UCSF Helen Diller Family Comprehensive Cancer Center

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Optimization of Adaptive Text Messages for Cancer Survivors II (OATS II)

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Study Intervention: Adaptive 12-week text message intervention using reinforcement learning to increase whole grain and reduce refined grain intake

[redacted]

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Revision History

Version 1.0	08-31-2022
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Version 1.3	12-01-2023

Protocol Signature Page

1. I agree to follow this protocol version as approved by the Institutional Review Board (IRB).
2. I will conduct the study in accordance with Good Clinical Practices (ICH-GCP) and the applicable IRB, ethical, federal, state, and local regulatory requirements.
3. I certify that I, and the study staff, have received the required training to conduct this research protocol.
4. I agree to maintain adequate and accurate records in accordance with IRB policies and federal, state, and local laws and regulations.

UCSF Principal Investigator

_____
Printed Name

_____ _____
Signature Date

Abstract

Title	Optimization of Adaptive Text Messages for Cancer Survivors II (OATS II)
Study Description	This study aims to develop a continuously adaptive text message-based intervention using reinforcement learning, a type of artificial intelligence, to increase the proportion of grains consumed that are whole grains in a racially/ethnically diverse group of colorectal cancer (CRC) survivors.
Study Intervention	Adaptive 12-week text message intervention using reinforcement learning to increase whole grain and reduce refined grain intake
Study Population	Participants for this study will include up to 60 CRC survivors for the proof-of-concept single-arm trial
Primary Objective	To determine the intervention's feasibility and acceptability
Secondary Objectives	1. To estimate the effect of the intervention on the percent of grains that are whole 2. To estimate the effect of the intervention on total fiber intake (g/d)
Recruitment Methods	Participants will be recruited through MyChart messages and letters from the UCSF CTSI Participant Recruitment Program, as well as clinician referrals at the University of California, San Francisco (UCSF) Helen Diller Family Comprehensive Cancer Center (HDFCCC) and the Zuckerberg San Francisco General (ZSFG) hospital.
Sample Size	Participants for this study will include up to 60 CRC survivors for the proof-of-concept single-arm trial
Duration of Study Participation	12 weeks
Unique Aspects of this Study	This study is the first to develop a continuously adaptive text message-based intervention using reinforcement learning, a type of artificial intelligence, to increase the proportion of grains consumed that are whole grains in a racially/ethnically diverse group of CRC survivors.

List of Abbreviations

AE	adverse event
BCT	behavior change technique
COM-B	Capability Opportunity Motivation – Behavior
CRC	colorectal cancer
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management System
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
GCP	Good Clinical Practice
HDFCCC	Helen Diller Family Comprehensive Cancer Center
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
PRMC	Protocol Review and Monitoring Committee (UCSF)
RL	reinforcement learning
ZSFG	Zuckerberg San Francisco General

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1 Introduction

1.1 Background on Dietary Interventions for Colorectal Cancer

Dietary interventions are a promising approach for reducing colorectal cancer (CRC) mortality.[1-3] Guinter et al. reported that individuals with a low American Cancer Society (ACS) nutrition guideline score (based on intake of whole grains, fruits and vegetables, and red and processed meat) pre-diagnosis and high score post-diagnosis had a 29% lower risk of CRC-specific mortality versus patients with low scores at both time points.[2,4] When examining the components in the ACS score among 992 stage III colon cancer patients, our team observed that those in the fourth quartile of proportion of grains that are whole had 35% lower risk of cancer recurrence and mortality compared to those in the first quartile (median % grains that were whole was 76% in 4th quartile vs.11% in 1st quartile).[1,4] An independent study of 1,575 people with stage I-III CRC reported that a 5-g/d increase in cereal fiber intake after diagnosis was associated with 33% lower risk of CRC-specific mortality.[5] Overall, there is strong evidence that a high-fiber diet rich in whole grains lowers risk of CRC mortality.

Most CRC survivors do not achieve recommended intakes of whole grains or fiber.[3,6,7] In a nationally representative sample of 1,550 cancer survivors, mean fiber intake was 15 g/d, half the 30 g/d recommended by the American Institute for Cancer Research.[8] Moreover, differences in diet quality may play a role in CRC disparities. For example, on average in the United States (US), Black people have lower intake of grains compared to non-Latinx White people.[9] Work from our team and others suggests that barriers to a high-fiber diet among cancer survivors include lack of time, energy, social support, access to healthy foods, and experience preparing high-fiber foods.[10-15] While several dietary interventions have been developed for cancer survivors, past studies have largely tested resource-intensive, multi-component interventions in non-representative populations.[16] These studies have observed changes in diet, but changes have often been small.[17] Thus, more research is needed to develop dietary interventions for CRC survivors.

