Statistical Analysis Plan
Does Knowing One's Estimated Colorectal Cancer Risk Influence Screening Behavior?

Principal Investigator: Uri Ladabaum
Biostatisticians: FeiFei Qin, MPH
Vandana Sundaram, MPH

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Prepared by: Quantitative Sciences Unit
Department of Medicine
Stanford University School of Medicine

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LIST OF ABBREVIATIONS

The following abbreviations and special terms are used in this Statistical Analysis Plan (SAP).

Abbreviation or special term	Explanation
CRC	Colorectal cancer
CRCRAT	Colorectal Cancer Risk Assessment Tool
FOBT	Fecal occult blood testing
FIT	Fecal immunochemical test
ITT	Intention-to-treat
SAP	Statistical Analysis Plan

1. BACKGROUND

Colorectal cancer (CRC) is the third most commonly diagnosed cancer among men and women in the United States and the third leading cause of cancer death. Although CRC carries significant morbidity and mortality, the 5-year survival is 90% when detected at a localized stage. Unfortunately, given that CRC screening is still underutilized, less than half of colorectal cancers are diagnosed at this localized stage. According to the data from the National Health Interview Survey (NHIS), only 58.3% of U.S. men and women aged 50-75 have undergone CRC screening using one of the following approved methods: colonoscopy, sigmoidoscopy, fecal occult blood testing (FOBT), fecal immunochemical test (FIT), double contrast enema, CT colonography, and stool DNA test. Numerous factors have been associated with suboptimal screening rates. These factors can be categorized into a non-modifiable factors (age, ethnicity, gender, educational level, health insurance, socioeconomic status) and modifiable factors (knowledge about CRC and screening, attitudes toward screening, and perception of risk for developing CRC). Modifiable factors are of particular interest given their susceptibility to change. More specifically, risk perception, or perceived susceptibility, as defined by the Health Belief Model, refers to an individual's subjective assessment of risk of developing a given health problem. Studies have shown that high-risk perception of developing CRC correlates with higher screening uptake. Similarly, underestimation of personal CRC risk is associated with lower screening uptake.

The National Cancer Institute (NCI) Colorectal Cancer Risk Assessment Tool (CRCRAT) is a validated online tool available to the general public, which estimates an individual's short-term and lifetime risk of developing colorectal cancer. The goal of this study is to determine if providing subjects with their personalized colorectal cancer risk will influence colorectal cancer screening behavior and intent. If the study leads to an increase in colorectal cancer screening rates in the group of subjects receiving this information as compared to a group that does not receive this information, then the investigators will propose that primary care clinics consider adopting the Colorectal Cancer Risk Assessment Tool into their practice in order to encourage colorectal cancer screening and prevention.

2. OBJECTIVES

Primary objective

To determine whether knowledge of one's colorectal cancer risk (as approximated by the CRCRAT), as compared to not receiving this information, increases colorectal cancer screening rates in subjects who have never undergone screening test for colorectal cancer.

Secondary objective

To determine whether knowledge of one's colorectal cancer risk (as approximated by the CRCRAT), as compared to not receiving this information, influences colorectal cancer screening intent and behavior in subjects who have never undergone screening test for colorectal cancer. This will be assessed by evaluating the following:

1) Colorectal cancer screening rates at 12 months
2) Colorectal cancer screening rates at 6 months
3) Change in screening intent at post-intervention as measured through stages in the Transtheoretical Model

3. TRIAL DESIGN

This is a two-arm, open-label, randomized controlled study. Men and women between 50-75 years of age who have never undergone a screening test for colorectal cancer (and who have no known history of Ulcerative Colitis, Crohn's disease, Familial Adenomatous Polyposis, Lynch Syndrome, Personal history of colon cancer) will be randomized to the colorectal cancer risk information arm (CRCRAT arm) or to the no risk information arm (control arm). The study period for subjects will end approximately 12 months post-randomization.

Stanford Primary Care Clinic subjects who meet eligibility criteria will be identified through a pre-existing outreach list. A brief chart review will be conducted to ensure subjects meet particular inclusion/exclusion criteria. A letter will be sent to eligible subjects (along with the HIPAA authorization form), describing the research study and informing subjects that they will be contacted in the near future. Subjects will be provided with the option to "opt-out" of being contacted. Subjects will be contacted a few weeks later to give all subjects adequate time to respond.

