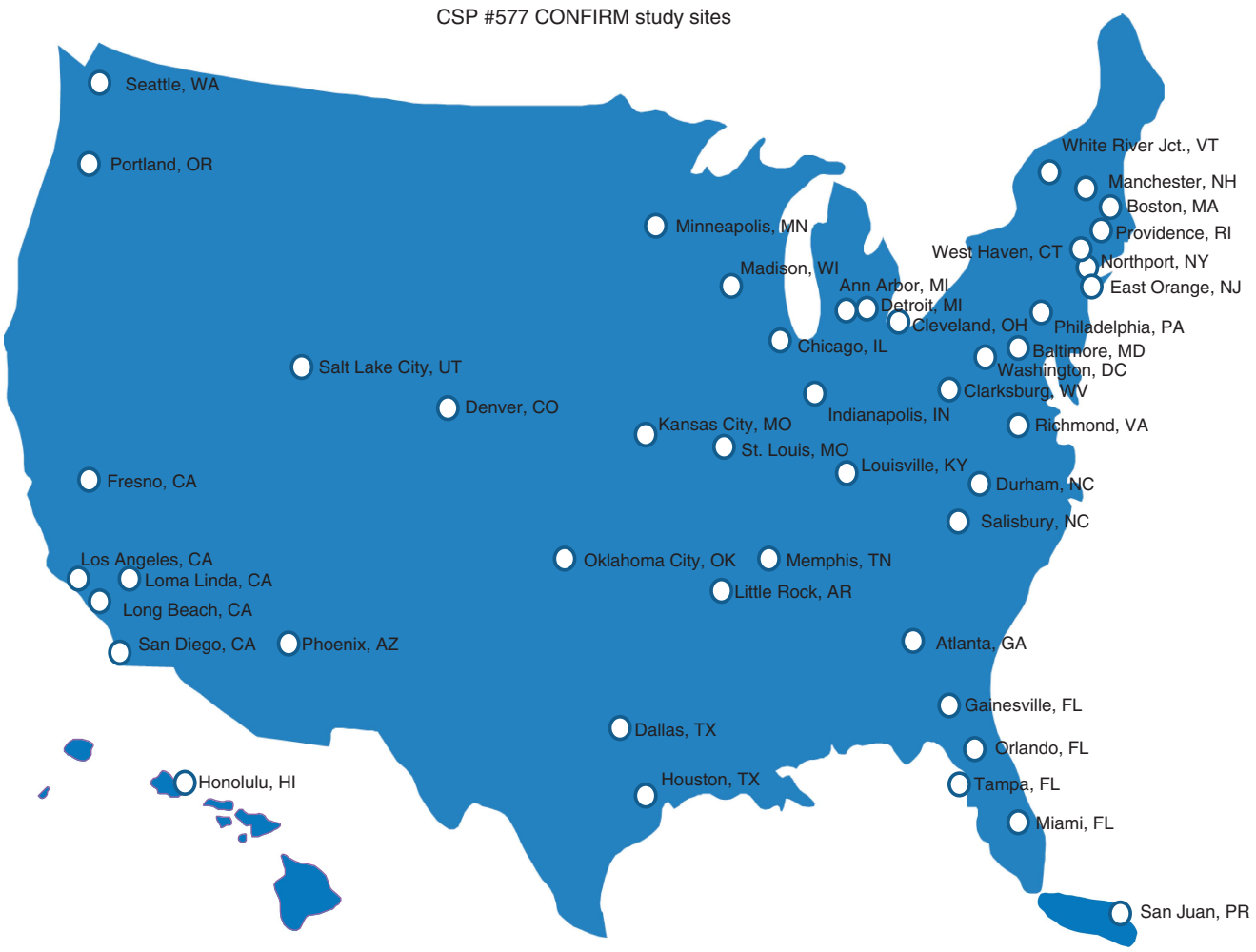

Figure 1. Study sites.

was stratified by medical center using a random permuted block scheme with variable block size. Those randomized to FIT were given instructions both orally and in writing on FIT completion and provided with a FIT kit at the time of the randomization (either in person or through the mail, for those who were enrolled via telephone). For those randomized to colonoscopy, the coordinator facilitated exam scheduling.

