Study Title: A Patient-Centered Intervention Using Technology to Reduce Colorectal Cancer Disparities in Primary Care

U.S. NIH Grant/Contract Award Number: 3R01CA207689-04S1
Protocol IRB ID: IRB201702765

Document: Study Protocol and Statistical Analysis Plan - Version 11/17/2023

University of Florida IRB-01
Protocol

1. Project Title:

A patient-centered intervention using technology to reduce colorectal cancer disparities in primary care

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3. Abstract:

The purpose of this study is to test the efficacy of a patient-centered, tailored message intervention delivered via virtual technology for increasing colorectal cancer (CRC) screening within guidelines among racial/ethnic minority and rural patients. This protocol focuses on specific aim 2 of grant NCI 1RCA207689-01A1. In specific aim 2, patients (N=1,500) will be recruited via a secure, clinical data warehouse to complete a patient-randomized test of the efficacy of the intervention for promoting initial and repeat FIT screening. Patients identified as eligible will be contacted through MyChart and email to test a web-based, culturally-sensitive virtual human intervention for CRC screening. The web-application provides information to encourage CRC screening. Therefore, this study is a minimal risk study.

4. Background:

Most tailoring interventions rely on fully-tailored print messages. However, there is growing evidence that minimal tailoring may be as effective as full tailoring in some circumstances and that utilizing virtual human technology (VHT) to deliver tailored CRC screening messages may improve uptake. Interventions using VHT offer numerous advantages, including the capability to be customized to the preferences of the patient. As such, the use of virtual technology could help improve CRC screening by increasing cultural congruence, self-efficacy, and active patient engagement with screening information.

The purpose of this study is to test the efficacy of a patient-centered, tailored message intervention for increasing CRC screening among racial/ethnic minorities and rural patients. The intervention is based on theory and research in the area of message tailoring. The process of tailoring requires customizing intervention content to be personally relevant to the receiver. When messages are perceived as personally relevant, they are more likely to have a lasting effect on patient attitudes and screening behaviors. The intervention content will be tailored to patients on theoretical constructs causally associated with screening behavior change. Our hypothesis is that exposure to a minimally tailored CRC screening intervention delivered via VHT will lead to improved cognitive processing of the intervention and increased adherence with initial and repeated annual FIT screening completion as compared to a fully tailored, text-only intervention.

5. Patient Eligibility and Recruitment

We will recruit an ethnically diverse sample of eligible patients (*N* = 1,500, 750 men, 750 women, evenly distributed across White, African-American, Hispanic/Latino) to complete the intervention.

Eligibility criteria: patients must be between the ages of 45 and 73, able to read English or Spanish at least at eighth-grade level, have an email account or the ability to receive texts, and be out-of-guidelines for CRC screening within recommended guidelines (i.e., <10 years for colonoscopy, <3 years for Cologuard, <1 year for FIT). The primary outcome in the current study is CRC screening compliance. Compliance will be assessed by electronic medical record review (MRR) at 6, 12, and 18 months after enrolling in the study. Patients will be considered compliant if they a) complete a home stool test with a negative result only, b) complete a home stool test with a positive result AND undergo a completion screening colonoscopy, c) complete Cologuard only, or d) complete a colonoscopy only. We will also examine potential mediators of intervention effectiveness, such as exposure to the intervention, psychological processing of content (e.g., comprehension, perceived message quality), and online records of communication with a healthcare provider about screening.

Recruitment locations: Online at University of Florida Health, online through social media and online at community events (e.g., UFHealth Cancer Center (UFHCC) Office of Community Outreach and Engagement (COE), Community Clinical Navigation (CCN) and Mobile Outreach Clinic (MOC)).