Eligible subjects will be contacted using an approved telephone script to provide verbal consent for participation in the study. If a subject agrees to participate in the study, they will be immediately randomized, using blocked randomization, to either the CRCRAT or control arm. Both groups will then undergo a pre-intervention survey designed to assess attitudes towards colorectal cancer screening. Study interventions will be administered during this same telephone encounter. The control and intervention arms will both be read general information about colorectal cancer. The CRCRAT arm will then be guided through a series of questions from the NCI Colorectal Cancer Risk Assessment Tool in order to calculate their personalized risk of colorectal cancer. This personalized risk score will be recorded and subjects will be provided with the information on their risk scores. Immediately following these interventions, both arms will undergo a post-intervention survey, which again assesses attitudes towards colorectal cancer screening. Over the next 6 and 12 months, subjects' electronic medical records will be reviewed for colorectal cancer screening status. Subjects who were not screened, per their electronic medical record, will be contacted via phone or mail to see if they were screened elsewhere and/or assess their current screening intent. Subjects will be contacted no more than 3 total times for this research study.

3.1 Statistical hypothesis for trial objectives

The primary endpoint is time to colorectal cancer screening by end of follow up at 12 months. This will be determined by a review of subjects' electronic medical records and patient self-report. Subjects for whom a screening result is not recorded in the

EMRs will be classified based on patient self-report of screening. The hypothesis to be tested is that an intervention which provides subjects with their colorectal cancer risk information, compared to not providing this information, increases colorectal cancer screening rates based on the primary endpoint.

3.2 Sample Size justification

A clinically significant improvement in the screening rate would be greater than or equal to 10-20%.
To calculate the appropriate sample size necessary for this study, we assumed uniform accrual over a 6-month period and minimum follow-up of 12 months for all subjects. Further assuming that the current standard has a screening rate of 50% by 6 months (or event rate of 50%) and that the intervention will increase this rate to 65% (or event rate of 35%, leading to a hazard ratio of 1.5), a total of 225 subjects will be needed.

3.3 Randomization and blinding

Subjects will be randomized 1:1 using block randomization stratified by gender (male/female) and age group (under 60 years old or 60 years old and over) to either the CRCRAT arm or control arm. The randomization scheme will be generated using the 'blockrand' package in R. The 'blockrand' function randomizes subjects to specified groups within sequential blocks; block sizes were randomly chosen from the set of 2, 4, 6, 8. The randomization scheme will be incorporated into REDCap in order to assign participants into the treatment groups. This is an open-label study with no blinding.

4. GENERAL ANALYSIS DEFINITIONS

The general conventions to be used for the statistical analyses and presentation of the data are presented below. Departures from these general conventions may be given in the specific detailed sections of this analysis plan.

1. SAS Version 9 or R Version 3 will be the statistical software package used for all data analyses.
2. Continuous variables will be presented with mean, standard deviation, median (25th percentile, 75th percentile), minimum and maximum values. Categorical variables will be presented as number of subjects and percentage of number of subjects by levels of the variable.
3. The number and percentage of responses will be presented in the form XX (XX) where the percentage is in the parentheses. Unless otherwise specified, the denominator for percentages will be the number of subjects in a given intervention group within the analysis population of interest. The denominator will be included when it differs from the standard analysis population.
4. All summary tables will include the analysis population sample size (i.e., number of subjects).

5. Change from baseline (as applicable) will be calculated for each period as follows:
   Change from baseline = Post-baseline value – baseline value.
6. Date variables will be formatted as DD-MON-YYYY for presentation. In the case of missing day, month, and/or year information, "NA" will be presented. For example, a date with a missing month and day will be presented as NANAYYYY.
7. Unless otherwise stated, statistical comparisons will be performed using two-sided significance tests. An alpha level of 0.05 will determine significance unless otherwise noted for a specified analysis.
8. When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts.
9. Unless specified otherwise, data will be presented by intervention and control subjects.

5. ANALYSIS SETS

The Intent-to-treat (ITT) Analysis Set is defined as all randomized subjects. Subjects will be analyzed as per their randomized intervention assignments.

The Per-Protocol (PP) Analysis Set is defined as all randomized subjects for whom 12 month follow-up visit data are available.

6. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

We will not conduct any interim analysis. There is no data monitoring committee. Adverse events are not being reported or analyzed for this study.

