TITLE: Colorectal Cancer Screening in Alaska Native Men

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A. Objective

Conduct a randomized controlled trial to test the effect of the adapted motivational messaging intervention on colorectal cancer (CRC) screening with Alaska Native and American Indian (ANAI) men.

B. Background

ANAI men in Alaska experience the most profound CRC disparities of any US racial or ethnic group. In 2019 the American Cancer Society reported a CRC incidence of 100 per 100,000 for ANAI men, nearly twice the next highest incidence (58 per 100,000) for non-Hispanic Blacks, and more than twice that for non-Hispanic Whites (46 per 100,000).[1] Similarly, CRC mortality in ANAI men was nearly twice the rate for non-Hispanic Blacks (47 vs. 26 per 100,000) and almost triple that for non-Hispanic Whites (17 per 100,000). Approximately half of CRC deaths could be prevented by screening, which detects lesions in pre-cancerous or early-stage disease, when 5-year survival rates are much higher.[2,3] Current guidelines recommend CRC screening for average-risk adults starting at 45-50 years old, but those in high-risk groups (such as ANs) should start at younger ages.[4,5] Nationwide, 58%-65% of non-Hispanic Whites meet CRC screening guidelines, compared to 45%-54% of ANAI people.[6,7]

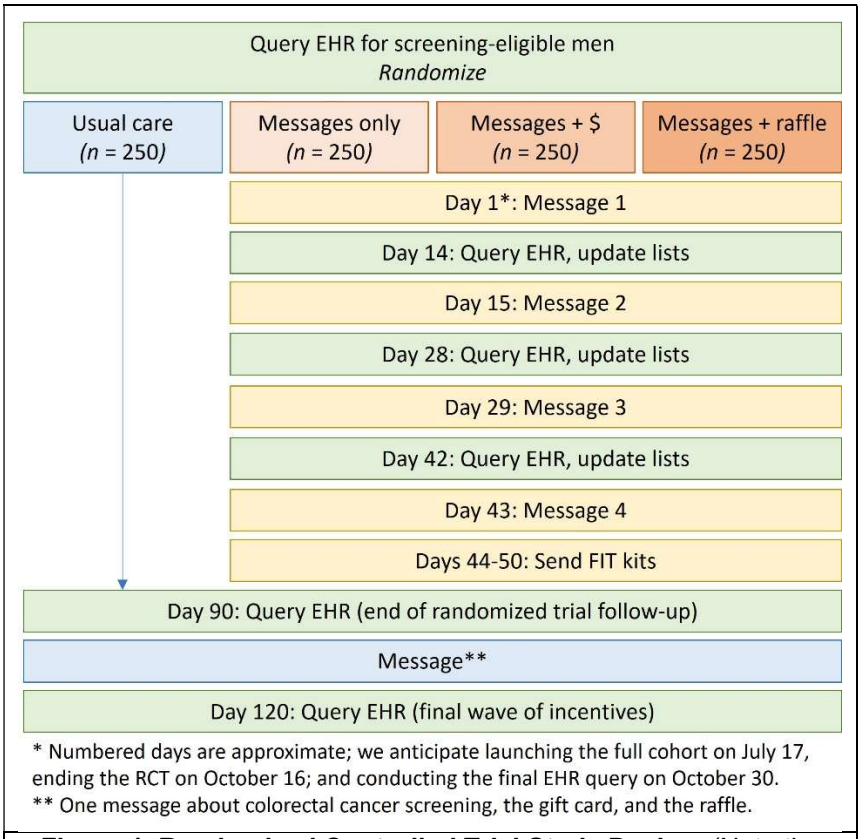

Figure 1. Randomized Controlled Trial Study Design. (Note the figure reflects a three-month follow-up; we were able to revise the timeline to allow six months of follow-up.)

In 2013 our team designed a text messaging intervention to promote CRC screening among ANAI customer-owners at Southcentral Foundation (SCF). The intervention involved sending up to 3 culturally informed text messages at 1-month intervals. All messages exclusively promoted colonoscopy. In a randomized controlled trial (RCT) with 2,386 customer-owners 40-75 years old, our intervention led to a 50% increase in CRC screening in ANAI women – but it had no effect in ANAI men.[8]

In light of these findings, the current study will test a version of the text messaging intervention that has been further adapted for ANAI men.