1.2 Background on Text Messaging as a Behavioral Intervention in Diverse Populations

Text messages are a promising tool for behavioral interventions in diverse populations. Nearly all adults in the US have mobile phones, and text messages are used by the majority of mobile phone users with little variation by race/ethnicity.[18,19] Text messages do not require heavy data usage or high digital literacy, are inexpensive, and can be used to apply behavior change techniques (BCTs) such as information, instruction, feedback, prompts/cues, social support, self-monitoring, goal setting, and action planning.[20,21] We and others have reported that text message-based interventions are feasible, acceptable and effective for dietary change.[10,11,18,22] In fact, data suggest that stand-alone text messaging interventions could be as effective as blended interventions that combine text messaging with other tools (e.g., coaching) for less cost.[18] Data are limited, however, in CRC survivors and people who identify with racial/ethnic minority groups.[17] Moreover, patients consistently desire a more tailored experience in text message interventions and the optimal frequency, timing, and interactivity of text messages are not known.[10,18,23]

Artificial intelligence solutions, including reinforcement learning (RL), may optimize digital health interventions in a scalable automated way. In 2019, Forman et al. reported on one of the first pilot studies to use RL in a weight loss intervention.[24] Their algorithm determined if participants would receive a coach call, a coach text message, or a non-tailored text message based on the frequency that participants self-monitored weight or diet, met calorie goals or physical activity goals, and weight loss. In a pilot study of 52 primarily White participants, the RL optimized intervention resulted in equal weight loss for half the cost of phone coaching. Yet, participants

desired more personalization, suggesting the need for message tailoring by individual characteristics and adaptation over time to account for behavior change and to maintain engagement.

1.3 Study Rationale

To address gaps and build on prior research, our team proposes to develop an adaptive text message-based dietary intervention for CRC survivors.[25] We will develop a RL algorithm to continuously adapt text message content and timing to increase whole grain and reduce refined grain intake. We plan to focus on CRC specifically because people with CRC have been under-represented in past behavioral intervention studies for cancer survivors, and the evidence for a role of diet after CRC diagnosis is strong.[1,5,16] Additionally, experience from multiple studies suggests recruitment of people with CRC to clinical trials may require a more targeted approach than survivors of other common cancers.[27,28]

1.4 Innovation

Past behavioral intervention trials have focused primarily on physical activity or weight loss.[29] Yet data suggest that diet is equally important for CRC survivors[1]. Optimizing a behavioral intervention based on diet, which cannot be passively measured, is a particular challenge that we will address in this proposal. The results of this study will inform the design of a scalable intervention with broad reach that we will ultimately test in a randomized controlled trial. Enhancing CRC survivors' diet quality has potential to reduce CRC mortality and greatly improve public health.

1.5 Risks/Benefits

Potential Risks

The risks involved in this study are few. There is a minor risk of loss of confidentiality, either through the breach of data collected via the Internet or text messaging or through the breach of secure study databases, physical files, etc. Dietary modifications may result in changes in bowel function, including but not limited to diarrhea, constipation, increased urgency, flatulence, and/or bloating. These changes are not expected to be clinically significant but could impact quality of life if they occur.

Potential Benefit of the Proposed Research to Participants and Others

The benefits of healthy diet are well established. Intervention participants may experience decreases in symptom burden and improved physical functioning and quality of life. This study will produce societal benefit regarding knowledge about how to optimize a text message-based intervention to improve diet quality in cancer survivors. Given the minimal risk of study participation and potential benefits, the risks to participants are reasonable in relation to the anticipated benefits to society.

Procedures used to minimize risk

- Numerous studies have demonstrated that healthy diet is safe, feasible, and beneficial for cancer patients and survivors.
- Participants will receive tips on how to alleviate or avoid digestive changes due to increased whole grain and fiber intake.
- Participants will be asked to contact the study team at any time if they have questions or concerns about the study.

- All study files, folders, and records will be kept in locked file cabinets that can be accessed only by study personnel.
- All data will be exchanged over an SSL-protected connection, and all data will be encrypted.
- The study database and all survey data will be collected and stored in REDCap, the HealthySMS platform, Twilio, and UCSF's Research Analysis Environment (RAE), which have protections needed for storage of PHI.

Limited private identifiable information necessary for the conduct of the study will be collected in the proposed research project. For example: names, phone numbers, and email addresses. This information will be stored securely in REDCap, the HealthySMS platform, Twilio, and UCSF's Research Analysis Environment (RAE; mytransfer.ucsf.edu), which have the protections in place and approvals for the storage of PHI.

Importance of Knowledge to be Gained

Promotion of a healthy diet is an important aspect of cancer survivorship care. This research aims to create an intervention that can be remotely delivered and is appropriate for implementation on a large scale. We believe that the minimal risk involved with study participation are reasonable in relation to the knowledge that is expected to result.

2 Study Objectives and Endpoints

2.1 Primary Objective

Primary Objective	Endpoint(s)	Time Frame
Determine the intervention's feasibility[1] and acceptability[2]	• Participants' responses to text messages that ask for a response • Participant surveys • Semi-structured end of study interviews	From 0 to 12 weeks

1) The intervention will be determined feasible if the median response proportion to text messages that ask for a reply is ≥ 70%, and the median score for the Feasibility of Intervention measure is ≥4.
2) The intervention will be determined acceptable if median scores on the Acceptability of Intervention and Intervention Appropriateness Measures are ≥4.

