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NIH Collaboratory Ethics and Regulatory Core: UG3 Consultation Call
Using Artificially Intelligent Text Messaging Technology to Improve American Heart Association's Life's Essential 8 Health Behaviors (Chat 4 Heart Health)
August 9, 2023; 4:00-5:00 pm ET (via Zoom)

Attendees:

- Core, Coordinating Center, and NIH: Joe Ali (Johns Hopkins University), Alex Fist (Duke University), David Magnus (Stanford University), Stephanie Morain (Johns Hopkins University), Pearl O'Rourke (retired), Tammy Reece (Duke University), Damon Seils (Duke University), Wendy Weber (NCCIH)
- Demonstration Project team: Sheana Bull (University of Colorado), Michael Ho (University of Colorado)

AGENDA ITEMS	DISCUSSION	ACTION ITEMS	OWNER
Brief review of Demonstration Project	Meeting attendees received the Research Strategy and Data and Resource Sharing Plan for Chat 4 Heart Health with the meeting agenda (see supplementary materials attached). Stephanie Morain facilitated the discussion. Core members, study team members, NIH representatives, and staff from the NIH Pragmatic Trials Collaboratory Coordinating Center introduced themselves. The Chat 4 Heart Health team members present included co–principal investigators Sheana Bull and Mike Ho. **Project overview**: Sheana Bull gave an overview of the project. Chat 4 Heart Health grew out of the study team's previous work on Nudge, an NIH Pragmatic Trials Collaboratory Demonstration Project. The study will use an artificially intelligent chatbot (but not a generative chatbot) to design and test messages that are persuasive, motivating, medically accurate, and helpful for patients with diabetes, hypertension, or hyperlipidemia in adopting the American Heart Association's Life's Essential 8 (LE8) lifestyle changes . Patients will be able to ask questions in their own way, and the system will use artificial intelligence to match responses that meet the intent of the users' questions. **Healthcare system partners**: Denver Health and Hospital Authority, Salud Family Health Centers, STRIDE Community Health Center **NIH Institute Providing Oversight**: National Heart, Lung, and Blood Institute (NHLBI)		

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	Study design: The study will have 3 arms: (1) generic text message to participants on the topic of the week (for example, tips for healthy eating); (2) chat bot; and (3) chat bot plus pharmacist support. The study will use an opt-out approach similar to that used in Nudge. **Outcomes**: The outcomes of interest are cardiovascular risk factors (such as blood pressure, cholesterol level, blood sugar).		
Status of IRB approval	The study will use the Colorado Multiple Institutional Review Board (COMIRB) as the single IRB of record. The study team has obtained IRB approval for qualitative formative work in the UG3 phase. They are working with patients and providers in the partnering healthcare systems to gain insight into how much tutoring will be needed on what a chatbot is and how it will be used so that participants can feel comfortable being exposed to and encouraged to use it. These qualitative interviews are underway. In addition, the study team has obtained IRB approval for pilot studies at 2 of the partnering healthcare systems.		
Risk (Does the project meet regulatory criteria for being considered minimal risk?); and consent (planned processes for relevant subjects)	The study team anticipates that the project will meet the regulatory criteria to be considered minimal risk. The study team plans to seek a waiver of consent. Pearl O'Rourke advised the study team to avoid referring to the materials as a consent form. Pearl O'Rourke asked whether the study team will follow patients who opt out. Mike Ho responded that, in Nudge, the study team went back to the IRB to obtain approval to access electronic health record data for patients who opted out. The study team can try a similar approach in Chat 4 Heart Health. Pearl O'Rourke asked if the study team would collect information on why patients opt out. Mike Ho responded that the study team can deploy a similar survey as was used in Nudge to collect this information. Stephanie Morain supported including a follow-up survey on reasons for opting out. David Magnus asked whether patients who receive the chatbot messages will know the messages are from a chatbot. Sheana Bull responded that the first message		

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	patients receive will explain this. David Magnus asked whether patients in the general text message arm will know that their messages are not from a chatbot, or if everyone will be informed that their messages might come from a chatbot. Sheana Bull shared her recollection that the initial message does not indicate this; rather, if a patient replies to the text message, it is standard practice to respond with an automated reply clarifying that the text messages are not from a live person and offering information about how to access resources. David Magnus encouraged the study team to consider whether sending an introductory message to participants may influence how they react to receiving the messages. If all participants receive the same introductory message, this could be important for how participants feel about receiving subsequent messages. David Magnus shared a link to the following article: • Hohenstein J, Kizilcec RF, DiFranzo D, et al. Artificial intelligence in communication impacts language and social relationships. *Sci Rep*. 2023 Apr 4;13(1):5487. doi: 10.1038/s41598-023-30938-9. PMID: 37015964.		
Privacy (including HIPAA)	The chatbot system logs telephone numbers; however, there is no exchange of names from the researchers' side. The study team will not disclose any personal information or protected health information. All content will be stored behind the university's firewalls. The opt-out letter will include this information. The study team will use healthcare system data to identify patients with diabetes, hypertension, or hyperlipidemia for the purpose sending out the initial messages.		
Monitoring and oversight	The study team intends to use the same data and safety monitoring board (DSMB) as was used for the Nudge study.		
Issues beyond this project (regulatory and ethics concerns raised by the project, if any)	David Magnus asked for more information about how the study team will use Amazon Mechanical Turk (MTurk). Sheana Bull responded that MTurk will help the study team get started on figuring out different ways people ask questions. The goal is for 85% of the chatbot responses to meet the intent of the question. In the beginning, this will likely be 65% to 70%, and it will increase with experience with organic users. David Magnus asked whether the study team is calculating the time it takes to complete MTurk tasks, and whether they will compensate MTurk workers accordingly. Sheana Bull thanked David Magnus for this point and responded that the study team will look into this.		

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	Pearl O'Rourke asked about the role of the pharmacist in the third study arm and whether it is reasonable to expect them to do what the study team is asking. Mike Ho responded that both of the healthcare systems that have approved the protocol employ pharmacists who are dedicated to population health, and the study team is hoping to leverage these pharmacists for the study. Pearl O'Rourke clarified that she likes the idea but is worried about potential workforce challenges. Mike Ho agreed and expressed surprise that the healthcare systems already have these types of pharmacist roles. Pearl O'Rourke suggested that the study team review the FDA's June 2023 Content of Premarket Submissions for Device Software Functions: Guidance for Industry and Food and Drug Administration Staff. She added that Chat 4 Heart Health appears to meet the criteria for not being considered a device; however, the IRB may ask questions about this. David Magnus expressed his view that the chatbot in the study is definitely not a clinical decision support tool, but that we do not yet know how the FDA will think about chatbots that communicate directly with patients. Sheana Bull added that the study team has a contact on the university's innovations team with whom they have discussed the issue, and the contact's thinking was consistent with the study team's view that the chatbot is not a medical device. The study team will monitor changes in the guidance, as this is an evolving issue. Joe Ali asked for confirmation that all of the chatbot data will remain in house. Sheana Bull replied yes.		
Other matters	None.		

BACKGROUND AND SIGNIFICANCE

At least 50% of the US population will develop two or more chronic medical conditions by age 45, with the prevalence increasing to >80% for those age 65 years and older. These chronic medical conditions include many CV diseases and CV disease risk factors (e.g., hypertension, hyperlipidemia, and diabetes). CV disease leads to significant disability, health care costs and death. With more CV conditions[13], the burden of disability for patients (i.e., limitations in activities of daily living, social function, physical function and cognitive function) as well as health care utilization (e.g., prescription medications, emergency department visits, hosptialization) increases.[13] *To successfully manage these conditions, patients need ongoing care facilitated by health care providers who can help them monitor and manage their CV conditions themselves in between episodic health care visits.*

Patients experiencing health disparities, those who are racial and ethnic minorities[14]; people with low income or low socioeconomic status (SES)[15]; rural residents[16] and people with limited English proficiency[17] are disproportionately affected by these CV conditions and suffer greater consequences from these conditions. The risk of diabetes is 77% higher for Black and 66% higher among Hispanic/Latino, than for White patients.[18] Hypertension control rates are lower among Non-Hispanic Black (48.5%) and Hispanic/Latino(47.4%) compared to Non-Hispanic White patients (55.7%).[19] These differences contribute to disproportionate rates of mortality as the attributable risk for hypertension and 30-year all-cause mortality is nearly double for Non-Hispanic Black than Non-Hispanic White patients.[6] Data show similar disparities for people with low SES,[20] rural residents and people with limited English proficiency.[21,22] *These statistics highlight an urgent need to address and control these CV risk factors, particularly among patients experiencing health disparities. Furthermore, most of the prior interventions addressing CV risk factor reduction have generally targeted individual risk factors rather than overall CV health as encompassed in the LS7 risk factors.*

Self-management (SM) involves focusing on an individual's role in managing chronic disease and has strong evidence of benefit for patients with chronic medical conditions.[2] Meta-analysis[23,24] and systematic[25] reviews of SM interventions have demonstrated improved self-efficacy, quality of life, health status, chronic disease measures (e.g., reduced A1C)[26], health behavior change (i.e., increased exercise) and reduced healthcare utilization. SM support programs[27] aim to change patient behavior. The American Heart Association has identified 7 key self-management behaviors that when optimized will collectively lead to better CV health, i.e., stopping smoking, eating better, being active, sustaining a healthy weight, manage blood pressure, control cholesterol and reduce blood sugar.[3,28] The LS7 score documents how well patients adhere to SM behaviors, with a score that quickly and effectively measures overall CV health ranging from 0-14, where 0-4 is considered "inadequate" 5-9 "average" and 10-14 "optimum" CV health.[29] Patients can be supported in their SM by maintaining collaborative partnerships[6] with health care providers, who facilitate access to interventions to increase patient relatedness to health systems leading to improved behavior, better disease control and better patient outcomes with reduced utilization of health care services. *To date, interventions have been focused mainly at the individual level and have generally been resource intensive (i.e., often requiring face-to-face visits), have enrolled small samples, and do not adequately address contextual factors including social determinants of health.*

As healthcare becomes increasingly complex, alternative team-based approaches to chronic care that include clinical pharmacists, are becoming common.[30] Clinical pharmacists have advanced training in chronic disease management that includes both non-medication behavioral interventions (e.g., motivational interviewing) and all aspects of medication management (e.g., selection, monitoring, adjusting). There is clear evidence of their positive impact on patient outcomes, spanning from smoking cessation to glycemic control and blood pressure control across various care settings (e.g., Federally Qualified Health Centers (FQHC), academic health centers).[31–35] These benefits have led to widespread integration and reliance on clinical pharmacists, but with added health system costs associated with paying another doctoral-level health care provider.[36–43]

Mobile telephones are common with 96% of US adults owning a cellphone.[44] **Use of text messaging to communicate is also common with 81% of cellphone owners using their phones to text messages.**[45] Text messaging in support of SM behaviors is an evidence-based, inexpensive and scalable mechanism to reach a broad population. Text messaging is used by people across the age spectrum, among racial and ethnic minority populations, rural populations[16], people with low (SES) as well as people with limited English proficiency.[17,46,47] Texting is an efficient and effective tool to deliver educational messages, promote behavior change, provide reminders for medication adherence, and support communication between patients and providers.[48–50] Meta-analyses of text messaging interventions have demonstrated improved health behaviors including physical activity[51], weight loss, chronic disease control (i.e., glycemic control and BP)[52–54] and medication adherence. Accordingly, text messaging technology provides a low-intensity, generalizable tool that can plausibly impact self-management behaviors for patients with chronic medical conditions. *However, evidence on systematic moderators such as optimal message content, conversational approaches that facilitate bidirectional messaging, timing and dose of messages is limited, and it is unknown if patients experiencing health disparities benefit similarly.*[55]

The use of text-message based artificially intelligent (AI) conversational chat bots is emerging as the next generation for technology-based health behavior interventions.[56,57] These emerging systems advance automated communication from fixed state *a priori* text message libraries that push out content tailored to user driven questions. Text messaging systems can send unidirectional and/or bidirectional messages, the latter employing a specific list of answers a user can pick (e.g., text '1' if you plan to eat fruit during breakfast). Chatbots used today typically support bidirectional communication using frequently asked questions (FAQ), which are a pre-determined set of questions that users must pick from a list. Users of FAQ chatbots are not able to deviate from these "pick list" questions. An AI conversational chatbot, in contrast, utilizes natural language processing (NLP) to classify the intent of a user-initiated question on specific topics and machine learning (ML) to continually update and refine the precision in offering a response that correctly addresses the intent of the question. This allows patients to initiate and direct organic text message communications to a specific phone number in support of self-management. Using *a priori* libraries focused on specific health behaviors that anticipate the intent of patient text-message queries, an AI chatbot can continuously use NLP to process questions and ML to update and refine messages to train the system to increase the precision in matching the correct response to user queries. A well-functioning AI chatbot using NLP and ML will return answers that are appropriately matched to user queries 80% of the time or more.[58] *As of now, we have little understanding of the incremental benefits of this nascent tailored and user-centric approach compared to standard text message systems.*

While the use of text messaging and AI to automate and scale messaging are important strategies to increase the impact of low intensity interventions, the content of messages matters. Our prior work with text messaging and recent work with the Nudge text messaging program provide evidence that messages with carefully designed content are superior to generic, "one size fits all" messaging. From our own work we have demonstrated impact on health behaviors and health outcomes, including screening for HIV, accessing and utilizing contraception, and seeking childhood vaccinations.[48–50] This work focuses on three strategies for health communication message design with evidence for impacting lifestyle behaviors: the use of tailoring to increase message relevance; the use of behavioral nudges to facilitate intuitive decision-making; and the use of persuasive messaging to increase motivation to change over time.

Tailoring SM interventions meets patient identified needs and increases the level of intervention effectiveness. A prior study[59] found that White patients had the lowest physical activity and highest adherence to insulin therapy whereas Hispanic patients were more interested in improving self-management behaviors, suggesting that targeted support to meet patient needs may be important. As another example, a tailored self-management intervention for Black patients with diabetes improved diabetes related clinical measures.[60,61] A systematic review of SM support interventions in low income and low health literacy patients showed that they were generally resource intensive and had inconsistent benefits. SM support interventions are effective especially when tailored to meet patient needs; but, data of its effectiveness in patients experiencing health inequities when deployed broadly using technology are limited.

Behavioral "nudges" from the fields of behavioral economics and cognitive psychology have the potential to augment the impact of text messaging interventions to support patient behavior change. The Dual-Process Theory of decision-making (one of two foundational theories supporting Dan Kahneman's 2002 Nobel prize in economics) states that people make decisions either 'intuitively,' quickly drawing on emotion and past experiences or 'reasonably' using a thoughtful, analytic approach. Nudges take advantage of the intuitive aspects of decision-making. [62,63] A nudge is defined as a small change in choice framing or choice architecture that "alters people's behavior in a predictable way without forbidding any options or significantly changing their economic incentives."[7] Behavioral nudges are more personalized and resonate better with patients, and have demonstrated impact on healthy eating[64], smoking[65], and physical activity[66,67]. A systematic review demonstrated the benefit of nudges to improve SM activities for patients with chronic conditions.[68] Use of persuasive message strategies can further impact message engagement. Theories in Health Communication emphasize the need to provide a message frame (e.g., with a positive or negative tone) to provide opportunities for bidirectional engagement that allow for senders to demonstrate pro-social characteristics, evoke an emotional response or include a narrative in order for audiences to resonate with and internalize message content.[69]
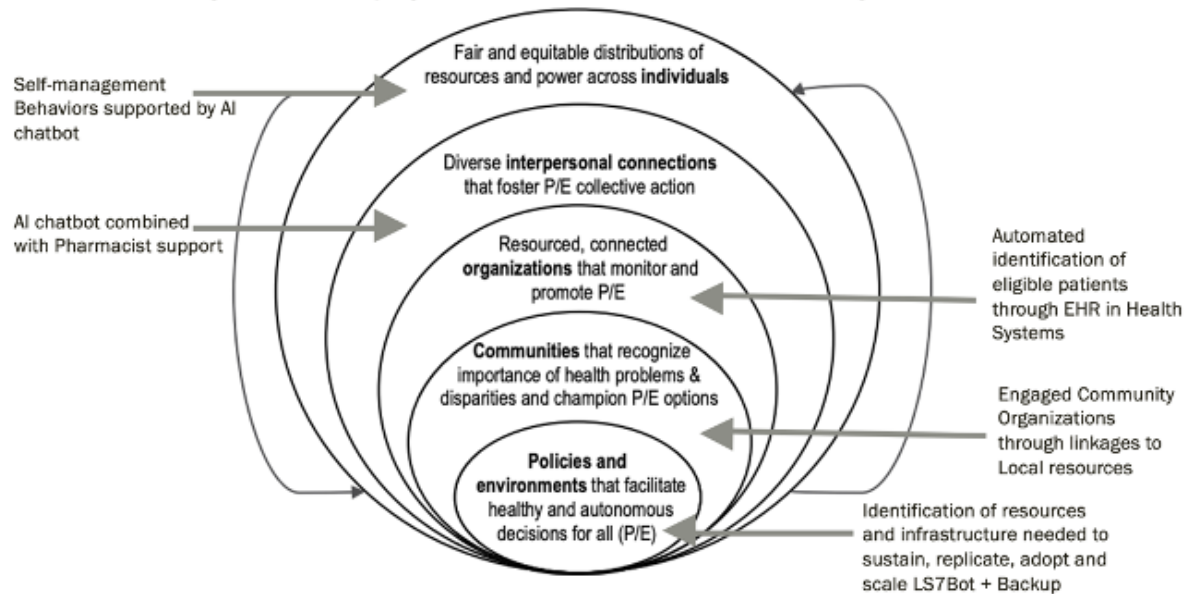
Interventions for SM are more likely to have a greater impact when addressing multilevel contributors to health inequities.[70] Per the social-ecological model, to effectively reduce CV risk, patients must have the knowledge and skills to adopt healthy behaviors; communities must have resources that align with cultural norms of the patients at risk; and health systems must have resources to identify and treat risk in an integrated, patient-centered manner.[71] SM interventions are primed for multi-level components that facilitate greater engagement with and support from interpersonal connections, health organizations, communities and environments to facilitate health. The "Social Ecological Model, Inside Out" proposed by Golden et al.,[72] explicitly emphasizes an approach to health equity through conceptualizing how individuals, their personal social networks and group affiliations co-create the context that drives policy development and supportive physical and structural environments to support health (see Figure 1). A key factor in this model is understanding how social

determinants such as access to safe places to exercise, reliable transportation and food insecurity are considered in the intervention development and implementation. We attend to multiple levels of the model by making our intervention fairly and equitably distributed, by fostering interpersonal connections between patients and pharmacists, by automating identification of eligible patients through the EHR; by linking patients to community resources that support improvements in social determinants of health and

Figure 1: An Equity Focused, Inside Out Social Ecological Model

through identification of infrastructural supports needed to replicate, sustain and scale the LS7 Bot + Backup intervention. As an example, an intervention that encourages paticipants to eat fresh vegetables and fruits but does not access whether this is feasible for participants or provide resources to find these foods at free or reduced costs will not equitably benefit all people. Our approach of using AI chatbot text messages, also allows us to engage with users and ask them about key social determinants, subsequently tailoring system responses to provide resources and strategies to achieve SM in the communities where people live.