Study interventions

FIT. Veterans randomized to FIT screening were instructed in the performance of the test and the importance of annual testing by study staff. We chose the OC-Sensor FIT (Polymedco, Inc., Cortland, NY), which is a single sample test, with a manufacturer's recommended cutoff for determining a positive result of 20 µg hemoglobin/g stool. This threshold for defining a positive test is used by laboratories across the VA. Initially, if the first FIT kit was not submitted within 28 days, a second kit was mailed. In December 2013, this interval was extended to 45 days after it was determined that many initial FIT kits were being returned in the 28–45-day window. FIT screening is offered each year for participants who either test negative or fail to return a FIT kit. This process is initiated ~10 months after the latest FIT result (or anniversary of randomization for those who do not return their FIT). As there is evidence that pre-notification increases screening uptake (13), a letter is mailed 45 days prior to the FIT kit reminding the participant that they are due for screening. This letter is accompanied by an annual survey that queries about any diagnosis of CRC, exposure to colonoscopy, or change in contact information (see **Supplementary**). Participants who indicate a CRC diagnosis or exposure to colonoscopy are contacted by study staff for details.

FIT kits are then mailed each annual cycle. If the test is not returned within 45 days, a second kit with a reminder is sent. Replacement kits are provided as needed (e.g., due to loss or damage). FIT kits are processed at a VA central lab in Albuquerque, NM and results are mailed directly to the study participant. The FIT result is also placed within the participant's local VA electronic health record (i.e., the site of initial recruitment) for routine clinical care purposes. For those with a positive FIT result, a letter is also sent to the local study investigator who is responsible for arranging for diagnostic colonoscopy and reporting the

Table 1. Inclusion and exclusion criteria

Inclusion criteria
Veteran eligible for VA medical care
Men and women aged 50–75 years
Able to provide informed consent
Exclusion criteria
Symptoms of lower gastrointestinal tract disease warranting colonoscopic evaluation, including:
>1 episode of rectal bleeding within the past 6 months
Iron deficiency anemia
Unintentional weight loss (>10% of baseline weight) over 6 months
Family history of CRC in a first degree relative at any age
Prior history of colonic disease including:
Inflammatory bowel disease (e.g., ulcerative colitis or Crohn's disease)
One or more colorectal neoplastic polyps
CRC
Prior history of colonic resection
Prior colonic examination, including:
Colonoscopy within the past 9.5 years
Sigmoidoscopy within the past 5 years
Barium enema within the past 5 years
CT colonography within the past 5 years
gFOBT or FIT in the past 10 months
Multi-target stool DNA test in the past 3 years[a]
Pregnancy
Prisoner
Significant comorbidity that would preclude benefit from screening
Participation in a concurrent interventional study pertaining to the colon or rectum
Likely inability to track the individual over time (e.g., no permanent address at the time of screening for study entry)

CT, computed tomography; gFOBT, guaiac fecal occult blood test; VA, Veterans Health Administration; CRC, colorectal cancer; FIT, fecal immunochemical test.
[a]Exclusion criteria added on 19 June 2015.

colonoscopy outcome or reasons for lack of colonoscopy to the CONFIRM VA CSP Coordinating Center in West Haven, CT. Once FIT positive, participants are not routinely offered additional FIT screening through the study. These participants are reminded annually about the need for colonoscopy given the prior positive screen, until colonoscopy is performed.

Colonoscopy. Participants randomized to colonoscopy are scheduled for colonoscopy using standard processes at their VA facility. If they fail to complete their colonoscopy, follow-up is performed per local policy. The VA encourages the use of a split-dose bowel preparation for colonoscopy (14), but the study does not mandate any special colonoscopic procedures, instrumentation, preparation, or endoscopic follow-up outside of the expectation of usual high quality clinical care. Study colonoscopies can be performed by any physician with colonoscopy privileges at the participating VA. Physicians in training (e.g., gastroenterology fellows or surgical residents) may participate in study colonoscopies only under the direct one-on-one supervision of the entire procedure by an endoscopist with colonoscopy privileges. While some VA facilities employ nurse practitioners or physician assistants to perform colonoscopy, these providers are not permitted to perform CONFIRM study colonoscopies. At some VA sites, screening colonoscopies may be referred to endoscopists outside the VA; CONFIRM participants who are referred outside the VA are followed in the same manner as those undergoing colonoscopy within the VA.

