Predicting and Addressing Colonoscopy in Safety Net Settings (PRECISE) Statistical Analysis Plan

NCT03925883

Version: February 15, 2024

Statistical analysis plan:
Predicting and Addressing Colonoscopy non-Adherence in Community Settings (PRECISE)

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1. Study design and specific aims

Predicting and Addressing Colonoscopy Non-adherence in Community Settings (PRECISE) is an individual-randomized clinical trial of a patient navigation intervention versus usual care to improve participation in follow-up colonoscopy in a federally qualified health center. The study consists of two phases: **Phase I** (Aim 1) is a milestone-driven planning phase to externally validate the risk-prediction score, stratify patients' probability of adhering to follow-up colonoscopy, and adapt patient navigation materials for the local context. **Phase II** (Aims 2–3) is a large-scale, targeted patient-randomized controlled trial that will include ~1200 patients across ~32 clinics in western Washington State.

The study has the following aims:

Aim 1: Validate externally the predictive risk score using Sea Mar Community Health Center's robust data including 29,000 patients age-eligible for colorectal cancer screening; stratify patients according to risk of non-adherence to follow-up colonoscopy; and adapt patient navigation program for the local context.

Aim 2: Assess the effectiveness, costs, and cost-effectiveness of a centralized, phone-based patient navigation program for follow-up colonoscopy receipt for patients at moderate risk or high risk for non-adherence. (See **Handling of Deviations and Protocol Amendments 9.1 and 9.2)**

Aim 3: Assess differences in the intervention arms in secondary outcomes (e.g. time to colonoscopy receipt, no-show/canceled appointments, colonoscopy quality) and moderators of intervention effectiveness (e.g. probability level, intervention dose, and patient age, ethnicity, and sex) (See **Handling of Deviations and Protocol Amendments 9.3)**

2. Patient Identification

Clinic staff will prospectively identify patients ages 50 to 75 with an abnormal fecal test (FIT) result. A pre-adjudication process will be completed to confirm eligibility for all patients by the patient navigator and a clinical team (including the study gastroenterologist).

Patients will be excluded if they have had a recent negative colonoscopy (within the past 3 years) or have a limited set of health conditions (e.g. metastatic cancer, on hospice or in a nursing home, end-stage renal disease, home oxygen use).

3. Randomization and blinding

Patients meeting clinical eligibility criteria will be randomized by the health center (Sea Mar) analyst to receive either the patient navigation intervention or usual care. Study identification numbers linked to patients will be uploaded into REDCap® on a weekly basis, for patients in the navigation arm, with date of abnormal FIT result. We anticipate that the time between patient identification and study randomization will take about 2 weeks. (See **Handling of Deviations and Protocol Amendments 9.4)**

Randomization will be performed using a stratified approach that considers patients' county of residence. We will use Sealed Envelope (London, UK)[1] to randomize patients 1:1 to navigation or usual care in blocks of 4 to 8 individuals, stratified on county of residence. For practical reasons, neither the research team nor the clinic staff will be blinded to randomization assignment. However, measures have been taken to preserve as much blinding as possible. Staff trained in navigation will not perform colonoscopy referral coordination (as part of usual care). Patients randomized to patient navigation are removed from the referral coordinator list to eliminate potential outreach by referral coordinators. In this way, the patient navigation intervention will <u>not</u> be overlaid on usual care, as doing so would result in multiple contacts from multiple clinic staff. (Consistent with usual care, referral

coordinators will contact referred patients who have not completed a colonoscopy making up to three phone attempts; patients who are not reached will be sent a letter.)

The randomization will result in 600 patients assigned to the patient navigation arm and 600 assigned to the usual care arm. We will assess rates of colonoscopy receipt at 1 year overall, and will perform a heterogeneity of treatment effect analysis to assess differential effects by age, sex, ethnicity, language preference, insurance status, and probability of adherence (based on the risk model), using data from the electronic health record.