Summary of evidence and gaps in knowledge: (1) We lack interventions that successfully address multiple CV conditions, particularly for racial/ethnic minorities, poor, rural, and non-English speaking patients, all of whom face disparities in chronic CV health outcomes. (2) SM can be successful but often fails to consider the complex social determinants of health on behaviors that can be amplified for persons experiencing disparities in chronic CV conditions. (3) One way to improve SM programs is to design interventions that acknowledge and support patients in addressing influences on their SM behaviors at the interpersonal, organizational and community level. (4) Interventions that are successful in facilitating SM for persons experiencing disparities can likely suffer from being too resource intensive or too complex for delivery. Therefore we must consider approaches that are easy for health systems to adopt, implement and maintain. (5) Using technology that relies on cellphone based text messaging is one such approach. Although we know text messaging can be effective to facilitate healthy behavior, we have not fully integrated emergent systems that utilize artificial intelligence in combination with strategic, evidence-based messaging to increase the impact of low intensity interventions, or evaluated the incremental benefits of adding health system-level, proactive pharmacist engagement..

How our intervention addresses these gaps: Our goal is to improve control of CV disease risk factors by engaging patients experiencing CV disparities with "LS7 Bot + Backup," an innovative technology-based SM intervention with linkages to health system providers focusing on control of the American Heart Association's Life's Simple 7 (LS7) lifestyle factors (blood glucose, cholesterol, blood pressure, physical activity, weight, diet, and smoking). Using a patient level randomized pragmatic trial design, we will test the comparative effectiveness of 1) generic unidirectional text messages; 2) theory-based, tailored and socially contextualized communications using an artificially intelligent (AI) text messaging chatbot for self-management support; or 3) Optimized AI chatbot messages with proactive pharmacist management for self-management support. We plan to enroll 6000 patients with sub-optimal control of their CV risk factors and poor adherence with medications to treat the CV risk factors since they are more likely to benefit from a SM support intervention. Further, given that Black patients, Hispanic/Latino patients , Spanish-speaking only patients, rural residents, and low-income patients experience disparities in CV outcomes, we will target enrollment to include these groups from clinics within 3 health systems that care for large populations of patients experiencing health disparities: 1) Salud Family Health Centers, an FQHC with 13 clinics including clinics serving rural Colorado residents, 2) Denver Health and Hospital Authority, a safety net health system for Denver county with 9 FQHCs, and 3) STRIDE Community Health Centers, a FQHC with 18 locations surrounding Denver County.

"LS7 Bot + Backup" has the explicit goal that if the intervention is demonstrated to be effective, it can be more broadly sustained within the 3 health systems of the study and disseminated to other health systems. We highlight key features of the study:

- We will enroll patients from FQHCs that care for high volumes of patients experiencing health disparities
- We will develop AI chatbot text message content in collaboration with patient, provider, community and health system stakeholders to ensure sociocultural, linguistic and community relevance. We have incorporated multiple levels of partnership including patients, providers, community advocates and health system leaders in all study phases guided by implementation science and equity frameworks
- We will deliver AI chatbot text messages that incorporate English or Spanish-language versions depending on patient choice. AI chatbot text messaging is scalable, leverages technology easily accessible to patients experiencing health disparities, delivers the intervention to patients wherever they are, provides a mechanism of communication between patients and the health system ensuring access, and can be tailored to the appropriate context to overcome barriers to self-management.
- We attend to multiple levels of an "inside out" social ecological model by making our intervention fairly and equitably distributed, by fostering interpersonal connections between patients and pharmacists, by automating identification of eligible patients through the EHR; by linking patients to community resources that support improvements in social determinants of health and through identification of infrastructural supports needed to replicate, sustain and scale the LS7 Bot + Backup intervention.
- We will evaluate the incremental effects and cost associated with adding proactive pharmacist management to AI chatbot text messaging to support self management.
- Our approach integrates implementation science, health equity, and digital health frameworks to address different intervention levels.
- We will utilize rigorous implementation science frameworks and methods to maximize real-world relevance, reproducibility, sustainability, and scalability, which will guide the following approaches: 1) user-centered rapid and iterative design methods for our AI chatbot text messages; 2) ongoing multi-level and representative partner engagement; and 3) development of an 'adoption, implementation, sustainability and dissemination guide' based on our PRISM evaluation.
- Focus on global CV health based on the LS7 score and targeting patients at highest risk for adverse events (i.e., those with uncontrolled CV factors and poor adherence to CV medications).
- We address control of CV risk factors (e.g., hypertension and diabetes) that are important quality of care metrics for our participating FQHCs

Previous Work:

Investigative team: We have assembled a transdisciplinary team of disparities researchers, social scientists, clinicians with CV risk prevention expertise, pragmatic trial experts, patient and health system operations leaders who are also diverse in terms of racial, gender and ethnic backgrounds. Many members of the research team are currently conducting a NIH Collaboratory multi-site text message intervention focused exclusively on medication adherence (NHLBI UH3 AT009845, called the Nudge study) that provides the foundation, experience and pilot data for the proposed self-management support intervention. Next, we summarize the current status of the Nudge study and our prior experience with other pragmatic trials.

Lessons learned from the Nudge study: The Nudge study is a patient level randomized control trial at 3 health system including a safety net hospital system with 9 FQHCs (Denver Health). The other 2 heath systems are VA Eastern Colorado Health Care System (1 hospital and 8 outpatient clinics through Colorado) and University of Colorado Health (11 hospitals across Colorado). EHR data is used to identify eligible patients using clinical (e.g., hypertension, diabetes) and pharmacy (e.g., blood pressure medications) data. Once eligible patients are identified, patients are sent introductory letters with the opportunity to opt-out of the study. If patients do not opt-opt, we follow their pharmacy refill data. Once they have a delay in refilling their cardiovascular medications, they are eligible for the study and randomized to one of 4 study arms (usual care, generic text messages, optimized text messages, and optimized text messages with AI chatbot) with the goal of improving adherence to CV medications in the year after enrollment.

As part of the Nudge study intervention, we have developed the initial technology infrastructure used to deliver text messages. This includes programming the software needed to deliver the text messages to patients, a library of text messages for each of the 3 study intervention arms, and the ability to respond to patient questions as they arise via text messages or follow-up telephone calls. As part of the text message library development, we engaged patient stakeholders across the 3 health systems, obtained feedback about the messages and iterated the message library with stakeholders over multiple rounds. We incorporated social and cultural adaptations to the messages to ensure that they resonated with patients. The finished message library includes 11 messages bin English and Spanish.

To date, we have sent out 13,444 study packets to patients with an opt-out rate of ~15%. We have enrolled 9,291 patients evenly distributed across the 4 study arms. The study population has been diverse with ~47% female, 16% Black and ~50% Hispanic/Latino. We have delivered 94,636 text messages to date, including 34,063 Spanish language text messages. Our study staff has responded to 112 study related text messages and pharmacists have responded to 443 clinical questions from patients. When clinical issues arise, the study pharmacists have also engaged the patient's primary care provider and made them aware of relevant patient clinical issues. We have ongoing stakeholder engagement with quarterly meetings comprised of patients, providers (e.g., physicians and pharmacists), and health system leaders (e.g., Chief Medical Information Officer). Preliminary interim analysis of the intervention has demonstrated ~10% reduction in the number of days that a patient had a gap in refilling their medication for patients receiving (a) optimized text messages and (b) optimized messages plus access to an interactive chatbot compared to (c) usual care. These findings highlight the impact of text messages—a low-intensity intervention--to change patient behavior and demonstrate our ability to develop text messaging technology infrastructure to conduct pragmatic research within large health systems.

Experience conducting pragmatic trials within health systems: Our team has worked collaboratively across diverse healthcare delivery systems—including our partners named in the current proposal. Dr. Ho has led 2 pragmatic trials focused on medication adherence in the VA both of which improved adherence to CV medications using interactive voice response technology. One trial included 3 sites and was a patient-level randomized trial while the other enrolled 15 sites in a cluster randomized trial. Drs. Peterson and Bull are now conducting a pragmatic trial of mobile application and time specific text messaging on long term cardiac rehabilitation outcomes for Denver Health patients (R61HL143324). Furthermore, Dr. Bull led the development and pilot testing of a COVID-19 AI chatbot that used NLP and ML to deliver bidirectional English and Spanish language messaging to improve access to and reduce hesitancy toward COVID-19 vaccines. The COVID-19 AI chatbot pilot study is being conducted at Salud and STRIDE, two of the health system partners for the proposed intervention. This COVID-19 chatbot has interacted with more than 4,000 patients to engage in over 5,000 conversations to offer information on vaccine eligibility, safety, boosters and to correct misperceptions about COVID-19 vaccines, and has a record of correctly classifying responses to correctly address >85% of questions asked. Dr. Daugherty has led several NIH-funded studies focused on health equity including a recently completed multicenter trial (including Denver Health) that recruited 960 patients (56% self-identified as African American or Black) testing an intervention on the negative effects of racial discrimination on hypertension outcomes.[73,74] Furthermore, Dr. Glasgow has participated in multiple health behavior change pragmatic trials and written broadly on pragmatic trials.[75–77]

Implementation science adaptations, PRISM, RE-AIM and sustainability: Dr. Glasgow, a co-investigator on this study, is a primary developer of both the PRISM (Practical, Robust Implementation and Sustainability Model) and RE-AIM Frameworks and has published extensively on their design and implementation, including technology-based investigations. He has collaborated with Dr. Bull on multiple projects.[31-38] The PRISM extends RE-AIM by also including key contextual factors that influence RE-AIM outcomes. With colleagues, Dr. Glasgow has also published on how RE-AIM can be used alone or in combination with other frameworks to guide adaptations and to promote equity (see also www.re-aim.org).[78,79] The Colorado implementation science team has also published extensively on mixed methods assessment and guidance of adaptations as relevant to planning, implementation and sustainment of complex interventions.[79–81] Drs. Glasgow and Trinkley have published together on applications of PRISM to health technology projects,[82,83] and Drs. Trinkley, Ho, and Glasgow have recently published on the integration of implementation science into learning health systems.[84] Dr. Jolles has published extensively on work with Latinx populations and multi-level partnerships in FQHC settings.[85–88] She has recently moved to University of Colorado School of Medicine to join our implementation science team and is already collaborating on studies utilizing her form and function approach to guide contextually and culturally appropriate tailoring and adaptations.

Our research work has resulted in adoption of new technologies, systems, policies or practices within the respective health systems. The Latinos Using Cardio Health Action to Reduce Risk (LUCHAR, meaning "to battle" in Spanish) was a tri-institutional collaboration between Denver Health, Kaiser Permanente Colorado and the University of Colorado focused on CV health interventions for Latinos in Denver, Colorado. Dr. Bull was a Co-PI on LUCHAR (1 U01 HL079208), and Dr. Peterson served as a Denver Health Co-Investigator for the project. LUCHAR facilitated the design of one of the earliest interactive computer tools showing a positive impact for patients to self-identify behavioral risk factors for CV disease and to develop a plan to mitigate risk.[89] LUCHAR delivered personalized education on nutrition, physical activity, and smoking behaviors using community-based health kiosks. With this tool, we demonstrated positive improvements in physical activity and nutrition behaviors for English and Spanish speaking Latinos. The team also developed one of the first disease specific registries across two healthcare delivery systems and utilized the system to identify patients at high risk for cardiovascular illness—of note was the utilization of the system to identify specific sociocultural factors such as acculturation that can moderate or mediate CV Health.[90] LUCHAR also facilitated exploration of racial bias in healthcare delivery, another component of social determinants of health; and the LUCHAR investigators were

among the earliest to document the relationship between implicit racial bias and quality of healthcare for Latino patients.[91,92] This work contributed to the design and implementation of multiple provider and clinician researcher training initiatives to address implicit racial bias in health care delivery in place today at the University of Colorado through the Colorado Clinical Sciences and Translation Research Institute (CCTSI)[93], including an immersion training that facilitates clinician researcher capacity building to successful collaborate with diverse communities in the implementation of research.

In part based on successful implementation of the Nudge text messaging for medication refill reminders at the VA and our pilot work demonstrating acceptability of text messages from patients, VA Eastern Colorado Health Care System implemented routine text messaging reminders to all of their patients for medication refills. Furthermore, we have adapted our COVID-19 chatbot for the Canadian Public Health Association to reach their 40,000+ provider and public health professionals with automated messaging about COVID-19 vaccines in Canada and are currently adapting the tool for use in Peru with parents of pediatric populations.

INNOVATION AND SIGNIFICANCE
Our proposed large-scale pragmatic trial is innovative and significant in a number of respects:

- Two of these health systems have not traditionally engaged in research (Salud and STRIDE) and this proposal provides an opportunity to engage new partners in research.
- Our proposed opt-out enrollment and AI chatbot text messaging-based intervention are cost-effective approaches to deliver self-management support on a large scale.
- Our opt-out approach allows us to enroll patients who are more likely to benefit from the intervention rather than patients self-selecting to enroll in a mobile health study who are more likely to be adherent. We have initial support for the opt-out strategy based on preliminary discussions with our IRB (COMIRB), which will serve as the IRB of record for all 3 health systems.
- Our broad, substantial and ongoing engagement of key stakeholders across patient, provider/pharmacist, organization and community levels uses innovative collaboration strategies which will enhance representation and generalizability of study findings.
- Use of rapid N-of-1 development and refinement studies (i.e. within subject assessments among a small sample of participants who review multiple iterations and intervention types as well as a nominal group method to more quickly optimize final intervention elements) both rely on underutilized yet highly appropriate strategies to optimize messages and build on the emergent literature suggesting optimization of messages may lead to better engagement with content.
- We study whether optimized AI chatbot text messages outperform generic text messages to impact LS7. This offers a critical contribution to behavioral science theory that is widely applicable to health communication for diverse outcomes and audiences.
- While there are a number of mobile applications that employ automated robots or 'bots' to communicate,[94,95] we know of no research that explores the effectivness of using AI chatbots that rely both on machine learning and natural language processing to support or promote healthy behaviors in general or CV risk factors in particular.
- Our proposed trial is innovative in the exploration of the impact of SM support using technology on a large scale within three diverse health systems caring for a large number of patients experiencing health disparities. Our scope is substantial and will offer an important contribution to better understand whether such a large system level effort is both feasible and impactful.

Finally, we will continue to work with the NIH Collaboratory Cores to learn and share best practices as we have done in the Nudge study. In terms of our participation in the NIH Collaboratory activities, we have given 2 grand rounds, presented at 5 conferences in collaboration with NIH Collaboratory members, led and published a paper that involved the Ethics Core leaders (Drs. Sugarman and Weinfurt), participated in 2 papers coming out of the work of the cores (*Enhancing the use of EHR systems for pragmatic embedded research: lessons from the NIH Health Care Systems Research Collaboratory* and *Accounting for quality improvement during the conduct of embedded pragmatic clinical trials within healthcare systems: NIH Collaboratory case studies*), and contributed to each of the core activities (Biostatistics & Study Design, Electronic Health Record, Ethics and Regulatory, Health Care Systems Interaction, Patient Centered Outcomes and Stakeholder Engagement).

Research Design and Methods Overview
*The objective of this study is to conduct a **pragmatic patient level randomized trial** to evaluate the implementation and effectiveness of 3 different automated patient communication approaches for self-management support to improve control of CV disease risk factors defined by AHA's Life Simple 7 risk factors.*

The proposed trial meets the criteria of a pragmatic embedded trial as outlined in the RFA. Using the **Pragmatic-Explanatory Continuum Indicator Summary (PRECIS-2) diagram (Figure 2) we articulate the specific elements of our proposed study that are pragmatic:**

Figure 2. PRECIS-2 diagram for the LS7 Self-Management Support + Bot

1) Eligibility: We will include all patients who meet eligibility criteria. Only patients who opt-out by returning a postcard will not be included; **2) Recruitment:** We are using the EHR to identify potentially eligible patients, so our recruitment procedures are feasible in most health systems. Patients will not have to meet in-person with study personnel to enroll in the pragmatic trial; **3) Setting:** We are using the same setting for the pragmatic trial as the usual care setting and the trial will be implemented across 3 very different health systems that are FQHCs delivering care to underserved patient populations-the settings to which we wish to generalize; **4) Organization intervention:** The intervention is be delivered automatically using AI chatbot text messaging to augment usual care so resource demands are low. Most systems have some level of pharmacist involvement so added organizational resources are not large; **5) Intervention flexi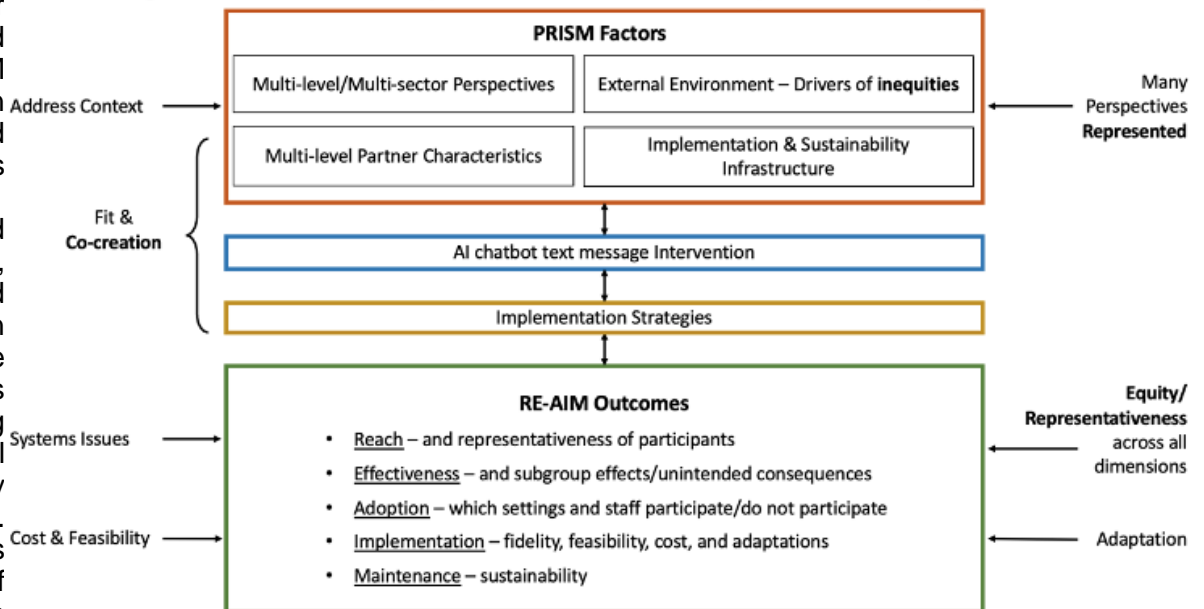bility (delivery):** In aim 1, we will design the AI chatbot text message content to ensure sociocultural, linguistic and community contextual relevance; **6) Intervention flexibility (adherence):** Patients randomized to the different study arms can opt out and there is no mandate to adhere to the content of the AI chatbot text messages; **7) Follow-up intensity:** There will be no explicit follow-up visits or end of study visit. All of the outcome data (LS7 assessment, medication adherence, patient self-efficacy, and clinical outcomes) will be obtained from the EHR and patient self-report via text messages at 12 months; **8) Primary Outcome:** Multiple studies have shown that worse control of the LS7 risk factors is associated with poor health status and adverse CV events. The outcome assessment will not require central adjudication or special training and utilize patient self-report and EHR data. We are however collecting more outcomes measures than would be usual in practice including costs; **9) Analysis:** We are proposing an intent to treat analysis and all patients will be analyzed unless they opt out.