Follow-up colonoscopy exams for those with a positive FIT or those with abnormal findings at colonoscopy are managed according to the usual practices of the VA centers. Likewise, those with a negative examination would be expected to have a recommendation to repeat colonoscopy in 10 years, per current guidelines (5), assuming screening is clinically warranted. As the study protocol does not dictate surveillance intervals, clinicians are free to make recommendations based upon their usual practice. Local site investigators were provided with current guidelines on colonoscopic screening and surveillance with the recommendation to share with their colleagues (15). As new surveillance recommendations are published, the VA National Gastroenterology Program disseminates these to all colonoscopy providers. Participating sites are instructed to adhere to the same requirements for colonoscopists for FIT positive colonoscopy as outlined for the study colonoscopy described above. Colonoscopy-arm participants are also mailed the annual survey as described for FIT-arm participants.

Outcomes

CRC mortality. Participant survival will be monitored for at least 10 years, with assessment through annual surveys and data reported to vital status registries, including the VA Vital Status File (16) and the National Center for Health Statistics' National Death Index (to determine cause of death). As our primary endpoint is CRC mortality, we will attempt to distinguish death from CRC as opposed to death with CRC. For those participants who are known to have been diagnosed with CRC but do not have CRC listed on their death certificate, adjudication will be performed by a dedicated committee (blinded to randomization status) to determine if the death was attributable to CRC based upon chart review. CRC mortality will be defined to be present when the death certificate records indicate CRC as a cause of death or when adjudicated as such.

CRC incidence. CRC incidence will be determined through the annual survey, as well as through centralized queries of VA databases, including the National Patient Care Files, the VA Central Cancer Registry, the Centers for Medicare and Medicaid database and the Surveillance, Epidemiology and End Results Program (SEER) database. All cases of CRC identified in either the VA Central Cancer Registry (17) or the SEER database (18) will be

classified as a CRC case given that these databases have strong quality control processes in place. Other suspected cases of CRC will be reviewed by the adjudication committee using the same approach described above.

Colonoscopy complication rates. To determine colonoscopy complications, study coordinators call participants 30–45 days following their study colonoscopy to ascertain if complications had occurred. Post-procedural phone call scripts specifically assess for bleeding, perforation, hospitalization, and cardiovascular events. Chart review was also performed prior to inquiring about any potential adverse events occurring between the initiation of the bowel preparation and 30 days after the study colonoscopy. In addition, national VA Corporate Data Warehouse data is queried to identify events occurring within 30 days of the colonoscopy that may have been missed. This process serves to identify events occurring in participants that could not be contacted by telephone despite a minimum of 3 attempts or to specifically inquire of participants that, when reached, may have forgotten. This process also identifies care (including colonoscopy and/or management of complications) that occurs at other VA facilities or even at non-VA facilities when the VA pays for that care. In addition to the above process for ascertaining complications, participants who report undergoing colonoscopy on their annual survey are queried about any complications of those procedures.

Colonoscopists' characteristics and neoplasia detection. Neoplasia detection has been shown to be quite variable across endoscopists (19,20). There is also evidence that the variation in adenoma detection is associated with subsequent outcomes, including CRC incidence and mortality (21,22). Therefore, the CONFIRM study will also examine the association between endoscopist characteristics and important clinical outcomes, including neoplasia detection, interval CRC, and complications. All colonoscopists were asked to complete an optional brief questionnaire concerning their training and colonoscopy experience.

Follow-up procedures & minimization of crossover

All active study participants are surveyed annually by mail for at least 10 years or until death. The survey includes a cover letter that not only reminds participants of their enrollment in CONFIRM, but it also reminds them of their randomization arm and makes special mention of any non-adherence concerns identified for the individual. For example, those who have tested FIT positive but have not yet undergone colonoscopy are asked to contact their physician and/or the study team for assistance. The data collection schedule is shown in **Table 2**.