2.2 Secondary Objectives

Secondary Objectives	Endpoint(s)	Time Frame
1. Estimate the effect of the intervention on the percent of grains that are whole[1]	Change in percent grains that are whole, assessed via food frequency questionnaire	0 to 12 weeks
2. Estimate the effect of the intervention on total fiber intake (g/d)	Change in total daily fiber (g/d), assessed via food frequency questionnaire	0 to 12 weeks

[1] Percent of grains that are whole = servings per day of whole grains / (servings per day of refined grains + servings per day of whole grains)

2.3 Exploratory Objective

Exploratory Objective	Endpoint(s)
Assess convergence of the RL algorithm	Proportion of messages targeting capability, opportunity, or motivation sent during the 12-week period, overall and by sub-groups (e.g., race/ethnicity)

3 Study Design

3.1 Schema

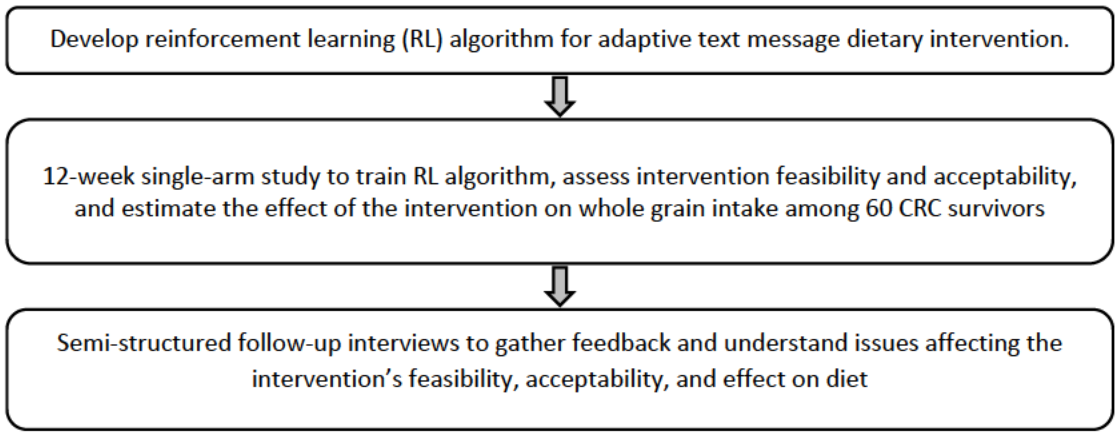

Figure 1: Overview of proposed approach for developing an adaptive text message-based dietary intervention for colorectal cancer (CRC) survivors.

3.2 Characteristics

This is a single-arm proof-of-concept trial. In this study, we will assess the feasibility and acceptability of a 12-week adaptive text message-based dietary intervention that uses reinforcement learning (RL; a type of machine learning) to determine what type of text messages to send, and when to send text messages, based on participants' diet behavior and engagement (replies to text messages). The target population for the intervention includes CRC survivors who speak and read English or Spanish.

3.3 Sample Size

We will accrue up to 60 CRC survivors. Participants who withdraw or are otherwise not evaluable will not be replaced.

3.4 Primary Completion

The expected primary completion date is 24 months after the study opens to accrual.

3.5 Study Completion

The expected study completion date is 30 months after the study opens to accrual.

4 Selection and Enrollment of Participants

4.1 Eligibility Criteria

4.1.1 Inclusion Criteria

To be eligible to participate in this study, an individual must meet the following criteria. Eligibility will be determined by self-report and/or medical record review.

1. Age > 18 years
2. Subject has provided informed consent
3. Diagnosis of colon or rectal adenocarcinoma
4. Not on active treatment at the time of screening and not expected to receive active anti-cancer therapy (e.g., surgery, radiation, chemotherapy) during the study period
5. At least 6 weeks since a major surgery and fully recovered
6. Owns a mobile phone and is willing and able to receive and send text messages
7. Able to speak/read English or Spanish
8. Based on a screening survey, eat grains and ≤50% of total grains are whole grains

4.1.2 Exclusion Criteria

None.

Our goal is to develop a broadly generalizable intervention. Patient demographics will be monitored closely during the accrual period. We aim to enroll approximately equal number of participants who identify as Black, Latinx, non-Latinx White, and Asian/Pacific Islander CRC

survivors. However, participants do not have to identify with one of these race/ethnicity groups to be eligible.

4.2 Recruitment Methods

The recruitment and screening procedures outlined below present no more than minimal risk to the privacy of the patients who are screened, and a screening log containing minimal patient health information (Protected Health Information (PHI)) will be maintained. For these reasons, we seek a waiver for the purposes of 1) reviewing medical records to identify potential research participants and obtain information relevant to the enrollment process; 2) conversing with patients regarding possible enrollment, 3) handling of PHI contained within those records and provided by the potential participants; and 4) maintaining information in a screening log of patients approached.

Participants will be recruited through MyChart messages and letters from the UCSF CTSI Participant Recruitment Program, as well as clinician referrals at the University of California, San Francisco (UCSF) Helen Diller Family Comprehensive Cancer Center (HDFCCC) and the Zuckerberg San Francisco General (ZSFG) hospital.

Recruitment of UCSF Patients

Potentially eligible patients may be identified through searches of the UCSF Cancer Registry, APeX, review of clinic schedules, and people who have participated in past studies and consented to be contacted about future research. The study team will review medical records of identified patients to assess initial eligibility. Potential participants may be contacted in clinic and/or e-mailed information about the study. The informational email will ask patients who do not wish to be called about the study to respond and let us know. If we do not hear otherwise, we may call patients to tell them about the study and ask if they are interested in participating. If they are interested, they will be asked to complete a brief screening survey either by phone or online using REDCap.