CHR analysts will assign a colonoscopy completion probability, based on the risk prediction model. These methods have been described previously.[2]

4. Sample size and power

Estimates of the ICC at the clinic level for CRC screening collected from several different studies range from .001 to .10, with the majority ranging from .02 to .05. The ICC for our prior CRC screening study in similar clinics (STOP CRC) was .03.[3] Though we anticipate a lower ICC for this study given that we will partner with a single large federally qualified health center (FQHC) with more uniform procedures and practices (i.e., less between-clinic variability) rather than eight smaller FQHCs in the STOP CRC trial, we will use an ICC estimate of .03 as a conservative upper estimate. Given that larger ICCs increase the design effect and reduce the power of the test, we will provide the minimum detectable odds ratios for the primary outcome for both a near zero ICC and an ICC of .03; we will base our analyses on an average cluster size of 42 patients per clinic (1200 abnormal FIT patients/32 clinics). Based on data from prior studies, we expect that 9% of patients will have a positive FIT, and 44% of patients under usual care will complete a follow-up colonoscopy within 1 year (based on chart abstracted data from 08/05/2017 to 08/04/2018 (N = 715 charts)). In a logistic regression framework, we will have 80% power to detect a difference of 12.9% (completion rate in intervention of 56.9%, OR=1.68) when accounting for the design effect and a difference of 9.2% (completion rate in intervention of 53.2%, OR=1.45), assuming no design effect at a two-tailed alpha level of .05. We believe a difference between 9.2% and 12.9% is both achievable and clinically significant. Notably, our minimal detectable difference is 2-3 times lower that the effect size reported in the New Hampshire Colorectal Cancer Screening Program (27 percentage points).[4]

5. Study outcomes

5.1. Outcome variables

Primary and secondary outcomes and process measures are displayed in Table 1.

Primary outcome: Our primary outcome is whether patients obtain a follow-up colonoscopy within 1 year of having an abnormal FIT result, as assessed through chart audit. Because the navigator's role involves tracking completed colonoscopies and communicating colonoscopy results to patients, it is likely that navigated patients will have more complete capture of colonoscopy events (our primary outcome) than usual care patients. To minimize bias in the collection of primary outcome data across study arms, the study team will implement an adjudication process, where systematic chart abstraction and medical records requests to referring gastroenterologists (GIs) will be performed by an abstractor who is blinded to study arm assignment (See Section 6 below). Starting after the 1-year evaluation interval, procedure and pathology reports from all study patients without electronic health record-evidence of a completed colonoscopy will be requested, and adjudicated by the project chart auditor; the GI and clinical champion will be consulted as questions arise.

Secondary outcomes include time to colonoscopy receipt and adequacy of bowel preparation (% adequate). We will also report colonoscopy outcomes (N, % adenomas and advanced adenomas detected; n cancers found). (See **Handling of Deviations and Protocol Amendments 9.3**)

Table 1. Study Outcomes

Variable	Definition	Numerator	Denominator
Primary outcomes			
Colonoscopy completed	A colonoscopy is completed within 12 mo of the patient's FIT positive test date	No. of patients with completed colonoscopy within 12 mo of FIT positive test date	No. of eligible patients enrolled in study, with exclusions for patients randomized in error
Cost and cost-effectiveness (See Handling of Deviations and Protocol Amendments 7.x)	Cost per program component, per-patient cost, and cost per additional completed colonoscopy	Difference in cost to deliver program	Difference in program effectiveness
Secondary outcomes			
Time to colonoscopy	Time from FIT positive test result to completed colonoscopy	Hazard of obtaining a colonoscopy by 365 days	No. of eligible patients enrolled in study, with exclusions for patients randomized in error
Adequate bowel preparation quality	Bowel preparation is considered adequate by the endoscopist performing the colonoscopy	No. of patients with adequate bowel preparation, preparation is (excellent, good, or fair) and no alterations are made to rescreening interval because of bowel prep quality**	No. of patients with a performed colonoscopy during the study period (include patients for whom the procedure was discontinued because of poor bowel prep)
Colonoscopy outcomes	Adenomas, advanced adenomas, or cancer detected	No. of patients with adenomas, advanced adenomas, or cancer detected (based on pathology report)	No. of patients with a performed colonoscopy during study period

5.2. Covariates

We will treat county as a covariate in all analyses as it was a randomization stratification variable.

5.3. Potential moderators of effectiveness

The following variables will be tested as potential moderators of effectiveness:

Potential Moderator	Categories
Sex	Male, female
Preferred language	English, Spanish, Other
Age	50–54, 55–59, 60–64, 65–69, and 70–75
Insurance status	Medicaid, Medicare, self-pay (uninsured), commercial
Probability of patient adherence to navigation (based on risk score)	Low: 0 < .52, Moderate: .52 < .63, High: ≥.63)