When mail is returned due to an invalid address, study personnel seek a current address through searches of the national VA databases, which are updated during healthcare visits. The study team also utilizes alternate contact information that was provided at the time of enrollment and can utilize national search firms, as needed.

Cross-over (e.g., screening colonoscopy performed in FIT arm participants) can jeopardize CONFIRM study aims. To minimize crossover, the study team asked sites to deactivate the electronic health record's CRC screening reminder once a Veteran was randomized in the CONFIRM trial. A note was placed in the electronic health record indicating that the Veteran is participating in the CONFIRM trial and detailing the randomization assignment. In addition, participants were given a laminated "wallet card" indicating their participation in CONFIRM and the arm to which they have been randomized, as well as a contact number should they have questions about study participation. Participants were asked to keep the card on their person and share it with their primary care physicians. However, for those participants who are non-adherent with two successive rounds of FIT screening or who fail to have colonoscopy within ~14 months of randomization, processes are in place to reactivate the reminder so that their clinicians can assess the need for screening. These non-adherent participants are also mailed a letter encouraging them to be screened using the randomized strategy and assistance with arranging that screening is also offered. This message is reinforced with annual letters, encouraging screening within the arm to which they have been randomized.

Quality assurance

The study leadership team regularly reviews reports detailing various aspects of the conduct of the study by participating site, such as completion of study forms, screening adherence, diagnostic colonoscopy after positive FIT, and colonoscopy quality metrics. These data are shared with the entire study team and any concerning findings are given focused attention with affected sites. In December 2014, the VA issued a policy on CRC screening that emphasized the importance of timely follow-up of positive FIT results and added a new requirement that all facilities monitor the quality of colonoscopy, with recommendations for tracking of bowel preparation quality, cecal intubation, and adenoma detection rates (14). In February 2017, the VA issued a memo to formally reemphasize the importance of timely management of individuals with positive FIT results.

Statistical considerations

Given the additional risk and cost of colonoscopy, the CONFIRM Planning Committee recommended powering the study to detect a 40% reduction in CRC mortality compared to FIT screening. Based upon prior studies of FOBT (23) and colonoscopy (24–26), we assumed a 10-year mortality from CRC to be 4.0/1000 in the FIT arm (i.e., 33% reduction compared to no screening) and 2.4/1000 in the colonoscopy arm (i.e., 60% reduction compared to no screening). We assumed a 1% annual rate of crossover from FIT to colonoscopy and a 0.5% annual rate of loss to follow-up. A sample size of 50,000 participants has >80% power to detect this 40% difference in 10-year CRC mortality (see **Supplementary**).

A comparison of time to CRC death in the screening colonoscopy arm vs. the FIT screening arm will be performed according to the intention-to-screen principle. The Kaplan–Meier product limit method will be used to estimate cumulative CRC mortality rates. A stratified log-rank statistic will be used to test differences in CRC mortality rates between the screening regimens to account

Table 2. Data collection schedule

	Screening	Baseline	30–45 day post screening colonoscopy	Annually	10 Years
Screening evaluation	X				
History of colonoscopy, FOBT, sigmoidoscopy, barium enema, CT colonography, family history, demographics, health care utilization, medications		X			
Lifestyle measures diet, vitamins, tobacco, alcohol, exercise; hormonal exposures (women)		X			
Randomization		X			
Contact information		X			
Colonoscopy quality info			X		
Colonoscopy findings			X		
Complications of study colonoscopy			X		
Complications of other colonoscopy				X	
Current contact information				X	
Health care utilization				X	
Recent colonoscopy				X	
Recent cancer diagnosis				X	
CRC incidence					X
Vital status					X
Cause of death					X

CRC, colorectal cancer; CT, computed tomography; FOBT, fecal occult blood testing.

for the stratified randomization by site. All time-to-event data will be censored at the date of death from causes other than CRC or at the end of the 10-year follow-up period for survivors (i.e., administrative censoring). A *P*-value of 0.05 (two-sided) will be used as the level of significance for the primary outcome. In a sensitivity analysis, a Cox proportional hazards model will be used to adjust for the following pre-specified baseline covariates: age, sex, race, body mass index, tobacco use, and aspirin/NSAID use to see if any of these variables have an impact on the effect of screening regimen on CRC mortality.