Recruitment and retention methods: We will recruit current patients from UF Health Family Medicine and UF Health Internal Medicine electronically using the UF Integrated Data Repository (IDR) to locate eligible patients who have consented to be re-contacted for research purposes through the Consent2Share (C2S) program. Additionally, we will recruit patients outside of C2S. This is done to ensure that our study does not replicate existing health disparities hinging on patients' knowledge of the program. A variety of socioeconomic, cultural, and historical factors are thought to impact patients' willingness to participate in medical research and these factors often map along racial and ethnic lines. Because our study seeks to serve populations that are traditionally underserved medically, including racial and ethnic minorities, it is important that we reach all eligible participants, not only the subset that has enrolled in C2S. We will also recruit from UF Health Family and Internal Medicine outside of the IDR in collaboration with clinic managers, providers, and staff who have identified a patient as eligible for the study. Finally, we will recruit UF Health patients through Facebook (See Social Media Advertising Campaign).

We will be recruiting patients with active MyUFHealth accounts as well as patients who are not enrolled in MyUFHealth. Patients who have an active MyUFHealth account will be sent a message in MyUFHealth inviting them to participate in the study that contains both the English and Spanish versions of the recruitment email and informed consent; patients will select a language based on their preferences (Phase 1 English Recruitment and informed consent; Phase 1 Spanish Recruitment and informed consent). At the same time, we will also send them a physical mailer (Physical Mailer: enrolled in C2S and MyUFHealth or Physical Mailer: not enrolled in C2S, enrolled in MyUFHealth; English and Spanish versions) to inform them, and request their participation in a research study. This is done to increase the participation rates of those patients who do not frequently check their MyUFHealth account or associated e-mail account unless they are expecting a message.

We will recruit patients who do not have active MyUFHealth accounts using in-person recruitment methods developed in collaboration with clinic managers, providers, and staff in the UF Family Medicine and UF Internal Medicine clinics. We will invite patients to participate in the study via a physical mailer (Physical Mailer: C2S and non-C2S enrolled, not enrolled in MyChart; English and Spanish versions) and a message to their email account. The physical mailer will include information inviting them to sign up for MyUFHealth if they have not already done so. The flyer will contain information about how to enroll in MyUFHealth. When available, the flyer may also include dates and times for sessions where a study coordinator will be present at a clinic to assist patients in signing up for an account in-person. Participants who are not enrolled in MyUFHealth will be encouraged to sign up for a session to answer any questions they may have but walk-ins will also be allowed during the designated timeframe. Trained study staff will assist patients in enrolling in MyUFHealth and accessing the website application on their

cell phone (if desired). We will also provide laptop computers for patients who do not bring their own electronic device but still wish to enroll.

We will also recruit patients identified as eligible by clinic managers, providers, and staff outside of the MyUFHealth system using UF Qualtrics. Patient name, ID, language preference, and email, along with demographic information (race, gender) will be entered into a Qualtrics portal which will generate a customized link that is included within an emailed message based on the patient's language preference, inviting them to participate (Phase 1 English Recruitment and informed consent; Phase 1 Spanish Recruitment and informed consent).

In addition, study staff will participate in community health fairs and events hosted or attended by the UFHealth Cancer Centers Office of Community Outreach & Engagement (COE) where study information will be presented by study coordinators and interested patients will have the ability to speak with study staff and receive details on how to participate in the study. At community events, the COE team provides CRC screening via FIT tests, improving access to rural and high-socioeconomic vulnerability (SEV) communities in the 23 county UFHCC catchment area as well as as well as providing navigation services to all screened individuals to ensure results are received by PCPs as well as individuals completing the screening, and navigation for any needed follow-up care for positive screens (i.e., colonoscopy services). This approach ensures that all individuals receiving screening are guided through the continuum of cancer care and linked to accessible services, in the community where they reside and at low- or no-cost. The study team will present colorectal cancer education via the Meet ALEX website application to interested community members meeting eligibility criteria and refer those completing the study intervention to the COE team to obtain FIT tests if requested by the individual. The COE team will provide FIT testing to all individuals at no charge.

