NIH Collaboratory Rethinking Clinical Trials®

Health Care Systems Research Collaboratory

Regulatory/Ethics Consultation Call:

Personalized Patient Data and Behavioral Nudges To Improve Adherence to Chronic Cardiovascular Medications (Nudge)

Wednesday, August 15, 2018

Meeting Participants

Sheana Bull (Co-Principal Investigator, University of Colorado), Judith Carrithers (Advarra), John Heldens (University of Colorado), Adrian Hernandez (Duke), Michael Ho (Co-Principal Investigator, University of Colorado), MariJo Mencini (Duke), Cathy Meyers (NIH), Tammy Reece (Duke), Lisa Sandy (University of Colorado), Jeremy Sugarman (Johns Hopkins), Wendy Weber (NIH), Barbara Wells (NIH), Liz Wing (Duke)

AGENDA ITEMS	DISCUSSION	ACTION ITEMS
Review of Demonstration Project	• Co-Principal Investigator Sheana Bull (University of Colorado) gave an overview of the Nudge demonstration project. The trial plans to use pharmacy system data across 3 healthcare systems to identify patients who have delayed refilling their prescriptions for managing chronic cardiovascular conditions. Data are downloaded nightly and stored behind a University of Colorado firewall. Participants are randomized to one of four study arms: (1) usual care (2) a generic text reminder to refill the prescription, (3) an optimized text reminder that includes additional prompts based on age, gender, and geographic location, and (4) the optimized reminder plus the ability to interact with a real-time chatbot to help identify and overcome barriers to refilling the prescription. After a refill delay of ≥7 days is identified, participants in the intervention arms will begin receiving these automated text messages ("nudges") on their phone depending on their randomized arm. • **Collaborative network partners:** o University of Colorado Health o VA Eastern Colorado Health Care System o Denver Health • **NIH Institute:** National Heart, Lung, and Blood Institute (NHLBI)	

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	• **Study design:** Nudge is designed as a mobile technology-delivered intervention embedded in 3 integrated healthcare systems. The trial will evaluate the effectiveness of theory-informed text messages intended to improve medication adherence and health outcomes in patients treated for chronic cardiovascular conditions such as hypertension, atrial fibrillation, coronary artery disease, diabetes, or hyperlipidemia. In the UG3 phase, the study team will develop and program a technology-based text message library and an artificial intelligence (AI) interactive chatbot content library to optimize content for a range of diverse patients. o **Primary outcomes:** Demonstrate feasibility of delivering the intervention and evaluate preliminary effects of text messaging within the 3 healthcare systems (UG3). Evaluate the effectiveness of the intervention through a mixed methods approach and apply the RE-AIM framework to inform the tailoring, adaptation, and expansion of the intervention (UH3). • During the UG3 phase, the study team will develop, test, and refine the text message intervention by enrolling patients as key informants in a series of N of 1 trials (20 participants) and convening a Stakeholder Panel (4 participants). This phase also will ensure the ability to retrieve and download pharmacy data, assign participants to study arms, send out correct automated messages, and follow up on the prescription refill behavior subsequent to receiving the message. • The technology platform has the capacity to detect whether the patient's phone is a landline and can send a voice message as an alternative. The study team plans to assess whether the text message is actually being sent to a text-enabled phone. • While the program can verify that the message is sent to the patient's device (via phone number recorded in the EHR), there is no ability to ensure that the patient is the person reading the message.	
Status of IRB approval	• The central IRB for all 3 trial sites is the Colorado Multiple Institutional Review Board (COMIRB), which has approved the initial application (UG3). The study team plans to submit an amendment to the protocol before the UH3 phase is implemented.	