- sex (patient navigation will be more effective in women vs. men)
- preferred language (patient navigation will be more effective in patients who preferred Spanish vs. English; participants who indicated other will not be included in this analysis
- age (patient navigation was more effective in younger vs older age groups, defined as (50–54, 55–59, 60–64, 65–69, and 70–75)
- Insurance status (patient navigation will be more effective in uninsurance adults vs. insured adults)
- Probability of patient adherence to colonoscopy without navigation (patient navigation will be more effective in patients having lower probability of adherence, based on risk score)
- See **Handling of Deviations and Protocol Amendments 9.6**

6. Statistical Methods

6.1. Primary outcome analysis

Primary analysis will rely on a modified intention-to-treat (ITT) that excludes patients from both arms who are randomized in error (determined to be ineligible based on information in the medical record that was missed during the eligibility determination process). Patients in the primary ITT data analysis will retain their randomization assignment irrespective of whether they received patient navigation. Two secondary per-protocol analyses are planned: one that excludes patients who were determined ineligible because they moved, or clinical reasons that occurred post-randomization; and a second that additionally excludes patients who were never reached by the navigator.

Sea Mar's EHR data will be transferred to CHR every 6 months via a secure file transfer. We will examine the distribution of all variables prior to analyses and verify all missing and out-of-range values. We will assess the ICC. If the ICC is .001 or above, we will use hierarchical generalized linear modeling to account for clustering of patients within clinics. If the ICC is less than .001, we will use adjusted logistic regression without accounting for clustering to optimize parsimony. Because the primary outcome is binary (i.e., follow-up colonoscopy, yes/no), we will use a model with a logit link and binomial distribution (i.e., multilevel logistic regression). The independent variable will be arm (dummy-coded) with usual care as the reference group. 'Clinic' will be modeled as a random effect. The model will include county as a covariate (fixed effect) as it was a stratification factor for randomization.

6.2. Secondary outcome analysis

Despite our pre-randomization chart review, we anticipate that some patients will be randomized in error. These patients were determined to be ineligible based on information about a health condition that preceded randomization. For this reason, we will report our primary outcome excluding patients who were randomized in error. In additional two secondary per-protocol analyses are planned, one that excludes patients who were determined ineligible because they moved, or clinical reasons that occurred post-randomization (These patients

may have their referral canceled after the pre-procedure visit with the GI and a clinical review of their medical history.); and a second that additionally excludes patients who were never reached by the navigator. Other secondary analysis will assess between-group differences in time to colonoscopy completion. Using the pathology report, we will also track colonoscopy-related quality measures, including adequacy of colonoscopy prep, detection of adenomas and cancer, and cancer stage at detection.

We will use the Cox proportional hazards regression model with shared frailty for time to colonoscopy completion. The shared frailty model is the survival data analog to random effects regression models that can account for the clustering effect of patients within clinics and Efron method to handle tied survival times. The independent variable will be study arm, which will be coded the same as in the primary outcome analysis. Significant hazard ratios >1 indicate that patient navigation has shorter times to colonoscopy completion and/or initiation of cancer treatment than usual care. For binary secondary outcome and process measures (e.g. time to colonoscopy receipt, adequacy of bowel prep), we will use the same modeling framework (e.g., multilevel logistic regression) as described for our primary outcome. (See **Handling of Deviations and Protocol Amendments 9.5)**

6.3. Analysis of possible moderators

Our preliminary data showed follow-up colonoscopy receipt varied substantially by probability strata (30%, 59%, and 93% for the low, moderate, and high strata, respectively), suggesting that assessments of clinically meaningful impacts could differ by probability strata. To determine whether adherence probability moderates the effect of the intervention, we will add probability strata (moderate, low vs. high) and the product of stratum and arm to the primary outcome model. The product represents the interaction of arm and probability stratum; a significant term provides evidence for effect modification. We will determine the nature of any interaction by examining the simple main effects using graphical methods. We will repeat this analysis using the continuous risk score in place of the risk strata. We will have 80% power to detect an odds ratio for the product term, which represents the multiplicative change from the odds ratio for the moderate probability stratum for arm compared to the low probability stratum for arm of 2.98 (or 0.34 in the opposite direction), accounting for the design effect, and 2.17 (or 0.46 in the opposite direction) assuming no design effect, at a two-tailed alpha level of .05. Previous literature has reported significant differences in the effectiveness of patient navigation for colorectal cancer screening across patient subgroups defined by:

- Sex (patient navigation will be more effective in women vs. men)
- Preferred language (patient navigation will be more effective in patients who preferred Spanish vs. English; participants who indicated other will not be included in this analysis
- Age (patient navigation was more effective in younger vs older age groups, defined as (50–54, 55–59, 60–64, 65–69, and 70–75)
- Hispanic ethnicity (patient navigation will be more effective in Hispanic patients vs. non-Hispanic patients)
- Insurance status (patient navigation will be more effective in uninsurance adults vs. insured adults)
- Probability of patient adherence to colonoscopy without navigation (patient navigation will be more effective in patients having lower probability of adherence, based on risk score)
- See **Handling of Deviations and Protocol Amendments 9.6**

We will perform separate analyses for each patient moderator. Because the examination of the moderating effects of patient characteristics is secondary and exploratory, this study is not formally powered for these analyses. Given the inherent lower power of moderator analyses, we will focus on the magnitude of product term coefficients.