Conceptual Model:
The overall goal for this work is intended to facilitate a SM intervention that can be widely accessed by patients experiencing disparities and readily adapted, sustained and disseminated in health systems. The PRISM framework is our overarching conceptual model that helps us stay focused on that goal. PRISM emphasizes design of interventions with

Figure 3: How PRISM (and RE-AIM Outcomes) Address Equity Issues

sustainability and dissemination in mind and close attention to the context, i.e., health system and social determinants, both of which are critical to improve self-management interventions for persons experiencing disparities. We will use PRISM to assess context and then design and evaluate contextual relevance in our generic and AI chatbot text message and proactive pharmacist support interventions. PRISM includes the RE-AIM outcomes identified above and highlights four categories of key contextual factors or determinants that influence implementation success: 1) organizational and participant characteristics; 2) organizational (health system and providers) and participants' (i.e., patients) perspectives on the intervention; 3) implementation and sustainability infrastructure (e.g., resources and support); and 4) external environment (e.g., regulations, policies, quality of care standards).[81,82,96,97]

PRISM is intended to be broadly applicable across disease states and types of implementations and thus is commonly used together with other determinant frameworks that provide in depth consideration of a specific area. Accordingly, we will

Figure 4. Overview of how PRISM is applied throughout the study planning, implementation, and evaluation with the other key frameworks: Health Equity in Implementation (green), Integrated Theory of mHealth (orange); *Equity domains - Health Equity and Engagement Core.
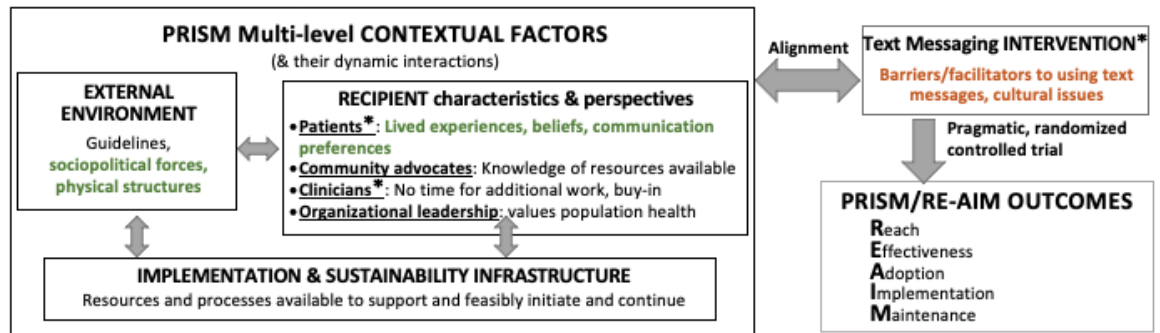

PRISM Multi-level CONTEXTUAL FACTORS
(& their dynamic interactions)

EXTERNAL ENVIRONMENT
Guidelines, sociopolitical forces, physical structures

RECIPIENT characteristics & perspectives
- Patients*: Lived experiences, beliefs, communication preferences
- Community advocates: Knowledge of resources available
- Clinicians*: No time for additional work, buy-in
- Organizational leadership: values population health

IMPLEMENTATION & SUSTAINABILITY INFRASTRUCTURE
Resources and processes available to support and feasibly initiate and continue

Alignment

Text Messaging INTERVENTION*
Barriers/facilitators to using text messages, cultural issues

Pragmatic, randomized controlled trial

PRISM/RE-AIM OUTCOMES
Reach
Effectiveness
Adoption
Implementation
Maintenance

use PRISM with other frameworks, i.e., the Health Equity in Implementation Framework[12], and the Integrated Theory of mHealth Framework[98] to guide detailed evaluations of equity-related contextual factors relevant to our target population, pertinent sociotechnical issues, and adaptations. Figure 4 illustrates how PRISM will be used throughout this study and how other frameworks will be used to complement PRISM. Details of the components in this logic model are described in relevant sections below. Table 1 offers a more detailed explanation of the purpose for each framework at different levels of the intervention.

Study overview: We will conduct the trial at 3 health systems that care for large patient populations affected by health disparities, including Black, Latino/Hispanic, Spanish speaking, low-income and rural patients. In Year 1 (UG3 phase), we will conduct stakeholder engagement (patients, providers, community advocates, and health system leaders) guided by PRISM and the Health Equity Framework[12] to further understand the context of the optimized patient communication, and to generate input on the sustainable design of automated communications that include attention to social determinants of health and ensure linguistic and community relevance. We will also engage these implementation partners to obtain feedback on intervention design, and outcomes as well as throughout the study to help address potential barriers to implementation, make necessary adaptations, help ensure sustainability of the program and plan for dissemination. Following refinement of the automated patient communication content, we will pilot the intervention at each health system to ensure that all aspects of the protocol have been operationalized and refine any potential barriers.

In Years 2-5 (UH3 phase), we will conduct a patient level randomized pragmatic trial comparing the following strategies: 1) generic text messages; 2) interactive AI chatbot text messaging incorporating tailoring to increase message relevance and address social context; behavioral nudges to facilitate intuitive decision-making; and persuasive messaging to increase motivation to change over time; or 3) interactive AI chatbot text messaging plus

Table 1: Integrated use of theories/frameworks to address different intervention levels and purposes

Theory or Framework	Primary Levels*	Purposes/Use
PRISM See *Figure 4*	Organizational system and provider-especially pharmacist levels, and secondarily community and individual	- Will guide efforts of the **Implementation Science Core** and activities - Focuses on alignment of intervention with organizational resources, characteristics and perspectives, while considering the influence of the patient and external environment - Emphasizes implementation infrastructure and designing for **sustainability** - Includes pragmatic **RE-AIM outcomes**
Health Equity in Implementation See *Figure 4*	Societal/ Community	- Along with Integrated Theory of mHealth framework will guide the efforts of the **Equity and Engagement Core** and its activities. - **Developed to be used with other frameworks** that are more broadly applicable - Focus on alignment of the intervention with **culturally relevant** factors (social determinants, lived experience); patient-clinician communication preferences; and societal context (community resources) - Guide representation and integration stakeholder perspectives to optimize **representativeness**/equity
Integrated Theory of mHealth See *Figure 4*	Individual (patient) and provider (pharmacist)	- Will support efforts to develop and implement the AI chatbot **tailored messages** - Focus on **sociotechnical** factors, designing mHealth with attention to access, engagement, social network theory, social support, social norms, self-efficacy, and behavior change

*Most frameworks address more than one level but have a strong focus on and are used in this proposal to address the primary level shown in the table

proactive pharmacist management. We have not included an usual care group because prior studies have generally found that control of the LS7 factors are not ideal and generic text messages have generally been more effective than usual care for behavior change. The study will randomize at the patient level rather than a

cluster level because: 1) our intervention uses automated and interactive text messages that are delivered directly to patients greatly reducing the risk of intervention contamination; and 2) we will include all patients who meet eligibility criteria into the study with an opt-out option for patients who do not wish to participate due to the low risk nature of the study intervention, consistent with the Nudge study.

We will include patients based on the following: 1) diagnosis of one or more of the following CV risk factors (i.e., hypertension, diabetes or hyperlipidemia), 2) the risk factor is at poor or intermediate health levels as defined by LS7 (e.g., BP$\geq$140/90 mm Hg), and 3) the patient exhibits poor adherence to prescribed medication to treat the CV risk factor as defined by a delay in refilling the medication within the past 6 months. While not part of the eligibility criteria, we are partnering with 3 safety-net health systems to further focus enrollment on Black, Hispanic/Latino, rural, low income and Spanish-only speaking patients. Patients meeting all inclusion criteria will be randomized to one of the three text messaging strategies. PRISM's contextual factor assessment and its RE-AIM outcomes framework (Reach, Effectiveness, Adoption, Implementation and Maintenance) will inform the development of the pragmatic outcomes relevant to multiple perspectives (patient, provider, health system). The primary outcome is change in LS7 risk score from baseline and 12 months following randomization. Secondary outcomes include other RE-AIM outcomes of patient reach, adoption, implementation, adaptation and maintenance; individual components of the LS7 lifestyle factors (e.g., BP control), patient self-efficacy, medication adherence, change in the Framingham risk score for CV disease[99], clinical outcomes (e.g., CV related hospitalizations), healthcare utilization and costs. We will collect outcome measures via a combination of patient report via text messages and EHR data. We will develop tools and an adoption, implementation, sustainability and dissemination plan guidebook if the intervention is effective. This guide will be used locally to maximize sustainability beyond study funding and also used for dissemination by other health systems considering adoption.

Organizational Structure: The Nudge Study Steering Committee consisting of the co-PIs, the clinical site PIs, and the core leads will provide oversight for the study. Five project cores will support the Steering Committee: (Administrative, Data and Statistics, Mobile Health, Health Equity and Engagement, and Implementation Science). Each of the cores will be responsible for different aspects of the planning and execution of the study. They will work collaboratively throughout the study. The Steering Committee will meet monthly throughout the study. Each core will meet as a group every two weeks and with the Steering Committee monthly. In our current Nudge study, we have operationalized a similar organizational structure.

During the UG3 year, each of the cores will have specific responsibilities and milestones (Table 2).

Steering Committee During the UG3 phase, the Steering Committee will be responsible for finalizing the study protocol and developing the study intervention manual. The Steering Committee will also oversee the pilot study in each health system during months 6-10 during which all aspects of the study will be implemented – including the identification and recruitment of subjects, the execution of the intervention and its implementation, and the assessment of outcomes. The Steering Committee will monitor the pilot study and make changes to the protocol based on this experience. They will elicit patient, provider, community and health system feedback, examine problems that occur, and revise and finalize the intervention. Members of the Steering Committee will actively participate and contribute to the NIH Collaboratory cores as we have done in the current Nudge study.

Implementation Science Core This core will be led by Drs. Glasgow and Trinkley with strong engagement from Dr. Jolles. During the UG3 phase of the project, this core will work with the other cores to draft detailed methods to assess context and align the intervention accordingly to maximize uptake and feasibility at each health system. The core will test and adapt these methods in Aim 2 as needed to improve contextual alignment. The Implementation Science core will also be responsible for monitoring implementation of the intervention in the UH3 phase, including 1) equitable patient reach of the intervention, 2) identification and evaluation of adaptations that are anticipated to occur in real-world settings, and 3) identification of strategies needed to promote continued engagement and sustainability during and for dissemination beyond the study funding. The core will also draft an initial adoption, implementation, sustainment and dissemination guidebook to enhance the potential for sustaining and disseminating the intervention beyond the study funding. The guidebook will be created in partnership with the Health Equity and Engagement core to proactively integrate health equity into all aspects. This guidebook will include materials and interactive tools being developed by Drs. Glasgow, Trinkley and team that will assist other learning health systems to adapt the intervention to enhance its equitable impact on patients. This core will include a health economist (Dr. Richard Lindrooth) who will develop plans to monitor and estimate implementation and replication costs during the UH3 phase.

Health Equity and Engagement Core This core will be co-led by Drs Stacie Daugherty and Monica Perez Jolles with a primary goal of ensuring that equity is embedded in all aspects of the study. We define equity as "the absence of unfair, avoidable or remediable differences among groups of people, whether those groups are defined socially, economically, demographically, or geographically or by other dimensions of inequality (e.g. sex, gender, ethnicity, disability, or sexual orientation)."[100] A key approach to achieving this goal is to facilitate an active engagement of diverse stakeholders in planning, conducting, analyzing and interpreting results, and disseminating study findings. We will include patients, health care providers, community advocate and health systems leaders from each health system as members of the core. The engagement process will be guided by the Health Equity Implementation Framework[12] and focus on three equity domains: a) <u>The patient</u>: as a recipient of the program, individual beliefs, preferences, health literacy, conditions of daily living, and culturally relevant factors will inform tailoring message content (e.g,. promotion of physical activity "being active" messaging will be paired with questions in the AI chatbot assessing the need for an indoor exercise option when safe and environmentally clean spaces in the neighborhood are not available); b) <u>The innovation</u>: the use of AI chatbot text messaging and its degree of fit with patients' daily living (e.g., AI chatbot text messaging being a more accessible option to patients with limited resources, and focus on how patients interact with the technology -- when do they use the technology, how do they use it); and c) <u>The provider</u>: competing demands from pharmacists, buy-in into the program, bias, and culturally relevant factors (e.g., perceived feasibility of the program, acceptability of their role and managerial support). Attention to these concrete domains will allow us to capture relevant factors within the multilevels of the organization, personal, interpersonal and community contexts (e.g,. ethnic enclases, acculturation, immigration policies) that could impact the successful implementation of the program, and expected outcomes. During the engagement and group process, we will also focus on fostering cultural humility and acknowledgement of power and resource differentials within the team. Our patient core members will provide expertise on how engagement efforts are received and suggestions for inclusiveness and diversity. The core will ensure patients and implementing team (including pharmacist) perspectives, as opposed to researcher-driven perspectives alone, are leading our efforts throughout the study.

During the UG3 year, specific core tasks include: 1) reviewing and informing recruitment and enrollment for

Table 2: UG3 milestones by cores		
Health Equity and Engagement Core	**Administrative Core**	**Data and Statistics Core**
Identify at least 1 patient, provider and health system leader stakeholder from each health system to participate in the stakeholder core	Obtain IRB approval at all sites	Draft data element definitions/specifications in collaboration with Collaboratory investigators and NIH staff
Review text messages and educational content for cultural, and linguistic appropriateness	Establish DUAs with all sites	Draft data management manual
Assess ethical issues of behavioral nudge messages	Collaborate with NIH Collaboratory Regulatory/Ethics core	Test methods for subject identification
Review study protocol for patient and health system acceptability	Obtain DSMB approval	Test data collection procedures
Work with stakeholder core to identify core members ensuring diversity and all relevant perspectives are represented	Establish sub-contracts	Test data transfer procedures
Review and tailor pilot study methods to ensure equitable reach among diverse patient groups	Finalize budget	Test randomization procedures
Develop randomization strata to evaluate intervention effects among patient groups with high rates of health disparities	Develop and test opt-out and consent procedures	Assess statistical power and finalize analytic plan
Review study procedures and protocols so that it aligns with the needs of the patients and health systems	Submit IRB modifications following pilot study	
Implementation and Dissemination Core	**Mobile Health Core**	**Steering Committee**
Adjust and refine implementation evaluation plan with stakeholders, emphasizing context and adaptations	Develop text and AI Chat bot, components	Draft study protocol
Draft cost analysis plan	Translate messages to Spanish	Draft intervention manual
Test implementation and cost analysis procedures in pilot study	Test and refine messages in series of N of 1 trials and nominal groups	Identify study team member to participate in NIH Collaboratory cores
Develop initial version of implementation, adaptation, and sustainment guidebook for learning health systems	Test text and AI chat bot components in pilot study	Oversee pilot study at clinical sites
		Revise study protocol and intervention manual following pilot study

Aim 1, and 2) reviewing text *a priori* and final message content for cultural appropriateness and patient relevance. In addition, they will review the study protocol and study procedures to ensure that the proposed study is acceptable to patients, providers, community advocates and health system leaders. In the UH3 years, we will

regularly engage the core, continuously seeking input and feedback on study progress and/or any issues that may arise. In the latter stages of the study, the core will provide valuable input as we think about sustaining the intervention within each health system.

Group process: We will use engagement practices tested in the field such as offering the option of having smaller groups to acknowledge power differentials (e.g., patient-provider and provider-decision maker), and to increase trust and comfort.[101–103] Preparation and debriefing meetings will also be offered to patients to increase their capacity to engage in group conversations, and to offer a safe space for feedback after the group meetings. Meeting agendas will be developed with input from the group. Overall, stakeholders will meet monthly through on-line and/or in-person meetings during the UG3 year and then quarterly during the UH3 years. The core co-leads will reach out to each group of stakeholders (i.e., implementers, decision makers, participating patients, and champions)[104] to use a hybrid approach to integrate stakeholder input by developing an on-line community across participating health systems, which will be complemented by local in-person groups and as feasible for stakeholders. By using this hybrid online and in-person meeting approach, we are also providing two layers of reliability as it relates to group processes, consensus and outcomes for our project.

The Health Equity and Engagement core will work closely with the Steering Committee and Implementation Science core to monitor reach and representativeness and ensure study methods facilitate equity in participation, delivery and retention among diverse patient groups. Finally, this core will work with the data and statistics core to ensure adequate sample sizes for understanding whether the intervention targets those populations at greatest risk for health disparities and leads to greater health equity. A feedback loop between this and the Implementation Science core will be created by having a monthly lead/co-lead core meeting. Each meeting will be audio-recorded and written notes will be verified with recordings.