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Risk classification	• The study team believes this project poses minimal risk to all subjects involved. There is no clinical intervention being proposed, and no personal matters will be discussed. • Those on the call discussed the risks to participants in both the UG3 and UH3 phases and agrees with the study team that both phases seem to be minimal risk.	
Consent	• In the UG3 phase, participants in the N of 1 trials will be identified using electronic data. Participants in the Stakeholder Panel will be recruited through relationships with the study team. The study team requested a waiver of written consent for both groups of participants as the study is low risk, the contact with participants will primarily take place remotely, and the IRB granted the waiver. • In the UH3 phase, hard-copy letters will be mailed to patients at designated study clinics. The letters will be generated and sent by the study team. Clinic directors have agreed to sign the letter on behalf of the study to inform patients about the study. Included in the letter is a return postcard for patients who wish to opt out. When patients have a 7-day gap in refilling the identified prescriptions, they will be randomized to the study arm, and those receiving a text message will have a second opportunity to opt out of the text messages. From the patients' perspective, the letters come from the clinic. • Those on the call discussed that while opt out makes sense for this study, it will be helpful to learn how patients respond to text messaging from clinics, whether they feel overloaded, and how institutions manage the amount of messaging sent to patients. • The study team will obtain feedback from patient engagement groups in each study setting about their perspectives on best methods of disseminating study findings to participants (e.g., link to a website, letter, or final text message).	
Privacy/HIPAA	• The COMIRB has granted a full waiver of HIPAA authorization for the UG3 phase of the study.	
Monitoring and oversight	• The sponsoring institute, NHLBI, will assist in convening a protocol review committee as a preliminary step before establishing an independent DSMB for the UH3 phase of the study. NHLBI wants to ensure that data and safety monitoring board (DSMB) members have the expertise to be mindful of embedded pragmatic clinical trials (ePCTs) as	Completed: The coordinating center sent the study team the related ethics paper

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	distinct from traditional RCTs with respect to, for example, pharmacy issues or information technology issues of data integrity. • Data monitoring plans are in place in each healthcare system to ensure accurate retrieval and storage behind the university firewall. Staff will also test accuracy of outgoing text messages. A person is designated at each system to ensure data security. • If clinical guidelines for cardiovascular medications were to change during the course of the trial, the study team would modify the protocol to include, for example, a new medication to treat a cardiovascular condition. New guidelines could be reviewed by the DSMB or from an *ad hoc* NIH group.	"Data monitoring committees for pragmatic clinical trials" (Ellenberg et al., Clin Trials 2015) and a template document to customize for DMC charters for PCTs.
Issues beyond the study	• A certificate of confidentiality will be automatically provided per new NIH policy. This certificate adds provisions for future research uses and confidentiality obligations for future data sharing. It was suggested that the study team review the new certificate requirements in advance so that the team is prepared for data sharing later on. • It is hoped that the study team can design the opt-out mechanism to be able to capture rates of opting out and reasons for opting out, which could be informative to other embedded PCTs in the future. The study team will consider doing this.	

Personalized patient data and behavioral nudges to improve adherence to chronic cardiovascular medications (Nudge)

Co-Principal Investigators: Michael Ho, MD, PhD; Sheana Bull, PhD, MPH

Protocol: 18-0630

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SPECIFIC AIMS

Up to 50% of patients do not take their cardiovascular medications as prescribed, which results in increased morbidity, mortality, and healthcare costs. Interventions to improve adherence have included patient education, reminders, pharmacist support, and financial incentives and have produced mixed results—some demonstrating benefits, but many producing small to negative results. Adherence interventions have been limited by 1) including adherent patients who may not need an intervention; 2) resource intensive approaches involving pharmacists; and 3) lack of attention to evidence-based strategies to motivate human behavior.

Brief behavioral interventions can influence decision-making and are impactful. Principles of behavioral economics have been incorporated into health interventions to "nudge" people to achieve improved health outcomes. A behavioral nudge is a small change in choice framing that alters people's behavior in a predictable way. A prior study testing financial incentives through elimination of copayments for cardiovascular medications in the year after acute myocardial infarction improved adherence by 4 to 6%; however, financial incentives are not generalizable and are unlikely to be sustainable. Behavioral nudges such as commitments (e.g. asking patients for demonstrated commitment to change through a pledge), norms (using examples of others who take action), and salience (making information or recommendations resonant through use of stories) build on a well-evidenced body of behavioral science theory and have been shown to improve health behaviors such as smoking cessation and weight loss. These have yet to be tested to improve medication adherence.