MyChart Recruitment at UCSF

We will also work with the UCSF CTSI's Participant Recruitment Program to use MyChart for recruitment along with cohort identification and direct mail for recruitment of patients who are not enrolled in MyChart. MyChart (Apex) conducts a search for patients based on the study's inclusion and exclusion criteria. This is a computer-aided search, meaning the computer — and not a person — searches patient charts. When a patient is identified as potentially eligible, they receive an email from MyChart that says to log in to MyChart to read about a study that they might be interested in. The email is short and is the same for every recipient—there is no patient-specific, study-specific or disease information in it. When the patient logs into MyChart, there is a new "Research" page with template information about participating in research and how to opt out of receiving recruitment messages. Then, the patient can click through to learn about a specific study that they may be eligible for. The study-specific language is attached to this submission.

Note: 1) The patient has the option of clicking a link/button to let the study team know that they are interested in learning more about the study. Only if the patient takes this action will the study team receive information about the patient. If the patient clicks "No thanks" or simply does not respond, they will not be contacted by the study team, they will not receive any follow-up emails from MyChart about this study, and their information will not be shared with the study team. 2) The messaging in all recruitment materials—email, MyChart research page, and study description—have been written to clearly state that the patient is being contacted about research, not clinical care. 3) We are also collaborating with the CTSI Participant Recruitment

Program (PRP), which will provide cohort identification and direct mail for recruitment of patients who are not enrolled in MyChart to address disparities that exist in MyChart enrollment.

Recruitment of ZSFG Patients

At ZSFG, providers will ask potentially eligible patients for permission to be contacted by the research coordinator about a research opportunity. If they say yes, the coordinator will contact the patient either in person in the clinic, or by phone or email. In addition, people who have participated in past studies and consented to be contacted about future research will be contacted about this study.

Compensation

To compensate participants for their time, participants may receive [redacted] gift cards [redacted]

4.3 Inclusion and Recruitment of Women and Minorities

4.3.1 Eligibility and Recruitment of Women and Minorities

Individuals of any sex, gender, race, or ethnicity may participate. We aim to enroll approximately equal number of participants who identify as Black, Latinx, non-Latinx White, and Asian/Pacific Islander. Participants can identify with more than one race/ethnicity group or may identify with none of these groups.

4.4 Inclusion Across the Lifespan

4.4.1 Age Range of Participants

Individuals ages 18 and over are eligible for this study. Children are excluded from the study because CRC is rare in children.

4.4.2 Study Design/Recruitment Considerations Related to Age Groups

Individuals ages 18 and over are eligible for this study. We will strive to enroll people who represent the age distribution of individuals affected by CRC. However, given the rapidly rising incidence of CRC among people <50 years old, we may over-enroll people <50 years compared to the distribution of cases in the overall population. This will ensure our results are useful for guiding CRC survivorship care for an increasing population of younger and middle-aged adults.

4.5 Participant Registration

A signed informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. An electronic copy of the signed ICF will be given to the participant and a copy will be filed in the medical record. The original will be kept on file with the study records.

All participants consented to the study will be registered in OnCore®, the UCSF Helen Diller Family Comprehensive Cancer Center Clinical Trial Management System (CTMS). The system is password protected and meets HIPAA requirements.

Each participating site is responsible for OnCore® registration of study participants consented at the site.

4.6 Assignment to Intervention

This is a single-arm study. All participants will receive the 12-week adaptive text message intervention.

5 Study Intervention

We aim to develop a dietary intervention that will continuously adapt text message content and timing based on factors that may include: participants' sociodemographic characteristics, dietary behavior, and engagement with the text messages.

Our theoretical framework is based on the Capability Opportunity Motivation-Behavior (COM-B) model which states that individuals' behaviors are the result of interactions between their capabilities, opportunities, and motivations. Applying the model to whole grain intake, CRC survivors must have:

1) capability – the physical ability to consume whole grains without side effects (e.g., gas, bloating, bowel frequency); knowledge and skills to select and prepare whole grains; and psychological capability to resist cravings and control urges for refined grains;

2) opportunity – whole grains must be available, affordable, and socially acceptable; and

3) motivation – motivated to eat whole grains and develop a plan for doing so.

Intervention Components

Adaptive text messages using reinforcement learning (RL)

After completing baseline assessments, all participants will receive text messages for 12 weeks. Most days, participants will receive 1-2 messages. Text messages will be sent through the HealthySMS Platform and Twilio. Message content will target COM-B components of capability, opportunities, and motivations. The RL model will use a bank of text messages to target COM-B constructs. For example, to address psychological capability, messages will increase knowledge of what foods are recommended and how to prepare them. Behavior change techniques will include providing information, feedback, self-monitoring, and prompts/cues to increase knowledge. To address physical opportunity, text messages will focus on how to economically shop for and prepare whole grain foods. Behavior change techniques will include restructuring the physical environment, prompts/cues, instruction, feedback, and self-monitoring.

We will use the most up-to-date approaches for our RL model. For example, this may include a multi-armed bandit algorithm that predicts the outcome or "reward" (e.g., eating whole grains the previous day [yes/no], or servings of whole grains eaten on the previous day) based on action variables (e.g., whether to send a message, message type) and contextual variables (e.g., individual characteristics, whole grain intake yesterday/past week). RL algorithms "explore" what text messages to send by sending messages randomly at first and then "exploit" the information, so that over time, the algorithm sends more of the messages that predict more frequent intake of whole grains. In our proposal, participants' replies to daily text messages asking about their intake of whole grains on the previous day will be used as the "reward" data.