A similar analysis will be used for CRC incidence with censoring occurring at date of death due to a cause other than CRC or at the end of the 10-year follow-up period. As CRC incidence is expected to be initially higher in the colonoscopy arm because of increased sensitivity for cancer relative to one-time FIT screening (27), with an expected fall in subsequent incidence (28), methods appropriate for a non-proportional hazard may be used.

STUDY OVERSIGHT

Ethical oversight of the entire study is provided by a single VA Central Institutional Review Board. Study progress is monitored monthly by an Executive Committee comprised of study leadership, subject matter experts and selected study investigators. An external independent Data Monitoring Committee (DMC), comprised of subject matter experts in CRC screening and biostatistics, reviews the trial on a semi-annual basis and has access to unblinded outcome data. The DMC membership reports to the study sponsor with their recommendations for study continuation or early termination, based upon review of data on issues, such as recruitment and safety.

DISCUSSION

The CONFIRM trial is pragmatically designed to compare the effectiveness of a screening strategy of colonoscopy to annual FIT screening for the prevention of CRC mortality; it is the largest intervention trial ever funded by the Veterans Health Administration. The CONFIRM trial is the only such trial in the US but there are three ongoing European trials that address similar questions. (29–31) All of these are large, prospective trials that compare colonoscopy to another approach (FIT, no screening or both); in the U.S., a no-screening control group would not be considered ethical since CRC screening in the average risk population is the standard of care.

There are many differences among the ongoing randomized clinical trials of colonoscopy, including the primary endpoints, duration for follow-up, and FIT interval (**Table 3**), but perhaps the most important is the basic study design. CONFIRM is fundamentally different in that all enrolled participants provide informed consent *prior to* randomization, indicating willingness to accept screening with either approach. This is in contrast to the European trials which randomize individuals from population registries without informed consent. Those allocated to a control (no-screening) arm

Table 3. Description of ongoing controlled trials of colonoscopy vs FIT or no screening

Study (country)	Size	Age at recruitment	Assignment of screening intervention	Comparison (ratio)	Follow-up years	CRC outcomes
CONFIRM (United States)	50,000	50–75	Consent prior to randomization	Colonoscopy- Program vs. annual FIT (1:1)	10	1° Mortality 2° Incidence
COLONPREV (29) (Spain)	57,000	50–69	Post-randomization invitation	Colonoscopy-one time vs. biennial FIT (1:1)	10	1° Mortality and Incidence
NordiCC (30) (Netherlands, Norway, Poland, Sweden)	95,000	55–64	Post-randomization invitation[a]	Colonoscopy one time vs. no screening (1:2)	15	1° Incidence and Mortality
SCREESCO (31) (Sweden)	200,000	59–62	Post-randomization invitation[a]	Colonoscopy one time vs. FIT at year 1 and 3 vs. no screening (1:2:3)	15	1° Mortality 2° Incidence

CRC, colorectal cancer; FIT, fecal immunochemical test.
[a]Control (non-screening arm) passively followed through registry data without consent.

are not aware that they are part of a study, while those allocated to a screening arm are assessed for eligibility and offered the predetermined screening option, but the study design readily allows for and records crossover between screening arms.