Outside the activities of the study, but in the concert with best practices for care coordination and according to standard practice community members or clinic patients that meet criteria for FIT testing are offered free test kits. The COE team provides all kit materials (including pre-paid mailer) and instructions on how to obtain the specimen. For all individuals completing FIT testing, from community events or clinic referrals, completed FIT tests are mailed to the COE team for on-campus processing at UF laboratory facilities (GCRC). Results are shared with referring providers and results are provided to patients, by the COE team, in letter form as well as a phone call. All communications are documented and shared with clinical teams for integration into the electronic medical records (EMRs).

We will also recruit patients through Facebook (See Social Media Advertising Campaign). Ads will be posted through the official UF Studies Facebook page (www.facebook.com/ufstudies) with assistance from the CTSI Recruitment Center, and UFHCC COE. The ads will link to the study Qualtrics portal previously described.

Approximately one week after initial contact, the patients that have not enrolled will receive an email message reminding them about the study (English and Spanish - Phase 1 Enrollment Reminder Script: E-mail). Patients who are enrolled in MyChart, either through the study or otherwise, will receive additional weekly reminders about completing the study (English and Spanish - Phase 1 Enrollment Reminder Script: Phone/Voicemail and Phase 1 Enrollment Reminder Script: Text message).

In light of COVID-19, staff were added to conduct quality control calls and add video conferencing to replace face-to-face assistance to participants. Staff in addition to community health workers (CHWs) on the research team will contact participants for quality control. Communication activities have transitioned to Zoom-PHI video conference calls for assistance with technical issues enrolling in the intervention.

Intervention: Patients will interact with an online educational application which delivers an educational message about FIT screening (Phase 1). They will be randomly assigned to receive a standard, text-based tailored message or a tailored message delivered by a virtual human. The message itself is

comprised of a brief core message about the importance of screening as well as up to 10 additional constructs which may influence decision to screen: message source, perceived severity, risk probability, perceived susceptibility, framing, perceived benefits, response efficacy, perceived barriers, narrative persuasion, and self-efficacy. In both conditions, the information is presented to patients as coming from a "virtual healthcare assistant" in the form of either VHT or a still image. Participants will be randomly assigned to see either a demographically-concordant or demographically-discordant virtual healthcare assistant. Patients seeing a concordant assistant will be matched based on race and gender. Participants seeing a discordant assistant will be mismatched on race or gender or both. Participants whose preferred language as listed in Epic is Spanish, or who were recruited through Qualtrics and self-selected Spanish as their preferred language, will receive a Spanish-language version of the intervention.

In both the text-based and virtual human versions of the intervention, some patients will randomly see constructs featuring interactions with the virtual human. These interactive segments ask patients information about their behaviors related to CRC and screening, such as the frequency with which they eat red meat and potential barriers to screening they face. These questions will be used to randomly deliver either a tailored response to the patient's feedback or a generic, non-tailored response.

Upon completion of the interaction with the app, patients will complete a short (i.e., 20 minute) algorithmic questionnaire that utilizes survey responses to assess attitudes and screening behaviors associated with CRC. Participants recruited through the IDR and UF Qualtrics will complete the questionnaire using web-enabled devices such as computers or tablets. Participants in phase 1 will be remunerated $30.00 for interacting with the app and completing the subsequent questionnaire.

After completion of the interaction patients will also complete a brief questionnaire (Post-intervention screener) to assess interest in screening, their screening status, and CRC risk. For patients who are unsure of their screening status or risk-level, project staff will conduct medical record review and/or consult with the PCP. Patients at low/average risk will be asked whether they would like to request a FIT test. Patients at high-risk will be asked whether they would like to speak with their primary care physician about colonoscopy. For all patients regardless of risk-level who click "Yes," the system will send a request to their primary care physician to consult with the patient. If a FIT order is approved, we will then send the appropriate FIT kit to the participant at the requested address. Participants will be reminded to complete and return their kits to their clinic or lab at 2 weeks (English and Spanish - FIT Kit Reminder A Script; e-mail), 4 weeks (English and Spanish - FIT Kit Reminder B Script; text message), and 6 weeks (English and Spanish - FIT Kit Reminder C Script; phone message) after being mailed the kit.