Participants' response rate to the daily question about whole grain intake is a primary outcome in this study. We will send a reminder message to participants who have not responded (e.g., "Please respond even if you ate 0 whole grains yesterday.") If participants do not respond a few days in a row, we will send a non-response message (e.g., "We haven't heard from you in a few days. Please respond to the text messages or contact our team at [study phone number].") If a participant does not respond for 7 consecutive days, we may invite them to a semi-structured

interview to understand reasons for non-response. Non-responders will continue to receive study text messages unless they request the messages be stopped (e.g., by texting back STOP or notifying the study team). All participants, including non-responders, will be asked to complete the surveys at 12 weeks to gather quantitative usability and acceptability data and estimate the effect of the intervention on diet behavior.

Educational material

At enrollment, all participants will receive printed materials defining the recommendations for whole grain intake, what is a whole grain, whole grain serving sizes, and cooking tips.

Intervention Components for Food Insecure Participants

We will use the Food Security module from the National Health Interview Survey to identify food insecure participants at enrollment. We will follow the standard of care at ZSFG for food insecure individuals: the study coordinator will provide a list of resources including food banks and meal delivery programs and facilitate application or SNAP benefits, if needed.

5.1 Delivery of Study Intervention

We will use REDCap, the HealthySMS platform (developed for prior work led by Dr. Aguilera), UCSF's Research Analysis Environment (RAE), and Twilio to conduct the proposed study. REDCap is a secure study management and database platform with mature features for online surveys and forms for data entry. HealthySMS is a web-based automated text messaging platform for use in health and social service settings, clinically and for research purposes. The system allows for scheduling of text messages to be sent automatically to individual patients or patient groups. It supports two-way communication between participants and researchers. The web-based platform enables the visualization of participants' data and contains a dashboard that allows for viewing data from multiple participants in one screen.

5.2 Interventionist Training and Tracking

Consistent implementation of the study protocol, measurements, and interventions is essential. Training manuals will be created. Data will be collected in REDCap through online surveys, HealthySMS and Twilio through text messages, recording of interviews on Zoom, and dashboards for study staff to enter data. We will monitor recruitment and study progress using a flow sheet template consistent with the CONSORT guidelines for reporting of feasibility trials to ensure we are meeting recruitment and retention goals. Members of the study team will meet weekly, or as needed, throughout the study.

5.3 Adherence Assessment

Intervention Adherence

Adherence to the intervention will be measured using number of replies to text messages that asked for a response.

Proposed Engagement Strategies for Retention

To prevent attrition, our study staff develop good rapport and open, responsive communication with participants. Participants will be provided with a phone number and email address to contact if they encounter issues with any aspect of the study. Staff will convey reminders of study tasks by phone, email, and/or text messages. Participants may be compensated with gift cards as described in Section 4.2. If a participant does not respond to a study-related request, up to five automated reminders will be sent and the study staff will reach out to the participant

via phone and/or e-mail. If we are unable to reach a participant after three more attempts, we will determine a participant lost to follow-up.

5.4 Participant Discontinuation/Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue a participant from the study for the following reasons:

- Unacceptable adverse event(s)
- Lost-to-follow up; unable to contact participant (see Section 5.5 - Lost to Follow-Up)
- Any event or medical condition or situation occurs such that continued collection of follow-up study data would not be in the best interest of the participant or might require an additional treatment that would confound the interpretation of the study
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

5.5 Lost to Follow-up

A participant will be considered lost to follow-up if he or she fails to reply to a study-related request after the study staff have sent the following attempts to contact:

- up to five automated email reminders
- study staff will reach out to the participant via phone and/or e-mail up to three more times

These contact attempts will be documented in the participant's study file. Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

6 Study Procedures and Assessments

6.1 Schedule of Activities

Period/Procedure	Screening/Baseline	Study Intervention Period	End of Study
	Visit -1 (D-84 to D1)	**Weeks 1-12 (D1 to D84)**	**Study Week 12 (+/-84 days)**
Administrative Procedures			
Consent[1]	X		
Medical Record Review, if available	X[2]		
Inclusion/Exclusion Criteria	X		
Other Study Assessments			
Sociodemographic and Clinical Variables survey	X		
Adverse Events (Recent Health Survey)[3]	X		X
Dietary Assessment Survey (FFQ)	X		X
Food Security Survey	X		X
Food Beliefs Survey (theoretical constructs)	X		X
Text Message Intervention Engagement[4]		Throughout	
"Reasons for Non-Response" Interview		See Footnote 6	
System Usability Scale (SUS)			X
Acceptability of Intervention Measure (AIM)			X
Intervention Appropriateness Measure (IAM)			X
Feasibility of Intervention Measure (FIM)			X
End of Study Interview (optional)			X

1 DocuSign or paper copy mail with prepaid return envelope
2 Participants will be allowed to self-report their clinical information if no medical records are available (e.g., patients for whom we cannot obtain records).
3 Pre-existing expected adverse events (e.g., diarrhea, constipation, etc.) will be assessed at enrollment via a Recent Health Survey containing questions from PRO-CTCAE, and emergent events will be assessed at 12 weeks. Medical records may be collected in the event that an SAE is observed.
4 Measured via text message response

5 Food Security module from the National Health Interview Survey
6 Only for participants who do not respond to text messages; If a participant does not respond to text messages for 7 days, we will invite them to a semi-structured interview to understand reasons for non-response.