Given this major recruitment difference, one would expect that the compliance with the assigned intervention would be higher and the crossover rate would be lower in CONFIRM relative to the other trials. In fact, initial results indicate relatively low compliance and high crossover in the COLONPREV trial (29). Like CONFIRM, COLONPREV is a two-arm trial comparing colonoscopy to FIT with a primary outcome of CRC mortality; COLONPREV has completed enrollment and reported their results through the initial screening round. The COLONPREV participation rates were 24.6% in the colonoscopy arm and 34.2% in the first round of the FIT, and the crossover rates were high. Among those who accepted a screening offer, 23.2% and 1.2% in the colonoscopy and FIT arms, respectively, requested the alternate screening test. In the NordICC trial, colonoscopy participation ranged from 22.9% in the Netherlands, to 33.0% in Poland, to 39.8% in Sweden to 60.7% in Norway (32). This variation is remarkable given that Poland, Sweden, and Norway each used the same invitation routines (while the Netherlands required a pre-procedure clinic visit), suggesting differences in screening uptake based upon cultural settings and beliefs. While adherence has not yet been reported in CONFIRM, it will likely be higher for each intervention since CONFIRM participants explicitly consented to have their recommended screening strategy determined through randomization, indicating a willingness to be screened and some level of equipoise about the two tests. Further, the acceptance rate of CRC screening is likely to be influenced by the screening culture of the countries involved. The 24.6% adherence in the COLONPREV colonoscopy-arm might be expected in a country with low overall CRC screening rates (33), but it would be unexpected in the US where CRC screening is considered the standard of care and colonoscopy is common. Current estimates suggest that over 60% of the population is adherent with CRC screening recommendations (8) and there is a national effort to reach an 80% screening rate by 2018 (34). The VA currently has exceeded 80% adherence with CRC screening since 2009.

Study design differences also impact the analysis and interpretation of the results. Low participation and high crossover rates in the European trials may limit the generalizability of an intention-to-screen analysis. The European trials will assess the willingness of their population to be screened, their choices among screening tests and the outcome of offering a CRC screening strategy to a European population. The CONFIRM study will present both intention-to-screen and per-protocol analyses and we expect that it will directly answer the question of the efficacy of a strategy of an initial colonoscopy vs. annual FIT screening.

There are several threats to the completion, interpretation, and applicability of the CONFIRM trial. Identification and accrual of individuals is time consuming and labor intensive. It is expected that CONFIRM will meet its 50,000 participant accrual goal by late 2017. The primary endpoint of this trial is CRC mortality at 10-year follow-up. CRC mortality has been steadily decreasing and survival after CRC diagnosis has been lengthening in the US (2), so it is possible that there will be fewer CRC deaths in the study population than were assumed in the sample size calculation. If the number of CRC mortality endpoints is lower than predicted, extending the follow-up of the study participants for all participants until 2027 will increase the average follow-up from 10 years to ~12.5 years, thereby increasing statistical power. Non-adherence and crossovers can threaten the validity of the efficacy result if the compliance rates do not reflect real-world experience, though the study team has made considerable effort to assure high quality performance of screening at every step of the process. Although an intention-to-screen analysis will be used for the primary outcome, a per-protocol analysis has been included in the analytic plan. Since the primary results of this trial will not be known for over a decade, there is always a threat that a new test will disrupt the current CRC screening options and make the comparison of colonoscopy with FIT less relevant. However, we expect that both FIT and colonoscopy will remain major screening test options for the foreseeable future.

CONCLUSIONS

The CONFIRM study is a large, pragmatic trial that will randomize 50,000 average risk adults to compare the effectiveness of screening colonoscopy vs. annual FIT screening for the reduction in CRC mortality, with expected study completion in 2027. CONFIRM leverages several key characteristics of the VA's integrated healthcare system, including a shared medical record with national databases, electronic CRC screening reminders, and a robust national research infrastructure with experience in conducting large-scale clinical trials. CONFIRM will be the largest intervention trial conducted within VA and will advance our understanding of CRC screening.

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CONFLICT OF INTEREST

Guarantor of the article: Jason A. Dominitz, MD, MHS.