Decision-making: We will engage the stakeholder group in decision making by presenting the pros and cons of each proposed action/tailoring option, and provide concrete recommendations for the group to consider. We anticipate the process will involve both solicitation via verbal input in group meetings and quantitative assessments via voting or polling. For each group processes, we will: 1) provide materials in advance so each group member is informed and prepared; 2) set goals for the group discussion, including how the group process will work; 3) collect systematic information to describe group input; (4) prepare summary reports to group members for feedback. Drs. Daugherty and Perez Jolles will monitor and review information provided by stakeholders, and move the project forward to complete each aim. They will stay in close contact through phone calls or emails as needed to provide an additional layer of accountability.

Mobile Health Core Dr. Bull will lead this core. During the UG3 phase of the project, the Mobile Health core will develop, test, and refine the AI chatbot text message components of the intervention in collaboration with the Health Equity and Engagement core. The usability of text and chat components will be assessed in a series of N-of-1 (i.e., within-subject) assessments. A certified translator will work with Dr. Bull prior to and during the N-of-1 and nominal group studies to ensure proper translation of all *a priori* and final messages in Spanish. All Spanish messages will be back-translated by an English/Spanish bilingual staff and discrepancies resolved.

Data and Statistics Core Dr. Plomondon will lead this core to develop definitions and specifications for data elements in collaboration with other Collaboratory investigators and NIH using previously identified common clinical outcome and resource utilization measures when available. The core will work with local EHR programmers at each health system to implement established practices for electronic data extraction and quality control methods for patient identification and outcome assessment. The core will develop procedures for data transfer between study sites and the University of Colorado data coordinating center that are secure and consistent with IRB and data use agreements. This core will develop the study randomization procedure and pilot the process. Dr. Carey, the study statistician in collaboration with the Collaboratory and NIH will confirm the statistical power to detect meaningful difference between study groups using data on sample size, numbers of sites, site-to-site heterogeneity, and outcomes. He will draft an analytic plan with hypotheses and tables/figures to be approved by NIH and protocol review committee.

Administrative Core This core will be led by Dr. Ho. This core will address all ethical issues and issues related to human subject safety oversight for the project, including development of opt-out consent and coordinating IRB review. We will use a centralized IRB approach for trial oversight with the Colorado Multiple Institutional Review Board (COMIRB) to facilitate both appropriate and timely study implementation. The core will also work with the DSMB and NIH Collaboratory Regulatory/Ethics Core to obtain approval of the study protocol. If the pilot study results in revisions to the study protocol, an IRB modification will be submitted. This core will put in place a data sharing plan that is HIPPA compliant and will ensure that all other contractual agreements necessary to conduct the study are completed. Finally, the core will develop a detailed budget.

Study Setting: We will conduct the study in 2 or more primary care clinics in each of 3 health systems (Denver Health Medical Center, Salud and STRIDE), selected because they have been designated as FQHCs serving large patient populations experiencing health disparities and are distributed across Colorado in urban, suburban, rural and frontier counties. Patients experiencing health disparities are disproportionately affected by CV risk factors such as hypertension, and diabetes, and frequently do not have these risk factors under control.

We are targeting these health systems and patients because improvements in CV risk factors can led to better health status and lower the risk of future CV events such as heart attacks and strokes. Furthermore these CV risk factors are important quality of care indicators that these health systems are measured on and compared to other health systems. There is recognition given to health centers achieving high performance on quality indictors through the Community Health Quality Recognition for chronic disease management such as smoking cessation, BMI screening and plan, hypertension control and diabetes control. In addition to assessing each of the individual risk factors in the LS7 as a secondary outcome which are of importance to our health systems for quality assessment, we will evaluate CV health based on the composite LS7 measures as an outcome which is of importance to patients. Therefore, our participating health systems have a significant investment in this project.

Patient, provider, community advocate and health system stakeholders from each health system will provide study input. In addition, we will engage our stakeholders to identify resources available locally to address social determinants of health which we will be able to incorporate into our educational material for patients (e.g., food banks, housing, transportation vouchers, access to goods such as medical supplies, access to information on financial assistance programs, educational programs, jobs training programs and legal assistance). Furthermore, the Colorado Multiple Institutional Review Board (COMIRB) will provide regulatory oversight for the study for all 3 health systems. We have had preliminary discussions with COMIRB and they were supportive of the opt-out study approach. Our current Nudge study is also overseen by COMIRB which has considerable experience with pragmatic health system trials.

Salud Family Health Centers (Salud) is a Federally Qualified Health Center (FQHC), 501©3 nonprofit, operating 13 clinic locations, 11 school sites and a mobile unit. Salud provides medical, dental, pharmacy and behavioral health care services focused on low-income, medically underserved populations as well as the migrant and seasonal farmworker population. Salud serves approximately 85,000 unique patients per year with a third patients having chronic conditions. Demographics include 67% Black, Indigenous, and people of color; 62% Latinx, and 2.6% Black. Salud has multiple clinics serving rural Colorado residents. Salud uses eClinicalWorks EHR which contains vital signs, clinical diagnoses, laboratory and pharmacy data.

STRIDE Community Health Center (STRIDE) is a FQHC with 18 health center locations providing primary medical care, dental care, behavioral health, and wrap around services, including two School Based Health Centers (SBHCs) and a mobile dental van. Its focus is on providing affordable and accessible medical, behavioral health, and dental care among low-income, uninsured, and underserved populations residing outside the City and County of Denver. In 2020, STRIDE provided over 110,000 medical visits to over 47,000 patients. Patients seen at STRIDE have a high burden of CV disease with 64.2% hypertension, 81%, hyperlipidemia, and 29.7% diabetes. Sociodemographics of those served by STRIDE include >95% of patients at >100% of Federal Poverty Level (FPL), 37% Hispanic, 9.2% Black and 3.4 Asian. STRIDE uses EPIC EHR which contains vital signs, clinical diagnoses, laboratory and pharmacy data.

Denver Health Medical Center (DH) Denver Health and Hospital Authority is an integrated health care system that serves as the primary health care safety net for the City and County of Denver, Colorado. DH includes nine FQHCs. DH serves an estimated one in four Denver residents, or approximately 208,000 individuals per year. Almost 60% of the patients seen are members of racial/ethnic minority groups (Hispanic 37%, African American 14%, Asian American 3%, Native American1%, and White 42%). More than 70% of DH patients live below 200% of the federal poverty level. The primary payment sources for DH patients in 2015 were: none 16%, Medicaid 21%, Medicare 4%, Medicaid Managed Care 7% and Private insurance 15%. Among patients followed in the community health centers 14,789 (15%) have hypertension, 5,876 (6%) have hyperlipidemia, and 9,077 (9%) have diabetes. Approximately 40% of patients with these diagnoses are prescribed 1 or more of the medication classes of interest. DH also uses EPIC EHR which contains vital signs, clinical diagnoses, laboratory and pharmacy data.

APPROACH OVERVIEW: Our evidence-based intervention operates at multiple levels with complementary components interacting to produce outcomes at the patient, provider and organizational levels. While the infrastructure for the intervention is fixed, there will be variability in exposure to the intervention and how patients interact with the AI chatbot and providers, across time and each health system. Given this, it is helpful to distinguish *functions* of the intervention from intervention *forms* to ensure intervention and implementation success. The function of the intervention is the core purpose of the change process that the intervention influences. The forms represent the necessary activities for the function to be realized. In Year 1 (UG3 phase), the Health Equity and Engagement, Mobile Health, and Implementation Science cores will come together to update the AI infrastructure and expand the message content to generate the LS7 Bot + Backup intervention. All cores will work in the UG3 phase to ensure our final intervention includes a clear articulation of purpose (i.e., it's function, to influence SM) with clear processes (i.e., forms, realized through AI chatbot and pharmacist support) to achieve that purpose. Co-investigator Jolles has documented how this approach can be useful to articulate how an intervention achieves its' effects even when implemented across heterogeneous systems, contributing to better success with intervention adoption and adaptation by organizations.[105]

We will update the infrastructure for our text messages for the Nudge study, expanding the content beyond medication refill adherence to incorporate LS7 topics and providing structure to facilitate pharmacist support. We will engage the Health Equity and Engagement core to ensure robust participation of patients, providers, community advocates, and health system leaders to provide feedback on the messages, intervention and implementation strategy design, and outcomes. We will also solicit routine feedback from these groups during the study to help address potential barriers to adoption and implementation and help ensure program sustainability. These activities will be guided by PRISM and the Health Equity in Implementation Framework to systematically assess the dynamic interactions of contextual factors (including SDoH and indices of health disparities) that influence success and sustainability of the implementation and its generalizability across populations experiencing inequities. To achieve the contextual assessment with a health equity lens, we will prioritize diverse representation across patients, providers (including pharmacists), community advocates and health systems. During months 0-2 we will obtain IRB approval for the study. Concurrent with these activities, we will establish the IT infrastructure across the 3 health systems and expand our *a priori* message content, activities which will not require human subjects approval. During months 2-4, we will conduct formative work with patients and identify patients potentially eligible for the study within each health system. During months 7-12, we will conduct the pilot intervention reserving months 10-12 for analysis of our pilot intervention results. During this entire year, the Health Equity and Engagement core will engage our patient, provider, community advocates and health systems stakeholders in various aspects of message development and pilot testing.
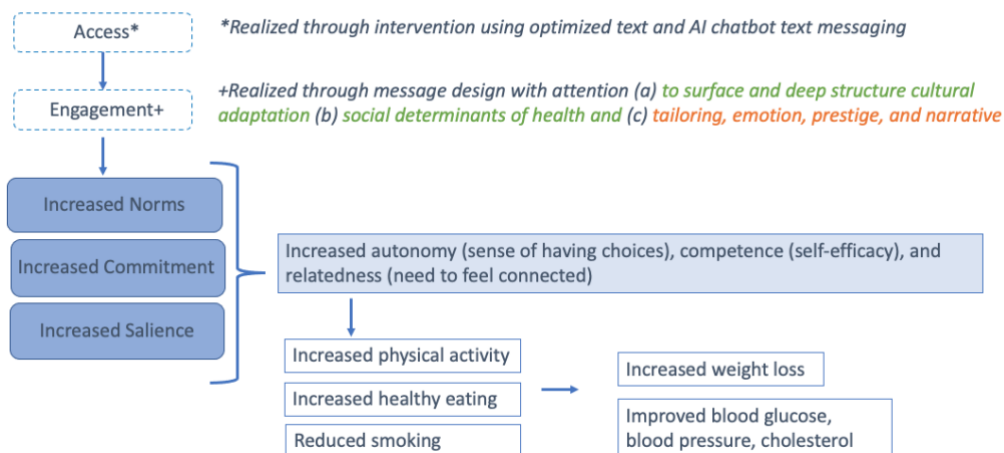
Aim 1 (UG3; Year 1): Iteratively update the infrastructure and expand content for AI text message chatbot with attention to social determinants of health and sociocultural contextual relevant to the target population through stakeholder engaged N-of-1 and focus group interviews and nominal group sessions.

Updating the technology infrastructure and expanding the intervention content : Dr. Sheana Bull will lead the work to update the technological infrastructure and AI text message chatbot and expand the automated communication libraries, including a library of generic text messages and a library of optimized AI chatbot messages. Dr. Bull and colleagues as well as others in the field have demonstrated that systematic and theory-based message content can be superior to generic content for improved program effects.[49,106,107] Outcomes from this work include a theoretical framework, the *Integrated Theory of mHealth*, that further considers the appropriate use of technology so **access** to health promotion content via technology considers technologies that are widely available and offer minimal barriers to use. **Engagement** with health technology requires careful attention to designing content that is persuasive, resonant and compelling. Together, access and engagement are two new constructs that must be integrated into existing theoretical and conceptual frameworks to maximize effects.[98] Figure 5 illustrates our theoretical model for this intervention, showing how Access and Engagement from the Integrated Theory of mHealth, presented at the top of the figure, are integrated with existing communication, social and behavioral science theory.

Access: We are facilitating access to this mHealth intervention by making content available through the AI chatbot text messaging infrastructure. Because text messaging is ubiquitious and nearly universally used by populations across the U.S. regardless of race/ethnicity, income and education.[108] Thus, it is a technologically appropriate strategy to employ to reach large numbers of diverse patients. Additionally, attention to access also requires attention to user literacy and numeracy. Dr. Bull has experience in health promotion content design that can appeal to and be understood by low-literacy/numeracy individuals. For this study, all messages will be kept at or below a 5th grade reading level.[109] Approaches to increased engagement include fostering identity with a group or community, achieved through cultural adaptation, the systematic modification of an evidence-based intervention to consider contexts in a way that it is compatible with the consumer's cultural patterns and values.[110] **Engagement**: We will facilitate message engagement through overt recognition of health equity domains of health in message

Figure 5: Adapted Integrated Theory of mHealth applied to Life Simple 7 content

Access* — *Realized through intervention using optimized text and AI chatbot text messaging

Engagement+ — +Realized through message design with attention (a) to surface and deep structure cultural adaptation (b) social determinants of health and (c) tailoring, emotion, prestige, and narrative

Increased Norms
Increased Commitment
Increased Salience

Increased autonomy (sense of having choices), competence (self-efficacy), and relatedness (need to feel connected)

Increased physical activity
Increased healthy eating
Reduced smoking

Increased weight loss
Improved blood glucose, blood pressure, cholesterol

content. Cultural adaptation also aims to improve the linkage between intervention components to the lived experience of consumers through both *surface structure* and *deep structure* adaptations. Surface structure

adaptations involve changes to an original intervention to address superficial aspects of a target population's culture, including language, music, food, and clothing. Conversely, deep structure cultural adaptation incorporates socio-cultural, environmental, and psychological factors, such as norms, tribal and religious practices[111] with attention to Social Determinants of Health. The Health Equity and Engagement core will be actively involved in work to tailor the messages and educational content to the relevant context and cultural adaptations. Message engagement will also be realized with a focus on designing content using tailoring strategies and persuasive messaging strategies, i.e., the use of emotion, prestige and narrative in message content. Tailoring of the content, frequency and timing of the messages will be approached through the use of a Functions and Forms matrix.[105] That is, we will integrate the input from all stakeholders to identify and align three areas: a) the motivating problem that the intervention is seeking to address; b) the program's standard core functions (i.e., structural and procedural goals and purposes to reach intended outcomes); and c) a menu of flexible actions/steps, tailored to the needs, preferences and priorities for each patient group/health system, to carry out each of the core functions (forms). For example, a core function of 'increase physical activity' could be aligned with a menu of customized options for patients (forms) that include exercising outside, use of an exercise app, and/or joining the local community center in their neighborhood. The product of this group activity will be an excel table that maps the patient/system needs, intervention core functions, and a menu of forms that can be tailored to various groups/health systems. We will track usage of tailored program's forms during the pilot phase.

In Figure 5, the green text refers back to the Health Equity Framework from the PRISM study conceptual model presented above; this framework will focus attention on the critical considerations of equity we posit will contribute to optimized message content. The Access and Engagement boxes are presented in dotted orange lines and engagement content also includes the orange text referring to the evidence-based strategies for design of message content. Once Access and Engagement are considered, the Integrated Theory of mHealth suggests any other evidence-based theoretical perspectives can be _integrated_ to design message content. In this project, we focus on content consistent with constructs from behavioral nudge messaging and the Theory of Self-Determination[112], i.e. development of patient self-management autonomy and competence as well as a sense of relatedness with providers and health systems. We posit that the use of effective nudge messages will build user norms for specific behaviors, invoke commitment to engage in those behaviors, and increase the salience of healthy behaviors. The message design process will result in content delivered through our AI chatbot that is the mechanism for behavior change. The content and delivery through the chatbot will improve the key constructs from the Theory of Self-Determination.[112] This content will be reinforced in study arm 3 that builds on relatedness through follow-up and support from the pharmacist.

Updating AI chatbot text message infrastructure: The first step for Aim 1 will be to develop the technology platform to facilitate error free delivery of messages via text to user cell phones and to program our AI chatbot to use natural language processing (NLP) and maximize the chatbot precision so that users are more often sent a response from our system that matches the intent of their query. The Nudge study chatbot was designed as a fixed choice bot, which does not employ the level of sophistication to engage users and employ NLP to facilitate more conversational engagement. During the COVID-19 pandemic, we built a more technologically current AI NLP chatbot system that operates via short message service (the textbot) to address questions from patients about the COVID-19 vaccine.[113] We will utilize this system and the process implemented to build the COVID-19 chatbot for the work proposed here. Specifically, we will first develop and categorize anticipated "intents"—i.e., the specific topics we believed people want to learn or ask about LS7. To generate a comprehensive list of intents, we will review topics of frequently asked questions about the seven topics in LS7 (blood pressure, lipid, blood glucose or weight management; smoking, healthy eating, and physical activity) from reputable clinical websites. Because we are delivering content that is contextualized to recognize challenges in adoption of LS7 behaviors (managing blood pressure, controlling cholesterol, reducing blood sugar, being active, eating better, losing weight, and stopping smoking) given social determinants of health, we will also build intents that anticipate questions about addressing, managing or overcoming social factors demonstrated as common moderators of healthy behavior for patients[114] receiving care at FQHCs (e.g., having enough food, adequate clothing, money for bills). Once we have an initial set of intents, we will generate multiple variations on questions that users could ask related to that intent so the system could be "trained" to infer the intent of a query based on many possible ways of asking a query. For example, one user may ask "When do I call my doctor if my blood pressure is high?", while another might ask, "what do numbers on my blood pressure mean?", and both queries would be matched to an "understanding blood pressure" intent.

Generating message library intents: To generate an initial library of question variations for each intent, we will rely on the Amazon Mechanical Turk (MTurk), a crowdsourcing platform where one can offer a small incentive for users to complete tasks. We will ask 50 MTurk participants to generate three to five variations of questions with the same intent for each of the LS7 topics and social factor intents, randomly assigning topics and factors until we have 25 variations on queries for each intent. This allows the system to have enough initial data to learn how to interpret user questions, tolerate misspellings, and recognize the underlying intent of each question. Although the crowdsourcing activity allows us to develop a robust set of question variations, there is

still the likelihood that we will not anticipate every possible variation on questions. When the system does not match a response to the question intent, it reverts to the fixed choice (also called a "pick list") set of responses, e.g., "I think you are asking about one of these four topics: (a) healthy eating, (b) cost of healthy food, (c) how to access a food pantry, (d) how much you can eat in a day. Please type the letter corresponding to the topic you wish to explore or try your question again." Our goal is to correctly match the response to the intent of the question at least 85% of the time. As more users engage with the system, we can review logs and re-classify content that resulted in a pick list to match an intent daily, which will increase the precision of the system. Using this same methodology, we were able to achieve 91% precision in matching responses to user intent for the COVID-19 chatbot after the system had engaged with 2,500 persons asking 4,000 questions.[113]

This chatbot will be hosted in a scalable cloud environment using Amazon Web Services. The NLP pipelines for textbot are built using Python 3.8 with NumPy, Pandas, and scikit-Learn, flask, npm, pm2 Python modules. The COVID-19 textbot has been load-tested to ensure adequate performance in response time to messages at different times of the day. The NLP pipeline probabilistically assigns incoming user messages to known question intents. The response to the incoming user message is then retrieved from the library of intents matched to appropriate responses.