For patients accessing the intervention through UF Qualtrics, screening status and risk will again be assessed with a similar procedure. For the patient FIT request message, an additional item will be included on the questionnaire asking them if they would like to request a FIT test. For patients choosing "Yes," physical address as well as email will be collected and stored in UF Qualtrics.

After questionnaire completion patients will be directed to a compensation survey where name, physical address, and email are collected for the purpose of distributing study compensation.

One month after the initial invitation and reminders (Phase 2), participants who have not completed Phase 1 of the intervention or did not request screening after completing Phase 1 of the intervention, will be re-contacted through MyUFHealth or email and re-invited to the study. Participants will be remunerated $10.00 for completing the intervention at Phase 2.

In Phase 3, participants who respond to the intervention will receive an invitation in MyUFHealth or email 12 months after the date of their initial recruitment inviting them to click on a link to receive a booster message encouraging regular, repeated screening and offering them the opportunity to request their annual FIT kit from their provider. Participants will then complete 5-10 short questions relevant to their

experience with FIT (e.g., “How easy was it for you to follow the instructions that came with your FIT test?”) and any pertinent changes to their health history (e.g., “Has anyone in your family been diagnosed with colorectal cancer in the past year?”). Participants will be remunerated $5.00 for completing the booster questionnaire.

In addition to the post intervention test, we will monitor Epic for participants' screening compliance (to determine whether they have engaged in behavioral change), whether they make appointments with their doctors (to establish whether they engage in informed decision-making with their healthcare provider) and whether they request repeat testing the following year (to track long-term behavioral change). We will also track whether people were diagnosed with CRC to see whether the intervention has significant impacts on detection of CRC rates among participants.

To ensure that our technology systems are functioning as expected and that patients have received their mailed FIT kits, we will conduct quality control calls with patients who do not finish the intervention, who do not respond to recruitment messages, or who do not have screening results entered into their MR. A research coordinator or community health worker (CHW) will call patients and ask if they encountered any technical difficulties in using the intervention, or if they received their FIT kit and encountered any difficulty using it. If the patient encountered technical problems, we will gather relevant details (such as web browser used) and pass this information along to our technology team. This will allow them to troubleshoot problems and increase completion rates. If the patient encountered problems with screening, we will again gather relevant details and provide the needed guidance/support.

6. Study Design

We will evaluate the VHT intervention using a fractional factorial experimental design embedded within a sequential, multiple assignment, randomized trial (SMART). The fractional-factorial design allows estimation of the optimal tailored message assuming only lower-order interactions and requires far fewer samples. For example, a full factorial design of 10 factors at two levels would involve runs of size 4,096 whereas a fractional factorial design that does not confound any pairwise interactions would involve runs of size 79. In short, the fractional factorial experimental design allows us to go beyond simply testing the efficacy of tailored vs. non-tailored messages by honing in on the specific elements of a message that are most salient to the patient.

We will also collect longitudinal data on outcomes associated with exposure to the intervention (Phase 3). Participants in the treatment arms who have completed their initial screening within the first 12 months of the study will receive an email invitation one year after the intervention. This message will invite them to view a booster of the intervention consisting of another message encouraging repeated screening. Compliance will be assessed via self-reporting and MRR for all patients as well as through tracking in MyUFHealth.

Sample Size Analysis
At each stage of randomization, the combination of tailored messaging factors follows a resolution 5 fractional factorial design. A sample size of 1,000 patients is sufficient to detect inferiority at a margin of 0.075 with 80% power. We note that performing this sample size calculation is non-standard as it requires estimating the best tailoring message, which requires optimizing over a potentially large number of potential tailored message combinations; we corrected for these multiple comparisons by inverting a projection interval. However, we plan to follow patients for a total of two years. Assuming 33% attrition over this time period, an initial sample of 1,500 is sufficient.