6.4. Sensitivity analysis

See **Handling of Deviations and Protocol Amendments 9.7**

6.5. Assessment of cost and cost-effectiveness

Once we have established the effectiveness of the patient navigation program, we will assess costs and cost-effectiveness from the health-plan perspective, both overall and by risk stratum (high- vs. moderate- vs. low-probability of adherence). We will follow best practices and be guided by previous economic analyses of patient navigation for CRC screening follow-up. First, we will assess the costs of implementing and maintaining the patient navigation program and estimate how costs of patient navigation differ when delivering the service to all patients, versus just those who have a moderate or low probability of undergoing a colonoscopy. Next, using the framework of cost-effectiveness, we will estimate the incremental cost-effectiveness ratio (ICER) as: (1) cost per additional completed colonoscopy, (2) cost per additional adenoma detected, and 3) cost per additional cancer detected.

Consistent with our previous economic evaluation of CRC screening interventions, costs collected will include those of (1) medical care related to cancer detection (e.g., colonoscopy, re-screening) and (2) the intervention delivery. Costs of cancer care will not be included. We will identify follow-up colonoscopy events and re-screening using EHR data, and apply costs using standard Medicare fee schedules. Intervention delivery costs will include health plan project management, patient identification, patient tracking, and navigator time, among others. Resources used to deliver the intervention will be identified using staff logs, interviews, and budget information. We will use national sources for wage rates for clinic and other staff (e.g., programmer) time. Research and non-research costs will be separated after discussion with intervention and project staff, and we will undertake a sensitivity analysis focused on replication costs (those costs most likely to be part of implementation). We will focus on near-term (within 1 year of positive FIT) costs and effects of the program, as our experience suggests those analyses are of most interest to decision-makers; costs will not be discounted owing to the 1-year timeframe.

We will estimate the intervention's ICERs using net benefit regression methods and will construct cost-effectiveness acceptability curves to illustrate the probability of navigation being cost-effective across a range of willingness-to-pay values. Using net benefit regression, we will evaluate differences in cost-effectiveness by subgroups, including baseline probability of adherence (moderate vs. low). After inspection, costs between the arms will be compared using methods appropriate for cost data (e.g., right-skewness, censored follow-up time).

While cost-effectiveness is critical to understanding the value of screening improvements, the costs of the navigation will vary depending on the amounts of specific services delivered. To address this, we will develop scenarios to illustrate how intervention costs change when fixed costs are spread over differing population sizes, and how patient population factors influence variable costs. Other scenarios will examine whether costs of navigation can be offset by gains to health systems, such as fewer repeat colonoscopies because of adequate colonoscopy prep and fewer late cancellations and missed appointments/no-shows. We will also assess the number needed to treat (e.g., patient navigation) in each probability stratum to achieve a successful follow-up colonoscopy. (See **Handling of Deviations and Protocol Amendments 7.6)**

7. Data auditing and validation

<u>Fidelity assessment and intervention dose (scientific rigor).</u>

Our fidelity assessment will be designed in accordance with established methods outlined by the NIH Behavior Change Treatment Fidelity Workgroup and will focus on: (1) the accuracy of data capture for our primary and secondary outcomes (measurement fidelity), and (2) rigor and consistency with which the intervention is delivered (intervention fidelity). As part of intervention fidelity, we will assess the intervention dose.

Intervention fidelity: To address intervention fidelity, research staff will monitor navigator calls with patients and provide feedback. A quality assurance tracker will be used by research staff to track content and timing of calls and identify areas for improvement. Any issues will be addressed during debrief meetings and booster training sessions.

- During the pilot, research staff will listen to a portion of patient calls for navigator coaching purposes.
- During the main trial, research staff will listen to 10 live calls every 3 months for the first year, and then 10 live calls every 6 months during the second year.

Qualitative patient interviews at the end of the program (n = 60) will gather patient-reported information on receipt of each call type, consistent with the NHCRCSP.