7. SUBJECT INFORMATION

7.1. Demographics and Baseline Characteristics

We will summarize descriptive statistics (mean, median, standard deviation, minimum and maximum) by study arm for all endpoints. Categorical variables, such as gender, site, race, ethnicity and medical history will be summarized using frequencies and percentages. Graphical tools such as histograms and box plots and the 95% CI will also be presented if relevant. Transformations, including the log-transformation, will be considered when appropriate. In some cases, methods that rely on assumptions other than normality may be considered including non-parametric approaches such as the Wilcoxon rank sum test. For the secondary outcome of change in screening intent, a comparison of means accounting for repeated measures will be applied.

7.2. Disposition Information

The disposition of all subjects who were randomized will be summarized including proportion completing the study, lost to follow-up, early termination and reasons for discontinuation (when available).

7.3. Protocol Deviations

Protocol deviations will be summarized by randomization group. The categories of major protocol deviations may include, but are not limited to, the following:

- Subjects were randomized, but did not meet inclusion or exclusion criteria.

8. EFFICACY ANALYSIS

Our primary efficacy analysis will be performed on the intent-to-treat population. We will also conduct efficacy analysis on the per-protocol population.

8.1. Analysis Specifications

8.1.1. Level of Significance

Unless otherwise specified, all statistical tests will be interpreted at a 2-sided significance level of 0.05, and all confidence intervals at a 2-sided level of 95%.

8.1.2. Data Handling Rules

We anticipate minimal missing data in this study since we are obtaining information via telephone and medical record review and will contact subjects up to three times. We will include partial data for those subjects who do not complete the 12-month follow-up. We will fully describe missing data for each variable and any pertinent patterns of missingness (e.g. how missingness is related to specific baseline measurements or time, if at all). If missingness is an issue, we will rely on statistical methods including multiple imputation or mixed effects regression techniques that will allow for systematic missingness that is related to observed features.

8.2. Primary Efficacy Endpoint

8.2.1. Definition

The primary endpoint is time to colorectal cancer screening by end of follow up at 12 months. This will be determined by a review of subjects' electronic medical records. Subjects for whom a screening result is not recorded in the EMRs will be deemed to have not had colorectal cancer screening.

8.2.2. Analysis methods

The primary endpoint is the time to colorectal cancer screening. The date of the pre-intervention survey will be considered Day 0. The date of screening will be considered the date of the event. The date of follow-up phone call will be considered the date of event for subjects for whom a screening result is not recorded in the medical record and who self-report that screening was done. We will conduct a Cox proportional hazards regression model with study arm to evaluate our primary endpoint. In the per-protocol population, we will conduct similar analyses and include age group and gender as independent variables.

8.3. Secondary endpoints

8.3.1. Definitions

1) Colorectal cancer screening rates at 12 months
The secondary endpoint is whether a subject has had colorectal cancer screening at 12 months. Each subject will have an indicator of "Yes" or "No" for whether they were screened for colorectal cancer at 12 months. This will be determined by a review of subjects' electronic medical records at 12 months post-randomization. Patient self-report on screening will be used for subjects for whom a screening result is not recorded in the EMR.

2) Colorectal cancer screening rates at 6 months
The secondary endpoint is whether a subject has had colorectal cancer screening at 6 months. Each subject will have an indicator of "Yes" or "No" for whether they were screened for colorectal cancer at 6 months. This will be determined by a review of subjects' electronic medical records at 6 months post-randomization. Patient self-report on screening will be used for subjects for whom a screening result is not recorded in the EMR.

3) Change in screening intent at post-intervention as measured through stages in the Transtheoretical Model.
Screening intent will be measured through stages in the Transtheoretical Model. Screening intent will be coded as a multi-level categorical variable: "pre-contemplation", "contemplation" and "preparation" using two specific survey questions (see Table 1). Change in intention to screen for colorectal cancer will compare responses at pre- and post-intervention.