Contextual assessment and alignment of the text messages with attention to Social Determinants of Health and other sociocultural issues: We will conduct at least 3 focus groups with multilevel stakeholders (patients, providers/pharmacists, community advocates, health system leaders) using purposive sampling to increase representation from diverse perspectives including those across the spectrum of health disparities. A semi-structured moderator guide will be informed by PRISM and the Health Equity in Implementation Framework and will be reviewed by the Health Equity and Engagement and Implementation Science cores to guide a systematic evaluation of contextual determinants that positively and negatively influence the success of text messages (content, dose, access to community resources). We will also ask these stakeholders to help identify resources available locally to address social determinants of health which we will be able to incorporate into our educational material for patients Our study conceptual model shown in Figure 4 illustrates how these three frameworks will be used in concert to assess and align the context with the intervention. These findings will be used to refine the intervention to be culturally relevant and aligned with the context with an emphasis on health equity and sociotechnical issues.

Ensuring message accessibility for low-literate and sight impaired populations: All messages can be accessed through text-to-speech functionality on phones. We will generate a brief tutorial for patients to access via a link to a video with detailed instructions on how to access phone settings (via iPhone or Android) and enable text-to-speech functionality. If patients are known to have accessibility issues, we will call their phone and ask them to select an option to open the link we send them in a text message or have the instructions read to them. Once text-to-speech in enabled we will send them the initial message and monitor engagements to ensure content is clear and correct. Our experience in delivering automated text messages and a chatbot through the Nudge study suggests a very small proportion (i.e., <1%) of patients will prefer this option.

Conducting N-of-1 interviews: We will purposively sample 10 participants from each health system with a balance of older/younger patients, men/women, those with one versus multiple chronic CV conditions and native Spanish/English speakers. We will ask participants during synchronous sessions to react to content presented during a live demonstration of the message content using an interactive AI chatbot text messaging platform through multiple N-of-1 (i.e. within subject) assessments that conform to evidence-based strategies for persuasive message design. Co-Investigator Glasgow and colleagues as well as federal agencies have advocated for the N-of-1 approach as ideal for rapidly iterating a user informed program with input from a range of stakeholders on all of the different interventions.[115(p),116–118] This approach offers a way for participants to quickly react to the platform (e.g., readability, speed of message delivery, anticipated ease of use), to quickly respond and iterate new versions of messages until consensus across participants can be reached. It also offers an opportunity to expose participants to multiple messages and obtain preliminary data on whether and the extent to which each intervention may be superior to usual care. If people indicate a greater likelihood that specific message content will motivate them to refill their prescription, plan for healthier eating, and/or commit to more physical activity for example, then we will infer that this type of content will be more persuasive than an alternative approach. *A priori* messages presented to N-of-1 participants will represent theoretical constructs intended to (1) increase norms, commitment, and salience, key components of behavioral nudge messages; and (2) facilitate a sense of autonomy, competence and relatedness, key components of the Theory of Self-Determinantion. The messages and system combine to create the mechanism through which patients will develop greater SM autonomy, competence and relatedness. See Table 3 for sample theory-informed messages in English—all

content will be translated into Spanish and reviewed by our Health Equity and Engagement core to ensure relevance of content and that it is appropriate for Spanish speakers. Because messages will include assessments of social factors that can modify behavior, we will explicitly ask participants to comment on how best to assess these topics through the AI chatbot text messages to minimize concerns about confidentiality,

privacy and relevance. We will deploy a content analysis of N-of-1 data (explained in greater detail in the analytic section) and update our *a priori* library of content for initial text messages and AI chatbot messaging to identify the range of popular approaches for communication of the LS7 intervention content.

Conducting nominal group sessions: After completing 30 N-of-1 interviews, we will convene up to three virtual nominal group sessions in each health system to further refine content and develop a final library of messages. The nominal group technique has been used in health promotion and in the design of mobile and digital health interventions[119,120] to facilitate the free exchange of ideas in a structured but non-hierarchical manner.[121] The nominal group is structured like a focused group discussion, where 6-8 participants are invited to react to and offer opinions on a series of topics. In a focused group discussion, the emphasis is on exploring a full range of ideas, including outliers. In contrast, the nominal group is focused on generating consensus. In a nominal group session, there are multiple rounds of engagement, beginning with an initial round explaining a goal (e.g., We want you to help identify the best message among these four to inform people about ideal blood sugar levels; please tell us if you like one or more better and why) and answering clarifying questions. In subsequent rounds participants identify their preference for message content and discuss their preferences with the moderator with a goal to gain consensus across diverse participants. In this round we will pay particular attention to message content that resonates for specific racial/ethnic groups and is relevant for low-income and rural communities; we will also review modifiable social determinants of health to consider if message content appropriately recognizes variable experiences with housing, income, employment, etc. that will influence self-management behaviors. It is beneficial if participants in a nominal group have different demographic characteristics so all can hear and contemplate diverse perspectives in working towards consensus on messages. This effort will also allow us a deeper understanding of how we can use message tailoring to maximum effect by asking patients both during the N-of-1 and Nominal group sessions to react to message tailoring examples. Common elements of tailoring include sending messages that identify a user by their first name or some other characteristic (excluding any protected health information), e.g., "people over 40," or "Salud patients often find."[122] The ability for patients to engage with the AI chatbot is a form of tailoring inasmuch as the user is driving the conversation to address their individual question. The contextual content we will provide to acknowledge social determinants of health is another form of tailoring. Finally, patients who are in arm 3 with access to a pharmacist will have even greater tailoring by engaging support for their specific self-management

Table 3: Sample a priori messaging for chat bot messages specific to Simple 7 screening and lifestyle concepts

Sample Weeks of intervention and focus	Examples of optimized messages	Examples of chatbot exchanges	Specific theoretical constructs present in messages
Reducing blood sugar	Hi Darlene! Monitoring your blood sugar might be tough, but so important for your health! Work to get your blood sugar to lower than 100 mg/dl—share your goal with a loved one! What questions do you have about tracking your blood sugar?	*What questions do you have about tracking your blood sugar?* **Can my blood sugar be too low?** *If your blood sugar levels are below 70, you should either chew 4 glucose tablets, OR drink 4 ounces of fruit juice or soda (regular, not diet!) OR chew 4 pieces of hard candy. Wait 15 minutes and check again. Call your provider if you cannot get your levels above 70 and they can help you.*	"Hi Darlene" is a tailoring feature (Integrated Theory of mHealth) "Monitoring your blood sugar might be tough" invokes emotion (Integrated Theory of mHealth) and increases salience of content (Nudge messaging) Sharing goals promotes relatedness invitation to engage with the chatbot facilitates autonomy; detail on how to address low blood sugar emphasizes competence by building a skill (Theory of Self-Determination)
Being active	Because you are over 40, when you become more active you increase your chances of living longer. And it might make you look good too! Make your plan to increase activity a little bit each day! What would most like help with to be more active?	*What would most like help with to be more active?* **I'm not into running or marathons** *You do not have to take on a major change to get good outcomes from being more active! Start small and build up to moving around 15-20 minutes each day. Is your neighborhood a safe place for you to start with a walk around your block?* **I don't think so. And I am not comfortable going by myself.** *If you aren't comfortable exercising outside, try brief bursts of activity like jogging in place or doing jumping jacks for a minute; repeat 5 times a day to start and you'll make progress fast!*	"Because you are over 40" is a tailoring feature and reference to looking good evokes emotion (Integrated Theory mHealth) Invitation to engage with the chatbot facilitates autonomy and allowance for autonomy in chat exchange by offering options (Theory of Self-Determination) Also addresses social determinants of health with acknowledgment that housing and environment may not support outdoor physical activity (Health Equity)
Eating better	Eating healthy can be tough. Here is a tip that we think might be easy to try—put your fork or spoon down after you take a bite and only pick it up when you have finished that bite. This slows you down and helps you eat healthy portion sizes. What questions do you have about healthy eating?	*What questions do you have about healthy eating?* **It costs a lot of money to eat healthy!** *You're right that eating well can be expensive. Try to focus on eating fruits that are in season. You can also take on a new hobby of growing some veggies at home. I can help you with either of these choices.*	Emphasizes competence by building a skill; invitation to engage with the chatbot facilitates autonomy and allowance for autonomy in chat exchange by offering options (Theory of Self-Determination) Also addresses a possible social determinant of health by acknowledging that eating healthy is costly and offering some feasible options (Health Equity)
Stopping smoking (if applicable)	Did you know there are many famous people who quit smoking? Barak Obama, Jennifer Aniston, and Prince Harry are just a few. You can do it too!	*What is something that keeps you from cutting back or quitting smoking?* **Everyone in my family smokes** *It can be hard for you to quit if people you love and live with are smokers. Some things you can try: making a "no smoking" rule inside the house and car; and/or letting your family know you want to quit and need their help*	Increased norms that non-smoking is desirable Increased salience by making the content about their family; increased commitment when asking for help to quit smoking (Nudge messaging)

issues. While there is evidence that tailoring does increase message relevance[123] and thus engagement,[122] there is not consensus in the scientific literature about how much tailoring is needed, and there is evidence that minimal to moderate tailoring will provide benefits equivalent to deep tailoring that makes content highly specific to every unique patient.[124]

We will convene one nominal group with 6-8 participants in each health system. Each group will be held via synchronous Zoom video conference and last up to 90 minutes. We will review findings to determine if a second group in each setting would be needed to gain a higher degree of consensus on the message content. Aim 1 will yield a library of contextually relevant messages to be deployed for the pilot and pragmatic trial. The library will be designed to be delivered over an 8 week period (consistent with one week for each of the LS7 topics; for people who are non-smokers, we will offer a week on a self-management topic of their choice; in the eighth week, the topic will focus on medication adherence and its importance given that all patients randomized to the study will have already demonstrated poor medication adherence). Each week for 8 weeks patients will be sent four messages that are specific to the topic for that week and with each message, they will be invited to engage with the chatbot to ask more questions about that topic. The first message of the week will be informational about the topic consistent with how the AHA provides information about LS7: 1) to understand readings and levels, 2) to encourage people to track levels, and 3) to offer specific skills building strategies. The fourth message will ask them to report out on short term (i.e., things they can do that week) plans for self-management for that topic and again invite their engagement with the chatbot to reinforce support for their plans.

Our AI chatbot system can facilitate branch logic conditioning by branching to provide responses based on patient specific queries. This infrastructure provides flexibility to facilitate tailoring of content to be responsive to individually specific preferences for information. Dr. Jolles in her role as Co-lead for the Health Equity and Engagement core will work with Dr. Bull to ensure that there is adequate flexibility in branch logic so that messages can be salient for users while not deviating from intervention fidelity.

Supporting health system pharmacists: Concurrent with the focus group, N-of-1 interviews and nominal groups, we will develop a training and capacity building effort to support pharmacists from each health system who will be integral to arm 3 of our pragmatic trial that links users of our AI chatbot text messaging to pharmacists for additional self-management support. Dr. Katy Trinkley will lead this effort and will use an optimized instructional design method to create a brief online training program and a series of resources (e.g. Frequently asked questions; community resources with links and contacts to provide patients; templates for reporting patient concerns in the EHR) for pharmacists. The training program will include access to three 1.5 hour training modules on Motivational Interviewing via telemedicine offered by the University of Colorado School of Nursing Continuing Education program.[125] Motivational Interviewing (MI) is an evidence-based approach for eliciting intrinsic motivation to change using open ended questions, reflective listening and decisional balancing that has been shown in systematic reviews to be superior to more traditional methods of supporting patient health behavior change.[126] We will also include an orientation to LS7 and resources from the American Heart Association that offer specific details on each of the 7 self-management components of LS7,[127] strategies to improve any of them, and articles providing further information. The training will also include explicit skills building in soliciting detail about patient contextual factors that impact self-management, including social determinants of health. Pharmacists will be oriented to resources such as the American Association of Family Practitioners website[128] that offers local resources such as food banks, housing, transportation vouchers, access to good such as medical supplies, access to information on financial assistance programs, educational programs, jobs training programs and legal assistance as well as information of resources from our health systems and stakeholder groups. The training will offer Pharmacists guidelines and templates for engaging with patients and to document and log each engagement. The training program has the following learning objectives: (1) to increase awareness of the LS7 components and content; (2) to develop skills in identifying and addressing specific LS7 self-management issues and social determinants of health that patients are facing; (3) to improve capacity to use motivational interview techniques to address one or more patient issues; (4) to enhance capacity to access and share resources that will support self-managment and address social determinants of health; (5) to standardize documentation of patient engagements into our study database and abstract relevant content from patient engagements into the EHR and (6) to develop a patient support procedures document with a step-by-step protocol for how to engage patients enrolled in their study arm. The training will be designed as a self-paced, fully asynchronous online module and will be housed on the Canvas Learning Management System.[129] We will ask each health system partner to identify the pharmacist(s) they will dedicate to the patient support tasks for arm 3 of our pragmatic trial and will ask them to complete the training during the UG3 year of the award.

Patient recruitment and enrollment: We will use the same patient inclusion criteria for the N-of-1 interviews and nominal group sessions as the pilot and eventual pragmatic trial. We will identify eligible patients using EHR data. There will be minimal exclusions criteria: 1) patients who do not have cellphone; or 2) enrolled in hospice or palliative care; or 3) Non-English or Spanish speaking; or 4) enrolled in another clinical trial if denoted in the EHR. Once patients are identified, we will send them a letter informing them of the study

with an opt out postcard. If they do not return the opt out card within 2 weeks, we will contact the patient to ask them of their interest in participating and obtain consent over the telephone.

Measures and analysis: Our purposive sample for N-of-1 and nominal group investigations in Aim 1 will allow for perspectives from Blacks, Hispanics/Latinos, Spanish-speaking language preference, low-income, and rural. We will create an *a priori* library of various versions for messages in both English and Spanish for each of these arms for review (See Table 3 for sample messages). Message order will be random for each participant. Participants will rate each text or chat bot message for readability, navigability (if using a URL to navigate to a website), engagement and persuasiveness using a star

Table 4: CV risk factors and medication classes for eligibility criteria	
Condition	**Classes of medications**
Hypertension	B-blockers, CCB, ACE-I, ARB, Thiazide diuretics
Hyperlipidemia	Statins, Ezetimibe, PCSK-9 inhibitor
Diabetes	Alpha-glucosidase inhibitors, Biguanides, DPP-4 inhibitors, Sodium glucose transport inhibitor, Meglitinides, Sulfonylureas, Thiazolidinediones, and statins

rating system similar to consumer ratings, where 0-1 stars is the lowest rating and 5 stars is the highest rating. For each message, we will be able to determine the mean ranking for each category across participants and will remove those messages from the library that are less popular following the N-of-1 trials.

For all qualitative data produced across Aim 1 (i.e., N-of-1 and nominal group sessions) we will capture audio recordings of focus groups and interviews and will transcribe these recordings. We will analyze these data using a thematic content

Table 5: AHA Life's Simple 7 CV metric categories			
	Level of health for each metric		
	Poor	**Intermediate**	**Ideal**
Total cholesterol	>240 mg/dl	200-239 mg/dl or treated to goal	<200 mg/dl
Blood pressure	SBP>140 mm Hg or DBP >90 mm Hg	SBP 120-139 or DBP 80-90 mm Hg or treated to goal	<120 mm HG/<80 mm Hg
Fasting plasma glucose	$\geq$126 mg/dl	100-125 mg/dl	<100 mg/dl
BMI	>30 kg/m2	25-29.9 kg/m2	18.5-25 kg/m2
Current smoking	Yes	Former<12 months	Never or quit >12 months
Physical activity	None	1-149 min/week moderate 1-74 min/week vigorous	>150 min/week moderate >75 min/week vigorous
Healthy diet pattern, number of components	0-1	2-3	4-5

analysis facilitated by use of Atlas Ti, enabling the investigators to code, index and retrieve participant responses containing key themes, concepts or events, and group them into larger categories. Coding and analysis of data will be facilitated by the use of a codebook that will be created prior to data collection, containing codes and categories (groups of codes) of themes, concepts, events, people, actions and things that may be encountered in the data (e.g., oral history "vignette" or "soap-opera" styles to convey preferences for structure of messages). These *a priori* codes will be based on what the investigators may expect to find based on the literature and what the investigators hope to find based on the research questions. Coding strategies will be based on the grounded theory techniques of open and axial coding, as described by Strauss and Corbin.[130] Open coding is used to categorize key concepts, categories and patterns of experience. Axial coding is used to specify the relationship of categories to the phenomenon under study. Summary coding will synthesize the relationships across themes to generate actionable responses, such as ensuring all messages are branded with a clinic name, or all communication with the chatbot about a risk event has to happen within one hour.

Deliverables and Milestones at the end of Aim 1: At the end of this aim, we will have developed an AI chatbot message system that is theory-based, contextually relevant with content attentive to equity issues, as well as generic text messages to facilitate LS7 behaviors that have been pilot tested with the intended target audience for the pilot and pragmatic trial. We will also have the curriculum with learning objectives and links to our web-based self-paced asynchronous training program for pharmacists to facilitate effective engagement with patients in arm 3.

Aim 2 (UG3; Year 1): Conduct a randomized pilot to demonstrate feasibility of intervention delivery and outcomes data collection to assess preliminary effects and to refine the intervention prior to widespread implementation

Aim 2 overview: Starting in month 6 of Year one, we will beta-test delivery of the text and chatbot messages in a pilot randomized trial within the 3 health systems. We will assess feasibility of identifying eligible patients, patient recruitment using an opt-out approach, and randomization procedures. We will assess patient and provider acceptability of intervention components, patient retention, and any adverse events including any unintentional inequitable results. Furthermore, we will assess intervention fidelity by assessing number of messages delivered for each of the LS7 topics and our ability to collect data on the LS7 and other outcomes, including missing data. Guided by PRISM, adaptations will be made as needed to improve alignment of the intervention with the context to maximize implementation success, sustainability and equitable outcomes.

Identifying study eligible patients: As part of the initial 6-month activities, we will develop identical study databases within each health system to identify patients using eligibility criteria identical to that for recruitment and enrollment in Aim 1.