Intervention dose. As part of the fidelity assessment, we will track consistency of intervention dose: the number and content of phone calls delivered by patient navigators based on data collected from the patient navigation tracking system designed in REDCap®. The standard protocol includes six timed phone calls that address pre-defined content areas; thus, dose will be calculated as the proportion of phone calls completed and/or content areas addressed (with 6 as the denominator).

NAVIGATION PROTOCOL TOPIC AREAS	**COMPLETE IF DELIVERED BY…**
Topic 1 – Introductory Call	Within 1-7 days of navigator assignment
Topic 2 – Barrier Resolution Calls	Flexible timing prior to procedure
Topic 3 – Bowel Prep Review Call	5-7 days before colonoscopy
Topic 4 – Day before Colonoscopy Check-In Call	Afternoon or evening before colonoscopy *(text message acceptable)*
Topic 5 – Colonoscopy Check-In Call	Day of colonoscopy *(text message acceptable)*
Topic 6 – Post-Colonoscopy Call	2-4 weeks after colonoscopy

8. Handling of Deviations and Protocol Amendments

8.1. Included all patients ages 50-75 with an abnormal FIT result, eliminated requirement of having moderate or high risk of follow-up colonoscopy non-adherence. Given the relatively low colonoscopy completion probability in the highest quintile group (65% vs. 93% estimated), we plan to randomize all eligible abnormal FIT patients. We will still prospectively calculate the patients' estimated probability of obtaining a colonoscopy, using the risk prediction model and preform subgroup analysis considering risk level as a moderator of effectiveness.

8.2. Eliminated cost and cost-effectiveness analysis. These analyses were eliminated because of COVID-19 resources constraints; through an official request to NCI dated 3/1/2021.

8.3. Eliminated no show/canceled appointments as a secondary outcome. We eliminated as an outcome no-show/canceled appointments because the number of referring GI practices would lead to inconsistencies and inaccuracies in the collection of these data.

8.4. Changed the randomization process. Following an electronic health record conversion, the original automated randomization in place at the partnering health center was disabled. As a result, from August 2021 through April 2022, patients were randomized weekly using the SURVEYSELECT procedure in SAS (Cary, NC).

8.5. Used Restricted Mean Survival Time for time-to-event analysis. To assess differences in time to colonoscopy completion between study arms (secondary outcome), we originally planned to use Cox proportional hazards and median survival time. Instead, we computed the log-rank test and restricted mean survival time (adjusted for county). Restricted mean survival time provides estimates of the mean time to event regardless of event rate whereas conventional median survival time is only computable when the event rate is 50% or greater. Moreover, restricted mean survival time is a more direct and interpretable measure of actual survival time, compared to a hazard ratio derived from a Cox model.

8.6. Added county and eliminated Hispanic ethnicity as potential moderators. County (8 unique counties in WA State) was added as a potential moderator, given possible variation by county in GI provider wait-times and other factors. We also eliminated Hispanic ethnicity as a moderator as it has a strong correlation with preferred language.

8.7. Added two sensitivity analyses to account for COVID-19-related care suspensions. Given possible impacts of COVID-19-related care suspensions, we performed a sensitivity analysis that assessed colonoscopy completion at 3 months, 6 months, 9 months, 12 months and 18 months following an abnormal FIT result. Additionally, we report number of completed colonoscopy every 3-months throughout the recruitment and evaluation intervals (July 2019 through December 2022).

9.0. References

1. Ltd. SE. Create a blocked randomisation list. . Accessed June 3, 2019. https://www.sealedenvelope.com/simple-randomiser/v1/lists

2. Petrik AF, Johnson ES, Slaughter M, et al. The recalibration and redevelopment of a model to calculate patients' probability of completing a colonoscopy following an abnormal fecal test. *J Med Screen*. Sep 4 2023:9691413231195568. doi:10.1177/09691413231195568

3. Coronado GD, Petrik AF, Vollmer WM, et al. Effectiveness of a Mailed Colorectal Cancer Screening Outreach Program in Community Health Clinics: The STOP CRC Cluster Randomized Clinical Trial. *JAMA Intern Med*. Sep 1 2018;178(9):1174-1181. doi:10.1001/jamainternmed.2018.3629

4. Rice K, Gressard L, DeGroff A, et al. Increasing colonoscopy screening in disparate populations: Results from an evaluation of patient navigation in the New Hampshire Colorectal Cancer Screening Program. *Cancer*. May 02 2017;123:3356-66. doi:10.1002/cncr.30761

8.8.