6.2 Study Procedures and Assessments

6.2.1 Screening Period / Visit -1 (Day -84 to Day 1)

Participants will complete eligibility screening online or by phone. Interested participants will then complete consent online via DocuSign or a paper copy of the consent will be mailed to them with an addressed, prepaid return envelope. The consent documents will include contact information for the study team, in case the potential participants have any questions.

After an individual provides informed consent, the following activities will be performed during the Screening Period:

- Medical record review, if available – age, insurance status, cancer diagnosis, stage, treatments, recurrence, metastases. This will not be required to assess eligibility.
- Inclusion/exclusion criteria review
- Enrollment Surveys:
    - Sociodemographic and clinical variables
    - Dietary Assessment (food frequency questionnaire; FFQ)
    - Food Security module from the National Health Interview Survey
    - Theoretical constructs assessed using a modified Food Beliefs survey
    - Pre-existing adverse events assessed by a Recent Health Survey, using questions from the NCI's Patient Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)

6.2.2 Study Intervention Period (Day 1-84)

- Text message intervention engagement (text message responses)
- Non-response interview (if applicable)

6.2.3 End of Study Intervention (Study Week 12 ± 84 days)

- 12-week surveys:
    - Dietary Assessment (FFQ)
    - Food Security module from the National Health Interview Survey
    - Theoretical constructs assessed using a modified Food Beliefs survey
    - Adverse events in past 12 weeks assessed by a Recent Health Survey, using questions from the NCI's Patient Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). Medical records may be collected in the event that an SAE occurs.
    - System Usability Scale (SUS)
    - Acceptability of Intervention Measure (AIM)

- Intervention Appropriateness Measure (IAM)
- Feasibility of Intervention Measure (FIM)

- End of study interview (optional)

6.2.4 Follow-up

Participants will not be followed after discontinuing the study intervention.

7 Reporting and Documentation of Results

7.1 Measures and Instruments

Dietary Assessment Survey (FFQ)

Participants will complete a validated food frequency questionnaire (FFQ) at enrollment and week 12.[30] The FFQ will ask about diet in the past 3 months. For each item, participants will be asked to report how often, on average, they ate the specified portion size in the past 3 months. Participants can choose from frequency options ranging from never or less than once per month to ≥6 times a day. To compute calorie and nutrient intakes, we will multiply the frequency of consumption of each food by the amount of each nutrient in the specified portion size using composition values from the U.S. Department of Agriculture and other sources.

The FFQ specifically queries intake of the following whole grain items: cooked oatmeal/cooked oat bran (including instant); other cooked breakfast cereal, including grits; whole wheat, whole grain oat, whole multigrain bread or pita; whole grain/whole wheat crackers; brown rice; whole grain pasta, e.g., spaghetti, macaroni; other whole grains, e.g., quinoa, barley, spelt, etc. Refined grains on the FFQ include: white, wheat, oatmeal (not whole grain) bread or pita; rye/pumpernickel bread or pita; tortillas: corn or flour, e.g., burritos, quesadillas etc.; other crackers; bagels, English muffins, or rolls; muffins or biscuits; pancakes or waffles; white rice; other pasta (not whole grain), e.g., spaghetti, noodles, macaroni, etc. Participants also report intake of cold breakfast cereal and the brand of cereal that they eat most often; cereal brand is used to classify their cold breakfast cereal intake as whole or refined grain. Using these data, we will calculate the percent of total grains that are whole, servings/day of whole grains and refined grains, and total fiber (g/d) at each time point.

The survey will be administered using REDCap. A paper FFQ will be made available for participants who are not able to complete the survey online.

Other Survey Data

Participants will be asked to complete additional surveys using REDCap at 0 and 12 weeks. Paper copies will be made available for participants who are not able to complete the surveys online.

Sociodemographic and clinical factors will be assessed at baseline.

At baseline and 12 weeks, a Recent Health Survey with questions from the NCI Patient Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) Measurement System will be used to collect adverse events (AEs) by self-report in study participants.

At 0 and 12-weeks, we will use validated surveys to measure theoretical constructs: the Food Security module from the National Health Interview Survey and a modified Food Beliefs survey (which includes self-efficacy, social support, self-monitoring, etc.).

At 12-weeks, we will assess usability and acceptability of the intervention via the System Usability Scale (SUS), Acceptability of Intervention Measure (AIM), Intervention Appropriateness Measure (IAM), and the Feasibility of Intervention Measure.[31] The System Usability Scale (SUS) is a valid and reliable 10-item tool for measuring usability.[32] The acceptability of each intervention component (e.g., behavior change messages, whole grain intake messages, educational material, food security support) will be evaluated separately.

End of study interview (optional)

Participants may be invited to complete an optional 15 to 30-minute end of study interview to obtain open-ended, qualitative feedback.

8 Adverse Events and Serious Adverse Events

8.1 Definition of Adverse Event (AE)

An adverse event (AE) is defined as any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention related.