Conducting the pilot RCT (months 6-10): Once a patient becomes eligible based on the clinical criteria, we will send patients a letter informing them of the study with an opt out postcard. If they do not return the opt out card within 2 weeks, we will randomize them to 1 of the 3 text messaging arms. We will randomize 30 patients from each health system to each of the three arms. This sample will comprise our pilot RCT participants and they will be censored from participation in the larger pragmatic trial. An advantage of this approach is that the mechanisms will already be in place for the larger pragmatic clinical trial to identify potential eligible patients. Once eligible, patients will be randomized (**Figure 6**). In our Nudge study, we developed processes to identify that a phone number(s) listed in the patient's EHR is a landline versus cellphone. We developed automatic interactive voice response telephone calls that will call the patient and describe the study with an opportunity for patients to enter their cellphone number if available. Based on our current Nudge study which includes DH patients, <5% of phone numbers in the EHR were landlines.

1) Generic text messages: The information content for these messages will be derived from trusted sources of medical information and contain links to websites such as American Heart Association. An example of such a message would be: *Remember to take your blood pressure today! You can find more information from the American Heart Association by clicking here.* Patients will be able to return texts with questions which will be addressed by the study team, including a clinical pharmacist if needed.

2) AI chatbot text messages: This AI system will utilize NLP and ML to facilitate bi-directional system-patient dialogue with messages that incorporate content utilizing tailoring, behavioral nudges and persuasive messaging as described above. An example message would be: *Make a promise to yourself to check your blood pressure today! Your goal is to have the top number at 120 or lower and the bottom number at 80 or lower.* Each message will end with a question for the participant that will encourage engagement with the AI conversational chatbot that allows greater opportunity to use theoretical content to engage patient autonomy, competence and relatedness, the mechanisms through which we will impact behaviors (See Figure 5).
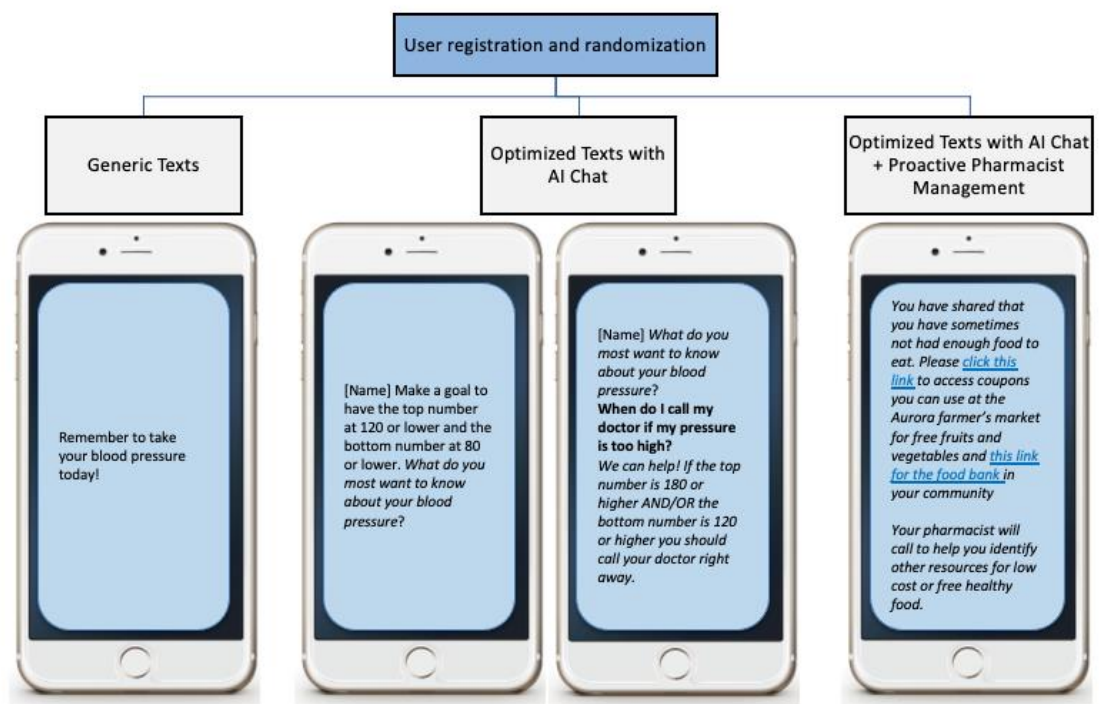
3) AI chatbot text messages plus proactive pharmacist management: The AI chatbot will be the same as arm 2. In arms 1 and 2, pharmacist will respond to clinical questions from patients in a reactive manner. In arm 3, pharmacists will review patient's baseline LS7 risk factors and proactively contact patients via telephone and/or the EHR patient portal to address any risk factor that is in poor/intermediate health categories. We are proposing proactive pharmacist involvement as a population-based approach to address patients with

Figure 6. Interventions to be developed and tested

uncontrolled CV risk factors. Prior studies[131] including meta-analyses and systematic reviews have demonstrated the effectiveness of pharmacist management to reduce CV risk factors (i.e., blood pressure, cholesterol and smoking). The proactive pharmacist involvement is increasingly common but our proposal is to actively link them to our AI chatbot to better facilitate tailored SM support. Pharmacists will proactively manage these patients and will be able to identify their specific SM needs through a review of the AI chatbot logs prior to engagement with patients using telephone or EHR portal.

To enhance external validity, patient-pharmacist interactions will not occur via text messages. Pharmacists trained to engage with patients (as described above) will review the LS7 risk factors for patients at the time of their enrollment; after they have received all 7 weeks of optimized messaging and then once monthly throughout the study follow-up period of one year. Pharmacists will provide additional lifestyle and behavioral counselling complementing the information from the text messages to improve control of LS7 risk factors and assist patients in accessing additional community resources as needed and available (e.g., food assistance,

social worker services, psychotherapy, recreational center) to support behavior change. The proactive pharmacist intervention will be tailored to the needs of individual patients in which a given patient may receive no calls because they are making progress on LS7 risk factors or that is their preference for clinician-patient interactions (Health Equity in Implementation framework), whereas another patient may receive multiple calls to support their behavior change, including more in depth guidance on how to access community resources within their transportation, language or financial constraints (Health Equity in Implementation Framework). For risk factors that require intensification of medications and/or addition of new medications, the pharmacist will do so based on clinical practice guidelines and according to their scope of practice (e.g., collaborative practice agreements). The pharmacist intervention will be pragmatic in that each pharmacist will work within their scope of practice to apply evidence-based approaches (guideline recommendations, behavioral intervention methods) to improve LS7 risk factors. They will rely on the patient support processes document they produced from their training program. After completing their training, but before initial patient enrollment, the pharmacists from each health system will convene together to discuss the goals of the study, share their processes and procedures, share resources (e.g., training resources, protocols, education materials), and identify areas where additional training would be helpful. The findings from this meeting of the study pharmacists will be used to revise and update the written procedures generated through the training program and will facilitate standardizing the pharmacist intervention while balancing the need to allow for individualization that occurs within usual care settings and each health system. Pharmacists will also make aware the patient's primary care provider (PCP) of any changes to the patient's medications and convey this information via the EHR. This provides a mechanism for the PCP to provide additional suggestions.

Once randomized, we will send patients an introductory text message about the study. In the message, we will briefly share LS7 risk factors and elicit baseline information via text messaging on lifestyle factors that are not available in the EHR, including current physical activity, healthy diet as defined by the LS7 categories and smoking status (if not available within the EHR). For those with missing baseline values for blood pressure, weight, total cholesterol or blood glucose, we will recommend that they get the appropriate testing or measurement as recommended in LS7. Finally, we will also assess via a text message survey the 6-item patient self-efficacy for managing chronic conditions. Self-efficacy for Managing Chronic Conditions is defined as an individual's confidence in his/her ability to successfully perform specific tasks or behaviors related to one's health in a variety of situations.

Self-management support information delivered to all three comparator arms: All patients will receive the same information content for self-management support via text messages. We are using the American Heart Association's "Life's Simple 7"[127], i.e., the seven most important predictors of heart health and also a pathway for achieving ideal cardiovascular health as a guide for the message library topics. These seven factors include managing blood pressure, controlling cholesterol, reducing blood sugar, being active, eating better, losing weight, and stopping smoking. Patients who do not use tobacco will be able to select content related to their chronic CV condition instead of tobacco cessation. Patients in arms 2 and 3 will receive the optimized AI chatbot text content designed in Aim 1 as described above. For patients in the generic message arm, we will generate three unidirectional text messages for each risk factor consistent with how the AHA provides information about LS7: 1) to understand readings and levels, 2) to encourage people to track levels, and 3) to offer general tips for success (e.g., Get active, physical activity helps control BP, weight and stress levels). The tips for success include medication and behavioral advice on how to improve risk factor control. The Life's Simple 7 curriculum will be designed for delivery over an eight-week period with each week covering one topic. In the final week, the topic will focus on medication adherence and its importance given that all patients randomized to the study will have already demonstrated delays in refilling their medications. In addition to these educational topics, we will also make available local resources to address social determinants of health such as food banks, housing, and transportation vouchers. We will engage our stakeholders and health systems to identify these local resources so that they are relevant to patients.

Because patients will be enrolled using an opt-out process, we will give everyone the option when they receive a text message the opportunity to opt-out from getting any messages from the system by indicating "STOP." Patients who select this option will receive no more messages although we will continue to collect data from the EHR including blood pressure, pharmacy data, labs (cholesterol and glucose) and clinical outcomes.

Measures and analysis (10-12 months):[49,98,106,132–137] Our primary outcomes for the UG3 pilot study are the completeness of data collection of the LS7 components at baseline, the completeness of response for the self-efficacy survey, and proportion of patients who remain in the study throughout the 8-week LS7 curriculum. Furthermore, among patients randomized to the optimized text messages plus proactive pharmacist management, we will assess the number and frequency of proactive pharmacist phone calls to patients, the clinical action taken by the pharmacist and status of the risk factor at the end of the pilot study. Secondary analyses will focus on a descriptive analysis of message engagement. We will log every message sent from and received by patients in the system along with time of day and day of the week and month. We will review logs and document the total number of messages by study arm and the range and frequency of queries to the AI

Chatbot. We will review whether and how often the "forced choice" option is returned from the AI chatbot to assess overall precision of the system in matching conversational responses to user questions. We will explore associations between message type and increased engagement with the conversational AI chatbot (e.g., messages that ask patients to make a commitment to engage in a behavior are associated with more queries to the chatbot; messages from the Chatbot that focus on building skills (e.g., "try taking a walk around the block every 2 hours today") are associated with having more follow up questions. This will result in a description of system functionality including the most popular and engaging content. In all analyses we will focus on issues of equity (representativeness) on all measures and engagement. Adaptations are expected and needed for real-world, embedded research to maximize impact (effect and equity) and sustainability.[79,138–140] Findings from this pilot will be used to adapt the intervention to improve alignment with the context of the health systems they are being delivered in prior to large-scale deployment in Aim 3.

Engaging stakeholders (patients, providers, community advocates and health system): Stakeholder engagement in research is an important and challenging task. On one hand, we want to avoid tokenism and want stakeholders to be as involved as they would like to be. On the other hand, meaningful engagement can require a substantial time commitment. Our study team has found through several iterations of patient panels that the engaged, high performing advisory panel is the best balance that respects both the panel's competing priorities while also keeping them fully engaged. We will develop a standing stakeholder panel derived in part from members of the Health Equity and Engagement core that will meet monthly during the UG3 year and then quarterly thereafter. Participants: The stakeholder panel will consist of at least 12 people – 3-4 people from each of the 3 settings (1 patient, one health care provider, either a physician or pharmacist, a community advocate or representatives of key community organizations (e.g., Food Banks or YMCA), and one person involved in the leadership or operations of the health system). Members will be recruited through relationships of the investigators at the 3 sites. Dr. Jolles and/or research staff will interview all members to assure that they are appropriate for an advisory role – in particular, they need to be able to understand competing perspectives and not be volunteering simply to push an agenda. Location: The panel will meet virtually given the diverse locations of our sites. For our current Nudge study, we have been convening virtual stakeholder panel meetings successfully over the past 2 years. Each member of the panel will be reimbursed $25 per meeting. Meeting content: During these two-hour meetings, study investigators will present the ongoing text message development to obtain feedback on the content and any adaptations needed to ensure sociocultural and linguistic relevance. The panel will also be asked to explore ethical considerations of using behavioral nudges and discuss strategies to address them to assure that the trial will be ethical from the perspectives of multiple stakeholders. Finally, the team will discuss implementation challenges and brainstorm with the investigators strategies to mitigate these. This partnership between the study team and our stakeholders will help make the intervention components and products more sustainable if effective consistent with recommendations from the NIH Collaboratory.[141]

Deliverables and Milestones at the end of Year 1 (at month 12): At the end of the UG3 phase, we will have completed pilot testing of the content and delivery of the text messages, conducted a feasibility study of the pragmatic trial at 3 health systems, and refined the intervention in preparation for widespread implementation. We will have developed a library of contextually relevant AI chatbot as well as generic text messages, AI chat bot infrastructure to store and deliver messages, a training program hosted on an online learning management system for pharmacists to engage with patients to support their self-management, and data infrastructure to identify patients eligible for the intervention. We will submit the finalized study protocol for approval. With this cokpleted work, we will be well positioned to start the pragmatic clinical trial in Year 2 (UH3 phase of the study).

Aim 3 (UH3; Years 2-5): Conduct a pragmatic patient-level randomized intervention of 3 text messaging delivery strategies for self-management support of CV risk factors. Primary outcome will be change in LS7 health score. Secondary effectiveness outcomes will include individual components of the LS7 lifestyle factors, Framingham risk score, self-efficacy, medication adherence, clinical outcomes (e.g., CV related hospitalizations), healthcare utilization. Implementation outcomes are discussed below and summarized in Table 6.

Following successful completion of the pilot study in Year 1 (UG3 phase), we will conduct the pragmatic patient level randomized controlled clinical trial at the 3 health systems starting in Year 2.

Participants: Within each health system, we will have identified eligible patients using EHR data.

Clinics: We will initially identify 2 clinics within each health system to enroll patients working with health system leaders to identify appropriate clinics. In particular, we will focus on clinics that serve high numbers of Black, Hispanic/Latino, Spanish speaking only, rural and poor patients (i.e., in numbers greater than observed in the general population). We will introduce the study to clinic providers and staff and answer any questions/concerns from the providers and staff. We will provide paper and electronic summaries of the study. In addition, we will offer each provider the opportunity to review lists of their patients who are eligible for the study based on the patient eligibility criteria outlined previously as they may deem that some patients are not good candidates for the study. We have followed similar procedures for our Nudge study. After these introductory

meetings, patients will be sent an introductory study letter signed by the clinic director with an opt-out postcard. The opt-out approach helps ensure that patients will be more representative of those receiving care rather than potentially healthier patients who self-select to enroll. If a patient does not opt-out, we will randomize them and follow them for at least 12 months after randomization. They will remain in the same study arm for the duration of the study and receive the same intervention type. Note the Nudge study utilized this approach and we have consistently observed opt-out rates at or below 15% across our three health system partners. None of the providers in clinics that we approached declined to participate in the study.

Analysis conducted in preparation for the study: We conducted preliminary analysis of the patients enrolled in the Nudge study from DH. Of 5662 enrolled patients, 4994 patients were either Spanish-speaking only, Hispanic, or Black. Of these patients, ~49% (n=2434) of patients would have been eligible for the current proposed intervention based on at least 1 or more CV risk factors (BP, LDL or A1C) in the intermediate/poor category as defined by LS7. Of these patients, 1,547 had an available follow-up LS7 measure at one year and only ~28% (n=438) had subsequent improvement in their risk factor control after 12-months of follow-up. These analyses suggest the following: 1) there are many patients experiencing health disparities with uncontrolled CV risk factors; 2) of those with uncontrolled CV risk factors, the majority do not have improvements in their risk factor control over time; and 3) there are significant opportunities to improve CV risk factor control.

Implementation of the Intervention (Months 13-42): Once a patient is eligible for the intervention, they will be randomized to 1 of 3 arms: 1) generic text messages; 2) optimized AI chatbot text messages leveraging tailoring, behavioral nudges and persuasive content designed to identify and resolve barriers LS7 recommendations. 3) Optimized AI chatbot text messages plus proactive pharmacist management.

Self-management support information delivered to all three comparator arms: All patients will receive the same information content for self-management support via text messages. We will deliver booster sessions of the curriculum at months 5 and 9 during the 12-month intervention period. Booster content for the generic message arm will send out one informational message each day for one full week about each of the LS7 topics. We will review AI chatbot logs for patients and identify those messages that generated the most positive engagement with the chatbot for each patient and each topic. We will create a "most popular" message library with this information and this will serve as the booster content for the optimized AI chatbot text messaging arms. Patients in these arms will also get one message per day with the "most popular" messages, and will again be invited to engage with the AI chatbot to answer any questions they have about that topic.

Aim 4 (UH3; Years 2-5): Evaluate the intervention using PRISM and a mixed methods approach to evaluate pragmatic clinical and implementation outcomes (reach, effectiveness, adoption, implementation, and maintenance) with an emphasis on equity and representativeness, and systematically assess contextual influences to inform sustainment and future tailoring, adaptations, and dissemination.

EVALUATION

We will use PRISM for evaluation with RE-AIM outcome measures and consideration of health equity **(see Figure 3)**. PRISM pragmatically focuses on four categories of contextual factors that influence implementation success: 1) organizational and participant characteristics; 2) organizational (health system and providers) and participants' perspectives (i.e., patients) on the intervention; 3) implementation and sustainability infrastructure (e.g., resources and support processes); and 4) external environment. These four elements will be assessed both qualitatively and quantitatively and will be critical to understanding how to sustain and further disseminate the intervention if demonstrated to be effective. The component RE-AIM (i.e., Reach and Effectiveness, Adoption, Implementation, and Maintenance) outcomes informs the development of pragmatic outcomes important to different stakeholder perspectives (e.g., executive-level decisionmakers, clinicians, patients). PRISM focuses on health equity by emphasizing both representation in terms of the persons involved in planning and evaluation for each outcome dimension, and especially the representativeness (equity) of outcomes across different groups or types of settings. Below we highlight the measures that we will assess a part of the RE-AIM outcomes evaluation.

Reach is defined as the proportion and representativeness or equity of the target population that participates in the intervention. To evaluate representativeness, we will compare intervention eligible patients with patients who do not opt out and participate in the study as we have done in the current Nudge study.[142] Next, we will also compare the representativeness of patients who do not opt out of the intervention to all patients who receive care in the same clinic.