C. Study Protocol

C.1. Study Design and Outcomes

This is a parallel-arm randomized controlled trial with four study conditions: usual care control; or usual care plus text messaging only ("Messages), text messaging and promise of a $50 gift card for completing CRC screening ("Gift Card"), or text messaging and promise of being entered into a raffle (~$200 prize value) for completing screening ("Raffle").

The original primary outcome was any completed CRC screening documented in the electronic medical record (EMR) during follow-up. During the intervention adaptation process, in response to community partner feedback we added scheduling a pre-screening visit or screening procedure as an additional primary outcome.

C.2 Randomized Trial. The RCT will be implemented over approximately six months. We will query the EMR to randomly select 1000 male ANAI customer-owners aged 40-75 years who are eligible for routine CRC screening. The cohort will be further randomized into one of the four study arms. Randomization will be

matched and stratified by age (40-49, 50-75) and location (Anchorage, Matanuska-Susitna Valley) to ensure balance of these factors in the study arms. **Figure 1** depicts the RCT study design. The age range of participants reflects SCF clinical practice guidelines, as well as the earlier mean age at CRC incidence among ANAI people compared with other races and ethnicities.

Intervention details

The intervention comprises a series of up to four electronic messages delivered by text to a mobile phone and/or by email. Messages are sent approximately 2 weeks apart (total duration = 6 weeks). After sending each message, we will query the EHR so that men who have completed screening do not continue receiving messages. Men who have scheduled but not completed screening will not be removed from the list, due to high rates of no-shows for colonoscopy appointments. For men in the three intervention arms who are still unscreened and therefore eligible to receive the fourth message, we will select a random subset to receive an unsolicited mailed packet containing the Fecal Immunochemical Test (FIT) kit with a pre-paid return envelope to the mailing address on file. The total sample size for this subgroup will depend on costs and logistical feasibility, but we anticipate sending approximately 125 kits per arm (approximate total 375). Anchorage-empaneled CO FIT kits will be returned to the SCF CRC team mailbox in MSD administration. The CRC team will receive the completed FIT kits and send the samples down to the ANPCC lab for processing. Valley-empaneled CO kits will be returned to VNPCC lab, which will be prepared and sent via courier to ANMC lab. The fourth message will be different for men who are and are not randomly selected to receive unsolicited mailed FIT kits. For men who are not selected, the message will encourage them to call and request a mailed kit. For men who are selected, the message will inform men that they will receive a kit for completing a FIT screening at home. To ensure equitable access to receiving incentives, all study participants in any of the four arms who complete CRC screening before the final data query will receive a gift card and will be included in the raffle.

Messages will be personalized by including the recipient's name in the message salutation. SCF phone numbers and videos will be hyperlinked for participant convenience. The messages will include an option to respond with "SCF" if the participant wishes to be contacted by SCF about screening options. If a participant responds "SCF", they will receive an automated response message and their primary care team will be notified of their interest. If a participant responds "Stop", they will not receive an automated response message and no further messages will be sent.

All men who complete colorectal cancer screening will receive the gift card incentive and be entered in the raffle, even if they were not informed in advance that this was possible. After the RCT is completed, we will send a final message to all men who did not receive any messages about gift card or raffle incentives and who did not complete screening during the study period. This message will inform the men that they can receive a gift card and be entered into a raffle if they complete screening within the next four weeks, and it will include the same contact information for accessing screening as the first message in Table 1.

Sample Size, Eligibility, Randomization, Recruitment/Informed Consent, and Compensation

One thousand customer-owners will be randomized in the RCT, with 250 assigned to each of the four study arms (**Figure 1**). Inclusion criteria are 1) male; 2) ANAI; 3) active SCF customer-owners; 3) aged 40-75; 4) no history of CRC or abnormal screening; and 5) due for CRC screening. Individuals who meet inclusion criteria but are at increased/high risk of CRC relative to race-, age-, and gender-matched peers (e.g., due to family history of CRC) are not eligible to participate.

The EMR will be queried to identify customer-owners eligible to participate in the study and to extract data for study outcomes. Only those individuals who are (1) members of the study team who and (2) members of the SCF Data Services department will have access to identifiable customer-owner information or be directly involved in the following study activities: determining the eligibility of customer-owners; de-identifying the data of eligible customer-owners; randomizing eligible customer-owners to control or intervention arms of the RCT; sending motivational messages to eligible customer-owners; and sharing fully de-identified participant data with other members of the study team for analysis.