Specific author contributions: (1) With respect to author contributions, all of the authors have approved the final version of the manuscript. The specific contributions are detailed below: Jason A. Dominitz: planning and conducting the study, collecting and interpreting data, and drafting the manuscript; Douglas J. Robertson: planning and conducting the study, collecting and interpreting data, and drafting the manuscript; Dennis J. Ahnen: planning and conducting the study, collecting and interpreting data, and drafting the manuscript; James E. Allison: planning and conducting the study, interpreting data, and drafting the manuscript; Margaret Antonelli: planning and conducting the study, and drafting the manuscript; Kathy D. Boardman: planning and conducting the study, collecting and interpreting data, and drafting the manuscript; Maria Ciarleglio: planning and conducting the study, collecting and interpreting data, and drafting the manuscript; Barbara J. Del Curto: planning and conducting the study, collecting and interpreting data, and drafting the manuscript; Grant D. Huang: planning and conducting the study, collecting and interpreting data, and drafting the manuscript; Thomas F. Imperiale: planning and conducting the study, collecting and interpreting data, and drafting the manuscript; Meaghan F. Larson: planning and conducting the study, collecting and interpreting data, and drafting the manuscript; David Lieberman: planning and conducting the study, collecting and interpreting data, and drafting the manuscript; Theresa O'Connor: planning and conducting the study, collecting and interpreting data, and drafting the manuscript; Timothy J. O'Leary: planning and conducting the study, interpreting data, and drafting the manuscript; Peter Peduzzi: planning and conducting the study, collecting and interpreting data, and drafting the manuscript; Dawn Provenzale: planning and conducting the study, collecting and interpreting data, and drafting the manuscript; Aasma Shaukat: planning and conducting the study, collecting and interpreting data, and drafting the manuscript; Shahnaz Sultan: planning and conducting the study, collecting and interpreting data, and drafting the manuscript; Amy Voorhees: planning and conducting the study, collecting and interpreting data, and drafting the manuscript; Robert Wallace: planning and conducting the study, collecting and interpreting data, and drafting the manuscript; Peter D. Guarino: planning and conducting the study, collecting and interpreting data, and drafting the manuscript.

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Potential competing interests: Douglas J. Robertson: Medtronic, Scientific Advisory Board (Medtronic produces the PillCam Colon 2 system); Dennis J Ahnen: Data Monitoring Committee Member for Cancer Prevention Pharmaceuticals' trial of sulindac and DFMO in FAP; Timothy J. O'Leary: i. GRAIL: Member of Population Health Study Scientific Advisory Board and ii. MioDx: Member of Scientific Advisory Board.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Colorectal cancer screening reduces cancer incidence and mortality.
- ✓ Colonoscopy and fecal occult blood testing are the two most commonly used screening modalities in the United States.
- ✓ There are no published head-to-head comparative effectiveness studies of colonoscopy vs. fecal occult blood testing for cancer mortality or incidence.

WHAT IS NEW HERE

- ✓ The VA Cooperative Studies Program has initiated the first US study (CONFIRM) comparing screening colonoscopy to annual fecal immunochemical testing.
- ✓ The CONFIRM Study will enroll 50,000 average risk adults and follow them for 10 years to assess cancer mortality and incidence.
- ✓ The CONFIRM Study is the largest prospective trial ever undertaken by the VA, and it leverages several unique features of the Veterans Health Administration, including its electronic health records and clinical reminders systems.

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APPENDIX A

Appendix A CONFIRM Study GroupCooperative Studies Program Coordinating Center, VA Connecticut Healthcare System, West Haven, CT key staff: Gary R. Johnson, MS, Beata M. Planeta, MS.

Local/co-local site investigators:

Site name	Facility name	Local/co-local site investigator(s): present and past
Ann Arbor	VA Ann Arbor Healthcare System	Stacy Menees, MD Sameer Saini, MD, MS Past: Phillip Schoenfeld, MD, MSEd, MSc
Atlanta	Atlanta VA Medical Center	Stephan Goebel, MD Past: Mohammad Wehbi, MD
Baltimore	Baltimore VA Medical Center	Erik C. von Rosenvinge, MD
Boston	VA Boston Health Care System	Gyorgy Baffy, MD, PhD Ildiko Halasz, MD Past: Marcos C. Pedrosa, MD, MPH
Chicago	Jesse Brown VA Medical Center	Lyn Sue Kahng, MD
Clarksburg	Louis A. Johnson VA Medical Center	Riaz Cassim, MD