Effectiveness: The primary outcome will be change in LS7 score. Secondary outcomes will include individual components of the LS7 lifestyle factors, patient activation, medication adherence Framingham CV disease risk score, and clinical outcomes (e.g., CV related hospitalizations). As described in the analysis plan, subgroup analyses will address equity issues.

Improvement in LS7 risk factor (Primary outcome): The objective of this study is to determine the impact of the different text message delivery strategies on self-management support and subsequent change in the LS7 risk factors. We hypothesize that the LS7 text message curriculum will improve patient self-management of the LS7 risk factors and there will be a significant change in the

Table 7. RE-AIM measures

RE-AIM Domain	Domain Description[102]	Measure	Data Source
Reach	Degree to which target population is engaged.	1. Number of patients with health disparities, have poor/intermediate LS7 health measures, and have poor medication adherence (eligible patients). 2. % patients who participate and opt out. 3. Representativeness of participants to the clinic patient population	Study database derived from EHR clinical and pharmacy data
Effectiveness	Success of the intervention to change outcomes equitably.	1. Change in LS7 risk factor (primary outcome) 2. Change in patient self-efficacy, medication adherence and Framingham CV risk score 3. Representativeness of change across different patient subgroups	Study database based on EHR data and patient report
Adoption	Degree to which interventions are taken up by organizations.	1. Clinics approached and clinic and provider willingness to participate in the intervention 2. Representativeness of settings participating	Study database
Implementation	Degree to which interventions are implemented as intended; adaptations made and delivery costs	1. Among patients randomized, how many texts were delivered per patient 2. Average number of weeks of LS7 curriculum completed by patients 3. Number of text messages received per patient regarding delays to filling medications 4. Representativeness of patients on items 1-3 above 5. Number, type, and description of adaptations using the modified FRAME method 6. Cost of the program and replication costs 7. Qualitative interviews to identify barriers and facilitators to implementation focused on: 1) organizational and participants characteristics; 2) intervention characteristics from the organizational (health care system and providers) and participants' perspectives (i.e., patients); 3) implementation and sustainability infrastructure (training and support); and 4) external environment.	Qualitative interviews and study database
Maintenance	Setting level: Extent to which the program be sustained over time? Patient-level: level and representativeness of improvements in LS7 risk	1. Identifying barriers and facilitators to maintenance at the end of the study. 2. Intent to continue (or adapt) intervention following grant support or scale up to other patient populations with different conditions 3. Representativeness across the above dimensions at both individual and setting levels	Post-implementation qualitative interviews and Study database

LS7 composite score between baseline and 12-months following study enrollment. The LS7 score assesses how well patients' CV risk factors are controlled with a score that quickly and effectively measures overall CV health ranging from 0-14, where 0-4 is considered "inadequate" 5-9 "average" and 10-14 "optimum" CV health.[29] We also hypothesize that the optimized AI chatbot text messages with proactive pharmacist management arm will show the greatest improvement in the LS7 risk factors compared to the optimized AI chatbot text messages alone and generic text messages. The primary outcome will be improvement in initial qualifying LS7 components (those categorized as intermediate or poor at baseline and observable in the EHR, including blood pressure, total cholesterol, blood sugar and weight) between baseline and 12-months. We will obtain these measures from the EHR and take the measurement closest to baseline of those between 3-month prior to enrollment date and 1-month post enrollment date. Study inclusion criteria requires identification of at least one LS7 EHR component as poor or intermediate, thus all patients will have at least one qualifying LS7 component obtained from the EHR. We will encourage patients to talk to their physician about obtaining a measure (i.e., blood draw or BP measurement) close to 12 months consistent with LS7 recommendations. For the 12-month measurement, we will take the value closest to the 12-month post enrollment date with a 3-month window prior to and after the 12-month enrollment date. As a sensitivity analysis, we will also identify the lowest score within this window and the highest score then repeat the analysis.

Individual LS7 components (Secondary Outcome): Secondary outcomes will include change in the individual risk factors of the LS7, including change in blood pressure, total cholesterol, blood sugar, weight, physical activity, health diet pattern and smoking between baseline and 12-months following enrollment. For patients without a baseline measure for an LS7 component derived from the EHR, we will encourage patients to talk to their physician about obtaining a measure (i.e., blood draw or BP measurement) consistent with LS7 recommendations. For the 12-month measurement, we will take the value closest to the 12-month post enrollment date with a 3-month window prior to and after the 12-month enrollment date. Since physical activity, health diet pattern and smoking are not observable in the EHR, we will ask patients via text to self-report their status at baseline and 12-months following enrollment. We will use evidence-based practices[143] for text message survey completion, including pre-survey reminder notification and 2 follow-up reminders. We will review the patient response data weekly to ensure data validity. We will call patients if they do not complete the surveys and for any data discrepancies.

Self-Efficacy for Managing Chronic Diseases (Secondary Outcome): The Self-Efficacy for Managing Chronic Disease Scale is a valid and reliable instrument available in English and Spanish. The English version is made up of 6-items on a visual analog scale, ranging from 1 (not at all confident) to 10 (totally confident). The psychometric properties of the scale include Cronbach's alpha of .88 across all studies, minimal floor and ceiling effects, sensitive to change, and moderate and significant correlations provide convergent validity evidence when measured against selected health indicators. Baseline higher self-efficacy was associated with lower health

distress, illness intrusiveness, activity limitation, depression and fatigue; improvements over 4 to 6-months in self-efficacy scores was associated with lower levels of the same health indicators.

Medication adherence (Secondary Outcome): We hypothesize that the self-support management intervention will improve medication adherence by reducing the number of gap days between medication refills given that patients will be provided educational messages about the importance of medication adherence to help treat uncontrolled CV risk factors. We will measure medication adherence by identifying the number of gaps (frequency) and the length of each gap (severity) for every patient and medication. The gap days will be determined using pharmacy refill data based on the date of refill, the number of days supplied, and the subsequent refill date during the 12-month intervention period. Worse medication adherence will be identified as an increase in either the frequency of gaps or the length (severity) of the gaps. We are currently using this same methodology in the Nudge study.

Framingham CV disease risk score (Secondary Outcome): We will use the Coronary Heart Disease (2-year risk) – First Event or the Recurrent Coronary Heart Disease, for those with established coronary heart disease or ischemic stroke risk calculator. Both risk scores use similar risk factors to calculate risk including systolic blood pressure, Cigarette smoking status, Fasting lipid level (totals and HDL Cholesterol), diagnosis of diabetes, and use of antihypertensive medication. We will have already obtained these measures as part of our assessment of the LS7. We hypothesize that the self-management support intervention will lower the calculated Framingham risk score between baseline and 12-months of follow-up.

Clinic events (Secondary Outcome): We will also assess for clinical events defined by emergency department (ED) visits or hospitalizations. Our hypothesis is that improved LS7 risk factor control will lead to decreased ED visits and/or hospitalizations. We will assess specific clinical events in which we would expect that improved LS7 risk factors would have an impact upon and conversely where poor adherence can lead to clinical deterioration necessitating

Table 7: Clinical outcomes and utilization by each CV risk factor			
Condition	**Classes of medications**	**Clinical events (ED visits and/or Hospitalizations) for the following**	**Healthcare utilization (clinic visits) for the following**
Hypertension	B-blockers, CCB, ACE-I, ARB, Thiazide diuretics	Hypertension urgency/emergency Heart failure Hypotension Myocardial infarction (MI) Stroke, Renal failure	Hypertension
Hyperlipidemia	Statins, Ezetimibe, PCSK-9 inhibitor	Rhabdomyolysis, liver failure	Hyperlipidemia
Diabetes	Alpha-glucosidase inhibitors, Biguanides, DPP-4 inhibitors, Sodium glucose transport inhibitor, Meglitinides, Sulfonylureas, Thiazolidinediones, and statins	Hyperglycemia Diabetic ketoacidosis	Diabetes

additional care. For example, poor adherence to antihypertensive medications can lead to uncontrolled blood pressure leading to hospitalization for heart failure or stroke. We will assess clinical events via the EHR within each health system.

Healthcare utilization (Secondary Outcome): In addition to the clinical events and adverse clinical events (discussed above), we will also measure healthcare utilization defined by routine clinical visits and/or other procedures associated with the clinical condition. We hypothesize that patients with more uncontrolled CV risk factors may be more likely to have clinic visits due to uncontrolled clinical conditions. For example, a patient with hypertension may not take their medications and therefore have uncontrolled blood pressure. They may have more clinic visits and have their medication uptitrated for better blood pressure control. It is also possible that non-adherent patients may be less likely to follow-up with clinic visits and they will have less healthcare utilization. Accordingly, it will be important to measure healthcare utilization to assess the impact of improved LS7 risk factor control as part of the study.

Health system costs. Using the same approach successfully employed in our prior studies, medical care costs will be estimated using a resource-based method previously developed to assign costs to encounter data.[76,77] Inpatient utilization will be measured using diagnostic-related groups (DRGs), outpatient utilization using relative value units (RVUs), and pharmacy utilization using average wholesale prices (AWPs). Inpatient costs will be estimated by applying national payment weights to DRGs, outpatient costs by applying a national conversion factor to RVUs, and pharmacy costs at 69% of the AWP during a reference year. Cost data will be analyzed using generalized gamma regression accounting for study arm and health system. This approach is very general and subsumes other common models for cost including gamma, weibull, and lognormal, thus providing protection against biases noted in these methods.[144]

Adoption: Adoption will be defined by the absolute number, proportion, and representativeness of a) settings and b) intervention agents who are willing to initiate the intervention. We will keep track of the number

of clinics that we approach and agree to participate in the study and their characteristics including PRISM factors. In preparation for the study, we have discussed the study with clinical leadership at each heath system and they have expressed support for the study (see letters of support). We do not anticipate issues with clinics participating in the study. Effectively, adoption is expected to be close to 100% at the site level since we will be implementing the intervention at 6 clinics across the 3 health systems. We will work with our provider and healthcare system leader stakeholders and continuously engage them during the study. Intervention agents will include primary care providers and especially pharmacists in participating settings. We anticipate close to 100% participation and will carefully track this as well as pharmacist participation and will analyze representativeness if participation is 90% or less.

Implementation: We will assess implementation by documenting a) fidelity-the percent of process objectives achieved; b) adaptations made by pharmacists and settings; and c) costs which are primarily staff time commitments associated with intervention implementation. In addition, we will conduct qualitative interviews with health system leaders, clinicians and patients focused on the four PRISM components that influence implementation success: 1) organizational and participants characteristics; 2) perspectives on the intervention from both the organization (health care system and providers) and participants' (i.e., patients) ; 3) implementation and sustainability infrastructure; and 4) external environment.

Fidelity and adaptations of intervention delivery: We will assess fidelity of intervention delivery across intervention components, patient subgroups, and time. Among randomized patients, we will assess the proportion of patients who receive all intervention components: number of weeks of the 8-week curriculum, number of weeks of the 8-week refresher curriculum starting at month 5, and number of weeks of the 8-week refresher curriculum starting at month 9. We will also assess for a dose-response relationship, i.e. if effects were different among those receiving more weeks of the curriculum compared to those receiving fewer and compared to those who issued a "STOP" message request. We will assess how well the AI chatbot text messages address the intent of the user's question and generate a precision estimate of the overall percent of messages that are correctly classified (i.e., provide the correct answer to patients without sending a "pick-list" such that indicates "I didn't understand your question. You can ask me about what healthy eating is, cost of healthy foods, where to buy healthy foods, or about healthy recipes or you can try asking your question in a different way." We will also assess the frequency with which the AI chatbot text messages are able to address patient identified issues outlined without having to refer to a pharmacist. We will also evaluate patient performance (e.g., proportion in which patient refills medications following reminder message).

Adaptations to the intervention or how the intervention is delivered are anticipated in real-world implementations. We will proactively monitor for and document adaptations. Documentation will be based on the FRAME and FRAME-IS classification system as modified by our research team for use with RE-AIM outcomes and includes a description of the contextual factors that led to the change, the type of change (e.g., change to education, change to text messaging language), when the change occurred (e.g., Aim 2 pilot) and why the change was made (e.g. to enhance which RE-AIM outcome).[79,138–140] All adaptations will be discussed by those involved at the health system (clinic, patients) and the research team prior to documentation. To address whether an adaptation was fidelity consistent, adaptation fidelity will be assessed using the form versus function method described by Dr. Perez-Jolles in which the function or core purpose of the intervention is preserved to maintain fidelity but the form or strategies that are used to customize the intervention to the local context can change to optimize the delivery of the intended function.[105] This evaluation of adaptations will inform the adoption, implementation, sustainment and dissemination guidebook described below. At the end of the study, we will assess the impact of moderator variables (e.g., health system, clinic, patient race/ethnicity and primary language) on implementation and outcomes.

Implementation Costs: The resources to both develop and implement the intervention will be collected.[145] Intervention resource categories to be examined include 1) labor involved in setting up the study infrastructure; 2) IT infrastructure (e.g., text messaging program development; 3) IT content delivery and maintenance (e.g., text messaging service); and 4) training and implementation time of pharmacists. We will separate development and implementation activities and costs so that healthcare systems interested in implementing such a self-management intervention program will have a better understanding of the start-up and ongoing investment needed. We will use existing instruments developed in prior studies (e.g., process maps and interview guides) and procedures to prospectively capture resource use associated with the intervention including what was done, who did it, how long it took, and what nonhuman resources were required. Increased utilization associated with the intervention (e.g., additional phone visits, prescription drugs) will be captured in the EHR. Intervention costs will be the long-term average cost of implementing the intervention excluding research and development costs.

Assessment of patient perspectives: In Year 5, after the intervention and follow-up period has ended, we will survey all patients via text messaging using a previously developed text messaging survey[146] (**Figure**

7). In a random sample of 80 patients who respond to the survey, we will also contact them via telephone to get more in-depth feedback through qualitative interviews on the intervention. The sample will be stratified evenly across patients in the 3 intervention arms and prioritize representativeness of diverse patients. We have conducted similar interviews with patients following adherence interventions. These interviews will evaluate issues such as ease of use and acceptability and help inform future adaptation of the interventions[147] as we plan for broader dissemination of the intervention (if demonstrated to be effective) to more clinics and patients with other chronic conditions.

Follow-up assessment of clinician and health system organization/setting perspectives: We will conduct key-informant interviews with up to 2-3 providers (6-9 across the 3 health systems) from each setting whose patients have received the intervention to get their feedback about the intervention and the intervention effects on their patient's self-management behaviors related to CV risk factors. For some providers, they may have received a note from the study pharmacist informing them of changes in clinical status with their patients and we will also interview the providers on their perceptions of that process.

Maintenance: We will also conduct key-informant interviews with health systems leaders (3-6 interviewees) in each setting who are responsible for institutional policies related to patient data-management, informatics and pharmacy. In these interactions, we will share findings from the research including costs and outcomes; and gauge their reaction to the findings. With any indication of positive outcomes, we will ask participants to describe their likelihood to maintain or modify the intervention within their setting, and to discuss any barriers and facilitators to maintenance. In collaboration with our standing stakeholder panel, we will review the study findings and evaluate what adaptations are needed for ongoing sustainability of the intervention beyond the study funding and for future dissemination of the intervention to additional populations and settings. To systematically evaluate contextually appropriate adaptations that are needed for equitable sustainment, the panel discussion will be guided by PRISM with the Health Equity in Implementation Framework. These findings will inform our guidebook for sustainment and dissemination which is described in the subsequent section.

Figure 7. Patient satisfaction survey

Satisfaction—'How satisfied have you been with the text messages?'

Usefulness—'How useful the text messages?

Easiness—'How easy were the text messages to use?'

Harm—'Was there any harm you experienced from the text messages and if so how much?

Future use—'How likely would you be to use this kind of text message system in the future?'

Responses to questions will be scaled from 1 to 5 where 1='not at all' or 'none' and 5='completely' or 'a lot'. with a 'do not know/uncertain' option.

Qualitative interview methods: We will develop detailed interview guides that we have used in prior studies and will pilot with a sample of potential interviewees. Then we will conduct in-depth qualitative interviews with stakeholders (e.g., patients, providers, community advocates, health system leaders) to evaluate the implementation of the intervention. In these interviews, we will focus on identifying potential moderators of the effectiveness of implementation efforts. This allows us to understand the context in which the intervention occurs and to capture factors that shape the implementation using PRISM. It will also provide insights into additional strategies that may facilitate or hinder the implementation effort at additional sites within each health system or more broadly at sites within the NIH Collaboratory. We have conducted these interviews for our prior research and evaluation projects.

We will initially interview 6-9 providers and 3-6 health system leaders (patient sample is described above) and will plan to conduct more interviews if additional data are needed by using a snowball sampling technique asking subjects to suggest people who can inform the evaluation until we reach saturation. Team members will reconcile interviews within one week of conducting them to ensure rapid analysis. We will utilize a Rapid Analysis[148] technique for qualitative data analysis. Pairs of evaluation team members will conduct interviews, and will review and clarify interview notes immediately following the interview. This approach allows for quick assessment of the content and gives a sense of variation or gaps in information.

Development of adoption, implementation, sustainment and disseminiation guidebook for learning health systems: The goal of this pragmatic study is to positively impact patient care in real-world settings during and beyond the funding period. Therefore, if our study is successful, we will develop a web-based implementation guide based on our results and lessons learned to support continuation of the embedded intervention and adaptation in other health systems settings. A web-based format will facilitate continual refinement and updates over time.The guide will compile the methods and evidence-based findings from all research related to this project. A central aspect will be resources and interactive tools that can be used by the study to guide adaptations that are needed as the context changes overtime to maintain equitable impact of the intervention while maintaining adherence to the core intervention functions. This guide will build on Dr. Glasgow and his team's experience building interactive, user-friendly tools[149] as well as current work to guide iterative evaluation of an intervention's alignment with the context and promote consideration of the

representiveness/equity of outcomes. This web-based guide will be freely and publicly available so that other health systems can use it to adapt the intervention to their unique, real-world context. Other health systems can review the material to assess the feasibility of implementing the intervention at their site and use the user-friendly tools to adapt the intervention for their local context.

Informed by our implementation evaluation, the guide will describe the core functions or purpose of the intervention and provide direction on how to make adaptations to the form of the intervention in a way that preserves fidelity and allows for sustainability.[105,150] This will also include examples of common strategies that can be used to adapt the intervention to the context and direction on how to monitor the impact of the adaptations on key pragmatic outcomes. The guide will be iteratively informed with input from our stsakeholder panel, with specific attention to the ease of its use by diverse users, including those without implementation science or research backgrounds. We will also invite the NIH Collaboratory to review and provide feedback on an early draft of the guide. Sharing the guidebook with the NIH Collaboratory also aims to promote dissemination.