Primary endpoints include compliance with screening recommendations (measured via MMR) as well as potential mediators of intervention effectiveness (such as exposure to the intervention, psychological processing of content, and self-reported communication with a healthcare provider about screening).

Secondary endpoints including cancer detection rates as well as long-term behavioral changes (i.e. whether patients request screening the following year). They will be analyzed as descriptive statistics without anticipated power calculations.

7. Data Management:

We worked with representatives of UF Health Network and MyUFHealth to situate the intervention within MyUFHealth. The interaction itself will be hosted using Virtual People Factory (VPF), a web platform which hosts virtual human interactions. We will use Amazon Web Service (AWS) to store data from the interaction as well as host the virtual human webpage. For our design, human subjects need to be randomized to see either a demographically-matched VH or a demographically-dissimilar VH. They will also see either a video recruiting message a UF Health provider or a written recruiting message with a photo of the provider.

Representatives from IDR will set up weekly pulls of eligible patients and will upload lists of these patients and their contact information onto a secure, password-protected server housed in the University of Florida's Health Sciences Center. Each human subject will be sent a message in MyUFHealth inviting them to click on a link. We will use script to append the subject's MyUFHealth ID number to the end of the link to create a customized URL. For patients initially recruited outside of MyUFHealth through UF Qualtrics, after entering name, patient ID, email, and demographics a unique ID will be created and appended to a customized URL link. Clicking on the URL takes the subject to the secure server housed in the University of Florida's Health Sciences Center. The secure server runs a program replacing the MyUFHealth ID number with a random Participant ID number before redirecting the subject to the virtual human app. The program records both numbers in a key document which is updated daily and uploaded to the secure, password-protected server.

In this way, no PHI leaves the secure UF Health network, but we can still record the subjects' interactions within the intervention and match their answers up with the survey data collected from MyChart. The participant ID number on its own contains no PHI. The only way the random participant ID number on its own could be used to identify human subject and access PHI would be to breach the security of the UF Health Sciences Center server and MyUFHealth. No PHI leaves the UF system. No PHI is transmitted to VPF or AWS. All data will be monitored systematically to identify any security weaknesses, and data files will be backed up to protect against data corruption.

After completing the intervention, participants will be redirected to Qualtrics, an online survey hosting site, to complete the post-test questionnaire. Their random Participant ID will be appended to their Qualtrics questionnaire, allowing us to link their responses to their actions in the intervention. Qualtrics data will be backed up regularly and stored in the secure, password-protected UF Health IT server.

Study staff will participate in community health fairs and events where study information will be presented and interested patients will have the ability to speak with our study staff to receive details on how to participate in the study. Consistent with study procedures, all participants receive a unique participant ID that prevents researchers to link participant data. The mapping between the actual patient ID and generated unique ID is only known to the research coordinator, COE director, and Assistant Director of Clinical Community Navigation in order to provide FIT test results (received or not; positive or negative screen). Other members of the research team will not be aware of the actual patient ID. This process ensures that study data is de-identified and PHI will be protected.

Data monitoring will be conducted by the Data Safety Management Committee (DSMC), consisting of Dr. Lok (PI), and Dr. Laber (Co-I). The DSMC will meet as needed to discuss the safety and integrity of the

data and will submit annual reports to the University's SMRC (Scientific Review and Monitoring Committee).

Data Retention Policy and Data Sharing

Data will be collected and retained in accordance with HIPPA requirements and standard procedures. Data about eligibility, recruitment, and patient progress through the study will be stored in a secure REDCap database that only the research coordinators, postdoc, and other necessary staff can access. We will store only the minimum amount of data required to determine patient eligibility for enrollment in the trial and the postdoc will regularly review all data for quality control and compliance.

We will retain data on EMRs reviewed in Epic for the duration of the trial and for as long as is required by law. Retained data will be provided to authorized medical providers at UF Health Family Medicine and UF Health Internal Medicine upon request to assist them in updating patient medical records and documenting discrepancies in CRC screening status.