Adverse event assessment:

A Recent Health Survey with modified questions from the NCI Patient Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) Measurement System will be used to collect AEs by self-report in study participants. The survey measures participant-reported frequency, severity, and interference of expected symptoms and also allows the participant to report the severity of unexpected symptoms. Most symptoms are graded on a 5 point Likert scale ranging from 0 to 4. Frequency responses are assessed by the question “How often do you have [symptom]?” and include: Never, Rarely, Occasionally, Frequently, and Almost constantly. Severity responses are assessed by the question “What was the severity of your [symptom] at its worst?” and include: None, Mild, Moderate, Severe, Very Severe. Interference responses are assessed by “How much did [the symptom] interfere with your usual or daily activities?” and include: Not at all, A little bit, Somewhat, Quite a bit, and Very much. For this study, assessments of frequency, severity, and interference are based on a 12-week recall period.

8.2 Definition of Serious Adverse Event (SAE)

A participant-reported AE that results in any of the following outcomes is defined as a Serious Adverse Event:

- Death,
- Life-threatening adverse experience*,
- Inpatient hospitalization or prolongation of existing hospitalization,
- Persistent or significant disability/incapacity,
- Congenital anomaly/birth defect, or cancer, or

- Any other experience that suggests a significant hazard, contraindication, side effect or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above,
- Event that changes the risk/benefit ratio of the study.

*A life-threatening adverse experience is any AE that places the patient or participant, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

8.3 Classification of Adverse Events

8.3.1 Severity

Severity of expected, non-serious AEs will be assessed using the PRO-CTCAE severity responses by the question "What was the severity of your [symptom] at its worst?" and include: None, Mild, Moderate, Severe, Very Severe.

Any participant-reported event that is deemed to be an SAE will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0, as developed and revised by the Common Therapy Evaluation Program (CTEP) of the National Cancer Institute.

8.3.2 Attribution of SAEs

Serious adverse events are further given an assignment of attribution or relationship to study intervention. Attribution categories are:

- **Definite** – The serious adverse event is clearly related to the study intervention.
- **Probable** – The serious adverse event is likely related to the study intervention.
- **Possible** – The serious adverse event may be related to the study intervention.
- **Unrelated** – the serious adverse event is clearly not related to the study intervention.

SAEs attributed to the intervention are not expected for this minimal risk study, but will be monitored, should they occur.

8.3.3 Expectedness

An adverse event is considered unexpected if it is not listed at the specificity or severity that has been observed, or the event is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

8.4 Adverse Events Monitoring

This study is a minimal risk level study that does not require monitoring by the HDFCCC Data and Safety Monitoring Committee (DSMC) as per the National Cancer Institute-approved Data and Safety Monitoring Plan. Ultimately, the PI is responsible for the safety and conduct of this study. However, the DSMC will provide Serious Adverse Event (SAE) review (if applicable), as well as review of all protocol violations and consent incident reports prior to submission to the IRB.

8.5 Follow Up of Adverse Events

All participants who experience adverse events will be followed with appropriate medical management in accordance with standard of care until resolved or stabilized.

8.6 Documenting and Reporting of Adverse Events

Adverse Events that are deemed to be SAEs will be documented in the study Case Report Forms (CRFs) and reported to the IRB, HDFCCC DSMC, and collaborators in accordance with all applicable institutional and regulatory requirements.

9 Statistical Considerations

9.1 Sample Size Considerations

9.1.1 Sample Size and Power Estimate

Sample size: up to 60.

We will consider our study to the median response proportion to text messages that ask for a reply is ≥ 70%, and the median Feasibility of Intervention Measure score is 4 or higher. The intervention will be determined acceptable if median scores on the Acceptability of Intervention and Intervention Appropriateness Measures are ≥4. With our sample size of 60 participants and assuming a standard deviation (SD) for the mean text message response rate of 25% based on prior work,[10] we will be able to detect an average text message response rate of 70% with a 95% CI of 64%-76%.[33]

For our secondary outcome of percent of grains that are whole, using a paired t-test to compare mean proportion of total grains that are whole at 0 and 12 weeks, alpha=0.05, a SD=23% for the mean change in proportion of grains that are whole,[10] 20% drop out, and 60 participants, we will have 80% power to detect a ≥9% change in proportion of grains that are whole.[34]

9.1.2 Accrual Estimates

- **Zuckerberg San Francisco General (ZSFG)** is a public safety net hospital that sees 40-50 stage II-III CRC patients/year; 80-90% of whom identify with a racial/ethnic minority group. We estimate 70% will be eligible for the proposed study (~30/year). We aim to enroll 10 participants from ZSFG.
- **UCSF HDFCCC GI Oncology Clinic** sees ~150 cases of stage I-III CRC each year; 40% of whom identify with a racial/ethnic minority group. Based on prior work, ~70% of these patients will be eligible for the proposed study (~105/year). We have also identified over 3,000 people who meet our clinical eligibility criteria using the CTSI Participant Recruitment Program services. We aim to enroll 50 participants from UCSF.

9.2 Statistical Analysis Plans

9.2.1 Primary Analysis (or Analysis of Primary Endpoints)

Descriptive Analyses: We will use descriptive statistics [means (standard deviation, SD) and median (interquartile range, IQR) for continuous variables and proportions for categorical variables] to summarize participant characteristics and baseline variables from the survey data as well as attrition and intervention adherence outcomes. We will quantify text message response rates using medians (interquartile range; IQR) for continuous variables and proportions for categorical variables. We will describe System Usability Scale (SUS) score,

Acceptability of Intervention Measure (AIM), Intervention Appropriateness Measure (IAM), and the Feasibility of Intervention Measure using median (IQR). A score >68 on the SUS is above average usability.