Statistical analysis and sample size: This study will be designed, analyzed and reported following the CONSORT 2010 guidelines (http://www.consort-statement.org/consort-2010).

Setting: Three health systems (DH, Salud, STRIDE) will be considered strata in the design and analysis.

Subjects: Eligible patients will be identified using EHR data. We will apply the following clinical criteria including patients with 1 or more of the CV risk factors of interest, at least one of these CV risk factors is in the poor or intermediate health category from the LS7 (i.e., total cholesterol, blood pressure and fasting plasma glucose) (Table 3) and have demonstrated medication non-adherence defined by a delay of 7 days or greater within the past 6 months in refilling one or more of their prescribed CV medication (**Table 2**). Patient exclusion criteria are minimal and include: 1) patients who have neither a landline or cellphone; or 2) enrolled in hospice or palliative care; or 3) Non-English or Spanish speaking; or 4) enrolled in another clinical trial denoted in EHR.

Randomization: Each patient will be randomized to one of the three study arms. Randomization will be stratified within each health system, using blocks of 3 patients to ensure balance in the study arms over time. Thus, within each system, each set of 3 consecutively enrolled subjects will be randomized to one of the three study arms. Study intervention will be initiated immediately upon randomization with delivery of text messages focused on self-management support for the LS7 CV risk factors. It is not possible to blind subjects to treatments, but data will be compiled so that analysts and statisticians will be blinded to treatment allocation.

Outcomes: Study subjects will be followed for at least 12 months following randomization for the primary outcome (LS7 EHR components measured poor/intermediate at baseline) and for secondary outcomes that includes individual LS7 components, medication adherence measured by gaps, patient self-efficacy, change in Framingham CV risk scores, clinical events (e.g., ER visits and hospitalization), healthcare utilization, and costs. Subjects who have more than one year of follow-up (up to 3 years depending on when they are enrolled during Years 2-3) will continue to be followed for secondary analyses to assess longer-term outcomes.

Primary analyses: This analysis will be completed consistent with the CONSORT guidelines (http://www.consort-statement.org/) based on the intent to treat principle using all patients randomized. Descriptive analyses will be used to describe the cohort and to check for balance across study arms within strata. The primary outcome LS7 will be calculated during the one-year period following randomization using the EHR. Secondary outcomes will be calculated from the EHR or obtained prospectively from patients by text-message based surveys. We anticipate there will be missing survey and EHR clinical data, which is addressed through our proposed analytic approaches detailed below.

Descriptive analysis. We will use means and standard deviations for continuous variables or counts and proportions for categorical variables. We will describe the following groups of patients, those: eligible, sent an introductory letter, opt out, enrolled at baseline, and complete follow-up. We will describe baseline characteristics of these patient populations. We will use standardized mean differences to assess the balance of patient characteristics across comparison variables, including patients who opt out versus those who enroll, and study arms among those enrolled. If any imbalance is detected among enrolled patients, we will adjust for those characteristics in the multivariate modeling approaches detailed below.

Modeling LS7. We will observe baseline and follow-up values for at least one LS7 measure for all patients enrolled and analyzed, and up to seven LS7 measures. LS7 measures measured poor or intermediate at baseline will be included. For each subject and LS7 measure we will assign a 1 if the patient improved from baseline to follow-up and a 0 if they did not. Individual observations will be assigned a weight of 1/k, where k is the number of LS7 measurements per subject, thus all subjects will have an equal weight whether we observe 1 or 7 measurements per subject. General linear mixed models (binomial family and logistic link) with random and fixed effects including weights will then be used to identify the probability of LS7 improvement from baseline to one year. Fixed effects will include treatment arm and patient characteristics at baseline that remain imbalanced post randomization. Random effects will include intercepts for patient and health system.

Modeling Medication Adherence. Medication adherence will be modeled by estimating the frequency and severity (length) of medication gaps. Subjects have the opportunity to gap when the days supply is

exhausted from a medication fill. The expected date medication is exhausted is defined as the days supply plus the medication fill date, adjusted for observed inpatient stays where patients would not exhaust their home medication supply. If subjects receive a medication fill on or prior to that date, they do not have a gap event. If they receive a medication fill after that date, the gap is defined as the length of time between that date and the receipt of a new medication fill. Patients prescribed a medication class will be at-risk of non-coverage for that medication class until: study dropout, death, or medication discontinuation/cancellation pharmacy order. If a gap does not occur a subject is assigned a 0 for that gap opportunity. If a gap does occur, a subject is assigned a 1 and the length of the gap is calculated. A two-stage modeling process will be used to first model the probability of a gap occurring, and then second model the expected length of gaps once they occur. Individual observations (medication and subject level) will be assigned a weight of $1/j$, where j is the number of medications per subject, thus all subjects will have an equal weight. Weighted general linear mixed models with random and fixed effects will be used for both stages. Fixed effects will include treatment arm and patient characteristics at baseline that remain imbalanced post randomization. Random effects will include intercepts for patient and health system.

Treatment Comparisons. We will identify differences between treatment arms using a linear scale for LS7 and medication adherence (additive effects). The parameters in the modeling approach for LS7 are estimated on the logit scale and typically transformed to an odds ratio. To identify linear differences, we will implement standardization using counterfactual methods for LS7, and medication adherence models. This method estimates the expected value of the outcome based on the modeling approaches described above assuming all study participants are exposed to arm 1, then again assuming exposed to arm 2, etc. These estimated outcomes are the basis of the treatment comparison. Uncertainty in these estimates will be quantified through bootstrapping. Covariates will be included in modeling approaches above if/when covariate imbalance is noted, but no other statistical variable selection will be performed. As there is no usual care arm, the primary hypothesis tests will be pairwise comparisons of all 3 treatment groups (3 separate tests), adjusting for multiple comparisons (0.05/3). Data will be analyzed using SAS (SAS Institute Inc., Cary, NC) and R[151] software.

Missing data: Patients with missing covariate data will be retained in the study and their missing covariate values imputed using multiple chained equation methods.[152] Patients randomized who later opt-out or drop out, their outcome data will be collected up to the point that they opt-out and will be analyzed along with completers in the primary intent to treat analysis. When outcome data cannot be obtained, every effort will be made to document reasons for these missing observations, and analyses will be carried out as recommended by Little, et al.[153] In particular we will base primary analyses on all observed outcome data and will use estimating equation methods weighted by the inverse probability of the outcome being observed. We will carry out the recommended sensitivity analyses based on pattern mixture models, by assuming various values for difference in means between observed and unobserved data and assessing differences in model conclusions.

Secondary and subgroup analyses. The secondary outcomes will be analyzed using similar approaches described above with appropriate models, such as Cox proportional hazards models for time to rehospitalization or repeated measures linear mixed effects models for longitudinal continuous surveys, with adjustment for multiple comparisons. Subgroup analyses will be performed to identify heterogeneity of treatment effect among the following patient groups of interest: Black, Hispanic/Latino, rural residents, patients with limited English proficiency, and patients with low-income.

Power and sample size: Required sample size was estimated for the primary outcome of improvement in baseline LS7 measures during the 12 months following randomization. Preliminary data on LS7 measures from 5,330 patients in Denver Health from Nudge study[142] indicated between 13-30% of patients showed improvement in LS7 measures over 12 months, depending on the measure. We therefore made the following assumptions: a) Significance using two-sided level 0.05 tests, b) Power at least 80%; c) Bonferroni adjustment for 3 pairwise comparisons among the 3 study arms, resulting in adjusted level 0.05/3; (d) The baseline probability of LS7 improvement in generic text group is 0.20 d) a moderate effect size corresponds to an increased probability of LS7 improvement of 0.05 in the AI chatbot group and 0.10 in the Ai chatbot plus proactive pharmacist group when

Figure 8.

compared to the generic text; e) a conservative effect size corresponds to an increased probability of LS7 improvement of 0.03 in the AI chatbot group and 0.03 in the AI chatbot plus proactive pharmacist when compared
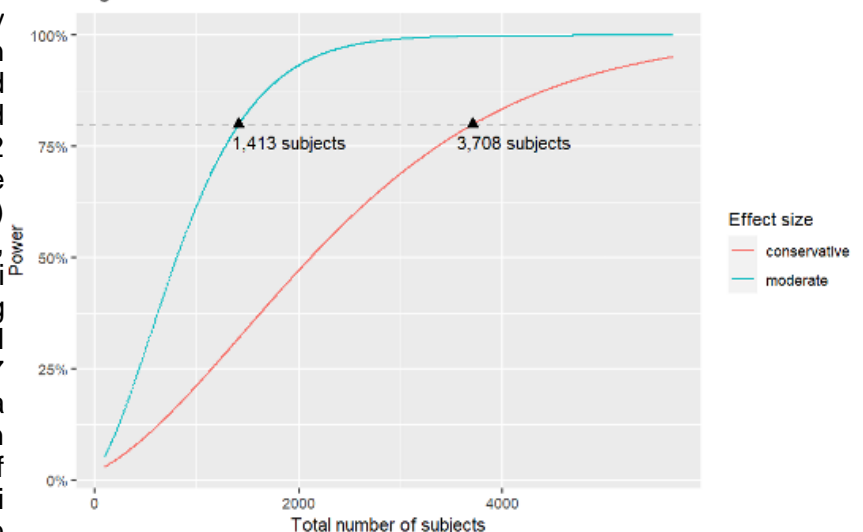
to the generic text. Using these assumptions, a conservative effect size, and a chi-square test assuming only one LS7 measure is available per patient, we estimate using sample size functions in R that we will need N=1,236 subjects per treatment group, total across the three health care systems, for a total of 3,708 subjects available for analysis. Assuming 20% dropout or loss to follow-up and a conservative effect size, we will need to randomize at least 4,634 subjects total for the three health care systems.

Available sample sizes: Based on very conservative estimates from each of our 3 health systems, we will have plenty of patients to meet our target sample size of 6000 patients for the study. At each of our health systems, we estimate that ~40% of the patients with hypertension, hyperlipidemia or diabetes will not have these risk factors under ideal control as defined by LS7 and among eligible patients, ~15% will opt out of the study based on our current Nudge study experience. We estimate that the prevalence of hypertension, hyperlipdiemia and diabetes will be ~7.5% of the 200,000 DH patients, ~30% of the 47,000 STRIDE patients, and ~15% of the Salud patients. Based on these conservative estimates of CV disease prevalence, percent of patients without ideal risk factor control, and percent of patients opting out, we estimate that there will be 5100, 4790, and 4335 eligible patients at DH, STRIDE and Salud, respectively or 14,225 patients in total.

Data Management: We will set up a distributed network across the 3 health systems and each health system will manage their own data in intervention delivery. We will set up parallel processes so that each site can monitor patients for eligibility. We envision that this will be the process for other health systems that want to adopt the intervention if the intervention is demonstrated to be effective.

Database Development: In Year one, the Data and Statistics core will identify all patients in each health system who are eligible for the study based on the following: 1 or more diagnosis of hypertension, hyperlipidemia or diabetes, at least one of the CV risk factors is in the poor or intermediate health levels defined by LS7, and poor medication adherence defined by a delay of 7 days or more in refilling the medication within the last 6 months. Patients will be excluded if: 1) patients do not have a cellphone; or 2) enrolled in hospice or palliative care; or 3) Non-English or Spanish speaking; or 4) enrolled in another clinical trial if denoted in the EHR; or 4) <18 years of age or >=89 years of age. Development of the study database will draw on previous registry- building efforts at study sites and our experiences with the multi-site Nudge study using standardized variable formats and definitions.

The proposed data elements will be extracted from the EHR and other electronic data sources at the study sites. The study database will have a series of data tables linked to a study patient ID (**Table 9**). The study sites have indicated that they have this data for all patients. This database will store the sociodemographic, diagnosis, laboratory and medication data used to identify eligible patients. Date of death will be included in the database and the database will be updated monthly. **To facilitate future research, we will create a de-identified dataset from the completed project that will be available for use by other investigators (see the Resource Sharing Plan for more details).**

Table 8: Database composed of Data Tables linked by a Fixed Patient Identifier	
Type of Table	**Data Elements**
Patient ID	Unique patient ID that allows for longitudinal assessment across all data tables.
Clinic ID	Unique clinic ID
Enrollment	Dates of entering or leaving the practice.
Demographic	Age, birth year, sex, race/ethnicity, residential address, insurance status
Practice	Primary care facility and primary care provider (and specialty care clinician, if applicable, e.g., cardiologist, nephrologist, endocrinologist)
Vital Signs	BP measurements, height, weight, BMI, and smoking status.
Laboratory	Laboratory tests and results (e.g., A1c, cholesterol, hemglobin).
Medications*	Drug name, dose, class, date dispensed, # pills, days supply, prescriber.
Allergies	Medication Allergies.
Co-morbidities with associated dates	Diagnoses associated with outpatient and inpatient visits
Utilization with associated dates	Clinic visits, procedures performed, ED visits, hospitalization
Patient reported outcomes	Physical activity, diet, self-efficacy questionnaire
Date of Death	Death date

Data Quality, Transfer, and Security: The Data and Statistics core will oversee all data-related activities, including patient eligibility registry construction, data quality monitoring, data security, data transfer, and maintenance of programming code libraries and data documentation. At each study site, an EHR programmer will extract data from the EHR and other electronic databases and run a program provided by the Data and Statistics core to format the data according to standardized patient eligibility data specifications. This data will be stored on a secure server at each site. The Data and Statistics core will oversee local and central data quality checks for proper formatting, completeness and consistency. A data privacy and security protections plan, consistent with the Health

Insurance Portability and Accountability Act and Sarbanes-Oxley Act, will be in place prior to project commencement. The Data and Statistics core will establish data use or business associate agreements for sharing data. At the conclusion of the study, data from each health system will be sent to the data coordinating center at University of Colorado for analysis of the primary and secondary outcomes by a secure file transfer procedure.

Potential Challenges and Considerations

Year 1 activities are ambitious. We agree while the Year 1 activities are ambitious, our team has extensive experience with each of the activities proposed during the UG3 phase: 1) developing and refining the content and delivery of the text and AI chat bot messages, 2) establishing the data infrastructure to identify eligible patients; 3) delivering telehealth interventions via text messaging; 4) working with FQHCs and patients experiencing health disparities; 5) engaging diverse stakeholders; 6) working with and developing measures based on the PRISM implementation science framework; and 7) conducting pragmatic clinical trials. We have successfully accomplished these deliverables in many prior studies. In addition, we have already demonstrated that it is feasible to identify eligible patients for the current study at one of the health systems.

What if the text messages are not delivered as planned? For Aims 2 and 3, we anticipate there may exist system failures, e.g., messages sent multiple times or incorrect branching. To ensure minimal disruption in message delivery, we will conduct system alpha testing at each health system to ensure correct message distribution and branching prior to conducting the trial. It is possible that even once we implement a pilot trial that there could be a system failure, such as sending three versions of a single message or sending a message in the middle of the night. We will minimize the impact of such an occurrence by having designated staff at each participating health system that can shut down the system and reboot as needed. We will continuously monitor for potential systems failures and deviations and implement standardized processes to correct them immediately.

Is there potential for contamination in the proactive pharmacist arm? It is possible that if we train pharmacists in motivational interviewing and proactive case management to support SM for patients they will engage with all patients in this manner, regardless of study arm. We are reducing the likelihood of this happening by sharing with them the specific list of patients randomized to the "proactive pharmacist" arm and will share with them the logs documenting chatbot engagement by each patient in that arm so the pharmacist will have a priori information on each patient's questions and SM experiences that can offer context for why they are struggling with SM outcomes. None of the settings where we are deploying the intervention are currently using a proactive population based approach so we think it unlikely they will begin doing this for everyone. However, we will monitor the patient portals for all patients enrolled to determine if pharmacists are proactively engaging with patients outside the "proactive pharmacist" arm and document this for our analysis.

What is the likelihood of successfully changing health behaviors or addressing social determinants? We are proposing a population-level intervention that uses ubiquitous technology (e.g., cellphones). We hypothesize that arm 3 (interactive AI text messages with proactive pharmacist management) will have the greatest effect and that the combination of the AI chatbot and pharmacist management will be able to successfully address medication adherence, SDoH and change health behaviors. We acknowledge that this intervention is not appropriate for more challenging cases or situations and these patients will need more intensive support from providers and the health system than can be provided by the various intervention arms. This intervention is not meant to supplant those resources but provide health systems with a low-cost, generalizable population-based intervention that can address a majority of patients who need reminders and support that is light touch while they focus their resources on the most difficult cases.

DATA AND RESOURCE SHARING PLAN

We believe this data will be unique and not readily replicated, thus we believe sharing the data will allow others to translate the research into knowledge and tailored interventions to improve self-management support.

Data Sharing Plan

All data collected as part of this project will be released in accordance with standard data sharing policies and procedures. All data will be made available to the broader scientific community after study results are published in peer-reviewed journals. Data will be made available in a timely manner, will be complete, and as accurate as possible.

Prior to making this data available, data would be redacted to strip all identifiers; and team-wide strategies would be put into place to ensure the unauthorized disclosure of personal identifiers would be reduced. Data will be further de-identified by removing indirect identifiers that could lead to "deductive disclosure" of participant's identities.

The data-sharing agreement will prohibit the recipient from transferring the data to other users, require that the data's security be protected by standard means and be used for research purposes only. After a requestor completes the data-sharing agreement, we will email the data through our UCD secured email system that requires users to create an account and sign-in with a username and password in order to receive and download any type of sensitive data.

Data gathered from key informant interviews and nominal groups will initially be entered into Microsoft Word files, and then analyzed in a qualitative software analysis program (ATLAS.ti). Because there will be small numbers of participants in the qualitative portions of our study we do not anticipate sharing raw data from individual participants in structured interviews or nominal groups. Therefore, our data from these portions will only include composite data which we will share after publication.

Sharing Research Resources

The study team will share technical and practical knowledge regarding the creation of the chat bot and text messaging intervention, upon request. Further, the study team would readily share all data collection instruments and assessment algorithms used in the project to qualified individuals within the scientific community with the agreement that they will appropriately acknowledge the study team who developed the instruments.

Software Sharing Plan

This study will develop a text messaging delivery software that will include an interactive AI chatbot. This software will be licensed and owned by the University of Colorado. The software will be made available to users who wish to implement the system in the clinic sites after negotiation of licensing and use fees. Additionally, investigators can also work with other systems to adapt the software and tailor it for their clinic setting.