Site name	Facility name	Local/co-local site investigator(s): present and past
Cleveland	Louis Stokes Cleveland VA Medical Center	Katarina B. Greer, MD, MS Margaret F. Kinnard, MD
Dallas	VA North Texas Health Care System	William V. Harford, Jr. MD
Denver	VA Eastern Colorado Health Care System	Jed E. Olson, MD Swati G. Patel, MD Past: Dennis J. Ahnen, MD Kenneth H. Berman, MD J. Andy Mengshol, MD, PhD
Detroit	John D. Dingell VA Medical Center	Fadi Antaki, MD
Durham	Durham VA Medical Center	Deborah A. Fisher, MD, MHS
East Orange	New Jersey Health Care System	Isabelita Cordoba Rellosa, MD Christopher Lenza, DO
Fresno	VA Central California Health Care System	Devang Prajapati, MD Helen W. Wong, MD
Gainesville	Malcom Randall VA Medical Center (North Florida/South Georgia VA Healthcare System)	Rebecca J. Beyth, MD, MSc Past: Shahnaz Sultan, MD, MHSc
Honolulu	VA Pacific Islands Health Care System	Joseph Manlolo, MD Past: Fernando V. Ona, MD
Houston	Michael E. DeBakey VA Medical Center	Rhonda A. Cole, MD Eric K. Taylor, NP
Indianapolis	Richard L. Roudebush VA Medical Center	Thomas F. Imperiale, MD Charles Kahi, MD
Kansas City	Kansas City VA Medical Center	Tarun Rai, MD Prateek Sharma, MD Past: Steven R. Warlick, MD
Little Rock	Central Arkansas Veterans Healthcare System	Curt H. Hagedorn, MD Past: Lubna Maruf, MD
Loma Linda	VA Loma Linda Healthcare System	Ronald Fernando, MD Christian S. Jackson, MD
Long Beach	VA Long Beach Healthcare System	M. Mazen Jamal, MD, MPH Douglas J. Nguyen, MD Past: Farrukh H. Merchant, MD
Los Angeles	VA Greater Los Angeles Healthcare System	Joseph R. Pisegna, MD
Louisville	Robley Rex VA Medical Center	Endashaw Omer, MD, MPH Dipendra Parajuli, MD
Madison	William S. Middleton Memorial Veterans Affairs Medical Center	Adnan Said, MD, MS
Manchester	Manchester VA Medical Center	Heiko Pohl, MD
Memphis	Memphis VA Medical Center	Claudio Tombazzi, MD Past: Toan D. Nguyen, MD
Miami	Miami VA Healthcare System	Paul A. Feldman, MD, MSC
Minneapolis	Minneapolis VA Health Care System	Aasma Shaukat, MD, MPH
Northport	Northport VA Medical Center	Edward Sun, MD Past: Robert D. Shaw, MD
Oklahoma City	Oklahoma City VA Medical Center	Mohammad Madhoun, MD William M. Tierney, MD
Orlando	Orlando VA Medical Center	Heather Hockman, MD Past: Christopher Lopez, MD
Philadelphia	Philadelphia VA Medical Center	E. Carter Paulson, MD Past: Martin Tobi, MB, ChB
Phoenix	Phoenix VA Health Care System	Michele Young, MD
Portland	Portland VA Health Care System	Nancy C. Ho, MD David Lieberman, MD Past: Ranjan C.V. Mascarenhas, MD
Providence	Providence VA Medical Center	Kittichai Promrat, MD

Site name	Facility name	Local/co-local site investigator(s): present and past
Richmond	Hunter Holmes McGuire VA Medical Center	Mitchell Schubert, MD Past: Juan Diego Baltodano, MD
Salisbury	W.G. (Bill) Hefner VA Medical Center	Frank S. Pancotto, MD
Salt Lake City	VA Salt Lake City Health Care System	Andrew J. Gawron, MD Amelia (Beth) Underwood, MD Past: Mae F. Go, MD
San Diego	VA San Diego Healthcare System	Samir Gupta, MD, MSCS Samuel B. Ho, MD
San Juan	VA Caribbean Healthcare System	Priscilla Magno, MD Doris H. Toro, MD
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St Louis	John Cochran VA Medical Center	Jill E. Elwing, MD
Tampa	James A. Haley Veterans' Hospital	Jeffrey A. Gill, MD Past: Susan Goldsmith, MD
Washington, DC	Washington DC VA Medical Center	Michael Yao, MD
West Haven	VA Connecticut Healthcare System, West Haven Campus	Petr Protiva, MD
White River Junction	White River Junction VA Medical Center	Heiko Pohl, MD