Qualitative data analysis: Audio recordings of interviews will be transcribed, translated to English (if needed), and imported into Dedoose software for structural coding and thematic content analyses.

9.2.2 Secondary Analysis (or Analysis of Secondary Endpoints)

We will compare intake of dietary factors, including whole grains (servings/day), refined grains (servings/d) and total fiber (g/d), before and after the intervention using paired t-tests. For example, for whole grains, our null hypothesis is that there is no difference in whole grain intake, on average, between 0 and 12 weeks. Our alternative hypothesis is that whole grain intake is higher at 12 weeks, on average, compared to 0 weeks. We will use mean (95% CI) and median (IQR) to describe intakes at each time point and change over time for normally and non-normally distributed continuous variables, respectively.

9.2.3 Exploratory/Correlative Analysis

The RL algorithm will initially send messages from the three COM-B categories (capability, motivation, opportunity) or no message at random. If a category is predictive of subsequent higher whole grain intake or engagement (responses to text messages), the algorithm will begin to send that type of message more often. We will use one sample tests of proportions to explore if the proportion of text messages sent from each of the three COM-B categories or no message differs from 0.25. For example, for capability messages, our null hypothesis is that the proportion of messages targeting capability is equal to 0.25. The alternative hypothesis is that the proportion of messages targeting capability is not equal to 0.25.

We will also explore whether the distribution of text message type varies by sociodemographic factors (e.g., age, gender, race/ethnicity) using chi-square tests. For example, our null hypothesis is that the distribution of text message type is the same across racial/ethnic groups. The alternative hypothesis is that the distribution of text message type differs across racial/ethnic groups.

10 Study Management

10.1 Pre-study Documentation

Before initiating this trial, the PI will have written and dated approval from the Institutional Review Board for the protocol, informed consent form, participant recruitment materials, and any other written information to be provided to participants before any protocol related procedures are performed on any participants.

The PI must comply with GCP/ICH guidelines and all applicable regulatory requirements.

10.2 Institutional Review Board Approval

The protocol, informed consent form, and all forms of participant-facing materials related to the study (e.g., advertisements used to recruit participants) will be reviewed and approved by the IRB. The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

10.3 Informed Consent

All participants will be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation. Participants must sign the IRB-approved informed consent form prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

10.4 Changes in the Protocol

Once the protocol has been approved by the IRB, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the PI and approved by the IRB prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to participants, an amendment may be implemented prior to IRB approval. In this circumstance, however, the PI must then notify the IRB according to institutional requirements.

The Study Chair and the UCSF study team will be responsible for updating any participating sites.

10.5 Case Report Forms (CRFs)

The PI and/or designee will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document study data for safety monitoring and data analysis. All study data will be entered into OnCore® or other CTMS used for the study via standardized CRFs in accordance with the CTMS study calendar, using single data entry with a secure access account. Study personnel will complete the CRFs; the PI will review and approve the completed CRFs.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the participant's medical records maintained by study personnel. All source documentation should be kept in separate research files for each participant.

In accordance with federal regulations, the PI is responsible for the accuracy and authenticity of data entered onto CRFs. The PI will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

All source documentation and CTMS data will be available for review/monitoring.

10.6 Record Retention

The PI is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each study participant. Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed participant consent forms). Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the research study. The PI shall retain records for a period of 2 years following the conclusion of the study.

10.7 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual agreement among the PI and collaborators.

10.8 Multicenter Communication

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter study. The UCSF Coordinating Center will also coordinate, at minimum, quarterly conference calls with the participating sites. The following issues will be discussed as appropriate:

- Enrollment information
- Cohort updates
- Adverse events (i.e. new adverse events and updates on unresolved adverse events and new safety information)
- Protocol violations
- Other issues affecting the conduct of the study

10.9 Regulatory Documentation

Prior to implementing this protocol at UCSF or any participating site, the protocol, informed consent form, and any other information pertaining to participants must be approved by the UCSF IRB. Prior to implementing this protocol at the participating sites, approval of the UCSF IRB approved protocol must be obtained from the participating site's IRB.

The following documents must be provided to UCSF HDFCCC before the participating site can be initiated and begin enrolling participants:

- Participating Site IRB approval(s) for the protocol, informed consent form, and HIPAA authorization
- Participating Site IRB approved consent form
- Participating Site IRB membership list
- Participating Site IRB's Federal Wide Assurance number and OHRP Registration number
- Curriculum vitae and medical license (if applicable) for each investigator and consenting professional
- Documentation of Human Subject Research Certification training for investigators and key staff members at the Participating Site

Upon receipt of the required documents, UCSF HDFCCC will formally contact the site and grant permission to proceed with enrollment.

11 Protection of Human Subjects

11.1 Protection of Privacy

Participants will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following provision of this information, they will be asked to sign the HIPAA form and informed consent documents. The

original signed document will become part of the participant's medical records, and each participant will receive a copy of the signed document. The use and disclosure of protected health information will be limited to the individuals described in the informed consent document.

11.2 Protection from Unnecessary Harm

Each clinical site is responsible for protecting all participants involved in human experimentation. This is accomplished through the IRB mechanism and the process of informed consent. The IRB reviews all proposed studies involving human experimentation and ensures that the participant's rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The IRB also reviews the informed consent document associated with each study to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits.

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