All study data will be obtained directly from the EMR and will therefore not involve active recruitment of any individual patient. Additionally, study data will not include any identifiable customer-owner information. We

have obtained a waiver of consent, which was granted warranted because 1) our study is designed to increase uptake of existing screening guidelines; 2) the intervention will not interfere with usual care; and 3) directly recruiting and consenting participants into the RCT might lead to heightened awareness and uptake of CRC screening, which could increase the risk of Type 2 error (failure to detect a beneficial intervention effect) in the RCT. All messages sent to customer-owners will include instructions for opting out of further communications.

There is no compensation provided for the RCT, because no customer-owner will be asked to contribute any time or effort to completing an intervention or engaging in data collection.

Data Collection

All study data will be obtained from the EMR. SCF Data Services staff will extract and de-identify data, and assign unique study IDs to individuals included in the dataset. De-identified data will be securely transmitted to Dr. Clemma Muller at Washington State University for analysis. The dataset will be stored on a HIPPA-compliant secure server that is backed up daily to an off-side location. Files at Washington State University will be password protected and accessible only to Dr. Muller. A member of the study team who also works in the SCF Data Services will retain a second copy of the de-identified study dataset on a password-protected, secure network server at SCF. **Table 1** lists the variables that will be extracted from the EMR.

Table 1. Measures to be extracted from the electronic medical record for the RCT

Variable	Categories or Units	Intended use
Age	40-45; 46-49; 50-59; 60-75	Eligibility, cohort description, subgroup analyses
Gender	Men only	Eligibility
Race	ANAI only	Eligibility
Screening history	Only people without previous abnormal CRC screening results	Eligibility
CRC history	Only people with no previous CRC diagnosis	Eligibility
Location	Urban/suburban; rural	Cohort description, subgroup analyses
Previous CRC screening history	Never screened at SCF; previously screened by colonoscopy; previously screened by other method	Cohort description, subgroup analyses
Duration of overdue screening eligibility	Years (to 1 decimal place)	Cohort description, subgroup analyses
Total SCF clinic visits in the past year	Count	Cohort description, subgroup analyses
CRC screening completed	Type of test Month in which test occurs	Primary outcome
CRC screening or pre-screening scheduled	Yes, No	Primary outcome

CRC = colorectal cancer; SCF = Southcentral Foundation

D. Statistical analysis

All data analysis will be conducted with Stata version 16 or later (StataCorp, College Station, TX) or R statistical software packages. We will report descriptive statistics for all study variables as counts and frequencies for categorical factors, and as means, standard deviations, and ranges for continuous factors. Descriptive results will be presented separately for men in the intervention and control conditions. Our inferential analysis will use an intent-to-treat approach, using data for all participants in the group to which they were assigned, regardless of events that occur after randomization. We will use logistic regression with marginal standardization to estimate the effect of the intervention on CRC screening. Results will be presented as risk ratios and risk differences with 95% confidence intervals. Marginal standardization estimates are

interpreted as the difference in CRC screening if everyone received the intervention compared to screening if no one received the intervention, in a population with the same distribution of regression model covariates as observed in the study sample. If deemed appropriate, the regression model specification may be adjusted (e.g., binomial regression) prior to conducting the statistical analysis. Our primary analysis will estimate the effect of assignment to the intervention group without adjusting for any covariates, as appropriate for a large RCT. Sensitivity analyses will adjust for any other variables that appear unbalanced between groups at baseline, and secondary analyses will evaluate potential modification of intervention effectiveness by variables such as age, location, and history of CRC screening.

E. Plan for Dissemination

Results from this study will be submitted for publication in the peer-reviewed literature and/or for presentation at scientific conferences. We will also seek out opportunities to share results with SCF and Tribal leadership, customer-owners, and other stakeholders. Documents containing study results (e.g., manuscripts, presentations) will not be made available to the public unless they have first been reviewed and approved by SCF Tribal Review.

Published results will include a summary of participant responses to interview and survey questions, as well as summary data from the RCT. These results will not include any information that would identify individual participants. These results may include direct quotations from interviews.

F. References

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8. Muller CJ, Robinson RF, Smith JJ, et al. Text message reminders increased colorectal cancer screening in a randomized trial with Alaska Native and American Indian people. Cancer 2017;123:1382-9.