Table 1. Definition for screening intent endpoint

Endpoint	**Coding**
Change in intent to screen comparing 6months and 12 months to baseline *"How much do you agree or disagree: I am intending to have one of the following screening tests within the next 6 months?"* *(Strongly Disagree, Somewhat Disagree, Somewhat Agree, Strongly Agree)* *"Have you scheduled one of the above screening tests to be done within the next year?" (No, Yes)*	*As noted above:* *Precontemplation (Strongly Disagree, Somewhat Disagree) = 0 (reference category)* *Contemplation (Somewhat Agree, Strongly Agree) = 1* *Preparation (scheduled a screening test) = 2* *Did not answer = missing*

8.3.2. Analysis methods

To evaluate the secondary endpoint of colorectal cancer screening rates at 12 months and 6 months, we will conduct a logistic regression model in the ITT population,

separately for each time point, with study arm as the independent variable. In addition, we will include age group and gender as independent variables when conducting analyses in the per-protocol population

We will also calculate the proportion of subjects who were screened by study arm at 12 months and 6 months, respectively. For the CRCRAT arm, the numerator will be the total number of subjects who were screened and the denominator will be the total number of subjects randomized to the CRCRAT arm. For the control arm, the numerator will be the total number of subjects who were screened and the denominator will be the total number of subjects randomized to the control arm.

To evaluate the secondary endpoint of change in screening intent at post-intervention, we will use generalized linear mixed models, specifically multinomial logit random effects models, which include study arm and account for time (pre-intervention/post-intervention) and with a random effect for subject.

In the per-protocol population, we will conduct similar analyses and include age group and gender as independent variables.

In addition, we will explore how knowledge, fear, or perception of absolute or relative colorectal cancer risk affect screening intent. We will run separate models to evaluate the impact of these variables by adding each of them to the primary model explained above to determine if there is a change in the outcome. The definitions for each of these variables are based on responses to survey questions and details are provided in Table 2.

Table 2. Definitions for knowledge, fear and perception of colorectal cancer risk

Variable	**Coding**
Knowledge: *Answered "Yes" to "Have you heard of at least one of the following colorectal cancer screening test?"* (FOBT, FIT, Stool DNA test, Sigmoidoscopy, Colonoscopy, Double Contrast Barium Enema, CT Colonography, Did not provide answer/not answered)	If nothing is selected, then knowledge = 0 If heard of 1 test, then knowledge = 1 If heard of 2 tests, then knowledge = 2 If heard of 3 or more tests, then knowledge = 3 Did not answer=missing
Fear: "*How much do you agree or disagree: I am afraid of finding colon cancer if I got checked" (Strongly Disagree, Somewhat Disagree, Somewhat Agree, Strongly Agree)*	Strongly disagree or somewhat disagree = 0 (reference category) Somewhat agree or strongly agree = 1 Did not answer = missing
Perception of absolute colorectal cancer risk:	Very unlikely or unlikely = 0 (reference category)

"*How likely are you to get colorectal cancer?" (Very Unlikely, Unlikely, Neither likely nor unlikely, Likely, Very Likely)*	Neither likely nor unlikely = 1 Likely or very likely = 2 Did not answer = missing
Perception of relative colorectal cancer risk: *"Compared to the average person, how likely are you to get colon cancer?" (Very Unlikely, Unlikely, Neither likely nor unlikely, Likely, Very Likely)*	Very unlikely or unlikely= 0 (reference category) Neither likely nor unlikely = 1 Likely or very likely = 2 Did not answer = missing

9. EXPLORATORY ANALYSIS

We will conduct exploratory analyses assessing if there is an association between CRCRAT score and screening rates and change in screening intent in subjects in the intervention group. We will also explore any association between screening rates and change in screening intent as well as assess the change in screening intent at 6 months and 12 months as measured through stages in the Transtheoretical Model in subjects who did not get screened at the respective time period. We will also describe the method of screening in subjects who did get screened.

In addition to the primary, secondary and exploratory analyses to be conducted at the end of the study, we will conduct baseline analyses at the end of enrollment of all subjects to assess how screening intent at baseline is associated with pre-intervention knowledge, fear, or perception of absolute or relative colorectal cancer risk. Descriptive statistics on the demographic characteristics and pre-intervention survey responses of the enrolled subjects will be provided at baseline. Variables will include age, gender, race, ethnicity, highest education level, annual household income, and medical history as well as baseline knowledge and perception about colorectal cancer risk.

Screening intent will be coded as “pre-contemplation”, “contemplation”, and “preparation” as defined in Table 1 above. Knowledge, fear and perception will be defined as shown in Table 2 above. We will perform univariable analysis for each factor as well as multivariable modeling using all factors to determine their association with the outcome. Missing data will be removed, and the analysis will be performed on complete cases only. Multinomial logistic regression models will be used, assuming that the independence of irrelevant alternatives assumption is met. Odds ratios and the associated 95% confidence intervals will be presented.

10. SAFETY ANALYSIS

There is no safety analysis for this study.