We will share data associated with the trial with outside investigators by depositing these data in Azkaban, a file sharing system approved by UF Integrated Risk Management. Data include participant responses to survey questions and information about participant interactions with the intervention, demographic data (including participant zip code), as well as select medical information such as screening status for CRC. Data will be deidentified where possible and data will only be stored on SharePoint for the duration of analysis, after which they will be removed from the system.

Data will be shared with investigators working at other accredited universities for the purposes of analysis. The names and Institutions of persons either given or denied access to the data, and the bases for such decisions, will be recorded. Participants will acquire IRB approval from their home institution to review data.

8. Possible Discomforts and Risks:

We anticipate that this study is deemed to be minimal risk. This study poses minimal risk to participants because it involves no medical treatment and the intervention itself consists of information that would be given to a participant in the course of a normal visit with his or her doctor. There is some psychological risk to participants who are not familiar with the technology, as they may become frustrated. However, we have developed the app in conjunction with potential users to ensure that it is as user-friendly and navigable as possible. The questionnaire does not contain any items that are likely to cause emotional distress. There is no social risk, as the participants will not be physically seen by the researchers. We have enacted all necessary technical protections to keep data safe and data will be de-identified.

Patients will be provided with a phone number to contact study staff. In the unlikely event that a patient wishes to not be contacted again, they will be removed from the study immediately and will stop receiving messages through MyChart as it pertains to the study.

<u>Protections for "Break-the-Glass" Patients</u>

The Epic EMR system has special protections in place for particularly sensitive medical documents or files, such as HIV status and information as well as data on specific psychiatric conditions. These documents or files are protected from view by a "Break-the-Glass" lock which, when opened, triggers a privacy audit. During the chart review process, it is possible that coordinators and other study staff may encounter Break-the-Glass documents or files, indicating a patient with special status.

We have enacted special safety procedures for this patient population to ensure their privacy while minimizing the risk of excluding them unnecessarily from recruitment and furthering disparities. First, research staff have been trained to immediately close the document or file and avoid proceeding if they encounter a Break-the-Glass warning. If the patient is enrolled in C2S, coordinators will continue reviewing the record to the best of their ability to establish eligibility without viewing any Break-the-Glass documents or files. If they cannot determine eligibility status, the patient will be exited from the study. If the patient is deemed eligible, they will be enrolled in the trial as normal. Patients who are not enrolled in C2S will be immediately exited upon discovery of a Break-the-Glass warning.

Second, patients with Break-the-Glass warnings will be deemed a special cohort within the framework of the clinical trial and subject to additional checks to ensure patient well-being. The DSMB, along with the clinic co-investigators, will review the records and participation rates of Break-the-Glass patients quarterly and will make decisions about continuing to enroll such patients.

Adverse Event Reporting

If any team member encounters or becomes aware of an adverse event, they should notify the PI and Postdoc within 5 business days. The PI and Postdoc will confer and inform the co-investigators, project officer, and University of Florida IRB about the event as appropriate. All team members have been made aware that they should inform the PI and Postdoc if they encounter an adverse event. Potential, but unlikely adverse events include participants talking to other participants about their study condition or misperceiving the intervention as a reduction in their healthcare services (e.g., virtual appointment instead of face-to-face appointment). The intervention team will discuss each adverse event and determine if changes to the protocol are necessary.

9. Possible Benefits:

Public Health Impact: The proposed study improves public health by contributing to research on how to best deliver effective screening messages to minority and rural patients. A primary goal of Healthy People 2020 is to increase the percentage of individuals screened for CRC across population subgroups to 80%. The proposed study will reduce health disparities and associated morbidity and mortality due to CRC by increasing FIT screening among minority and rural populations through a novel, culturally sensitive intervention. By leveraging existing infrastructure within the health system (i.e., clinical data warehouse), we will create a cost-effective communication strategy for delivering personalized screening messages to diverse patient populations.

10. Conflict of Interest:

There are no real or potential conflicts of interest in regards to this research project for any members of the study team.