Mobile and digital technologies for health promotion and disease self-management [1-3] offer an intriguing and as of yet untested opportunities to adapt behavioral 'nudges' using ubiquitous cell phone technology to facilitate medication adherence.

In the proposed study, we plan to develop and program a theoretically informed technology-based (a) nudge message library and (b) chat bot content library using multiple and iterative N of 1 within subject studies to optimize content for a range of diverse patients and convening a Stakeholder Panel to provide input on the messaging and study process.

In future studies, we hope to build off of this work to improve medication adherence and patient outcomes. We hope this work will help us to identify patients with chronic cardiovascular conditions taking medications to treat hypertension, atrial fibrillation, coronary artery disease, diabetes and/or hyperlipidemia. We would then build off of this progress to identify episodes of non-adherence through gaps in medication refills and send individual motivational and encouraging text messages.

BACKGROUND AND SIGNIFICANCE

Patients commonly fail to adhere to cardiovascular medications, resulting in an increased risk of adverse outcomes. Pharmacy refill data is routinely used to describe the prevalence and outcomes of medication non-adherence using one of two measures, the proportion of days covered (PDC) or the medication possession ratio (MPR). Both measures are calculated by the number of days supplied for a medication divided by the observation period with a range of 0 to 1.0, with 1.0 implying perfect adherence. Non-adherence is commonly

defined as a PDC or MPR <0.80. Prior work has found that 20-50% of patients with cardiovascular diseases (e.g. hypertension, hyperlipidemia, diabetes, atrial fibrillation, or coronary artery disease) have poor medication adherence. For example, in our prior work, we found that ~28% of patients were non-adherent to dabigatran, a direct oral anti-coagulant which is intended to reduce the risk of thromboembolic events among patients with atrial fibrillation. In the same study, we demonstrated poor adherence was associated with increased risk of mortality or stroke (HR 1.13, 95% CI 1.07-1.19 per 10% decrease in adherence as measured by the proportion of days covered or PDC). A similar association between medication non-adherence and adverse outcomes has been demonstrated for other classes of medications including anti-platelet medications, B-blockers, ACE inhibitors or ARBs, oral diabetes medications, and statins, all of which are used to treat cardiovascular diseases. The accumulated literature has shown that medication non-adherence to CV medications is common and results in suboptimal outcomes; thus effective interventions are needed to improve medication adherence.

Mobile telephone text messaging interventions, a form of mHealth technology may be promising in improving medication adherence. Mobile telephones and text messaging are ubiquitous. People increasingly use this technology regardless of age, socioeconomic class and primary language. A recent meta-analysis of mobile telephone text messaging medication adherence interventions for chronic diseases demonstrated that text-messaging interventions approximately double the odds of medication adherence. This increase translates into adherence rates improving from 50% (assuming this baseline rate in patients with chronic disease) to 67.8%, or an absolute increase of 17.8%. Another meta-analysis of text messaging to improve health behavior outcomes, including but not limited to medication adherence, found that personalized messages have greater effects than those that do not. While these meta analyses demonstrate the potential for text messaging interventions, the underlying studies were markedly heterogeneous, leaving questions about the best strategies for message design, the impact of generic vs. tailored approaches, optimal message timing and intensity and whether bi-directional messaging is useful. Authors of both reviews concluded the results should be interpreted with caution given the short duration of studies and reliance on self-reported measures. These preliminary data on the influence of text messaging interventions are cause for optimism. However, it is not yet known how this type of intervention might be optimized at scale and whether doing so will improve outcomes.

Behavioral “nudges” from the fields of behavioral economics and cognitive psychology have the potential to augment the impact of text messaging interventions to further enhance medication adherence. Normative theories of decision making, such as expected utility theory, are based on the ideal that all people approach decisions rationally and are able to weigh the risks and benefits of various interventions. In medication adherence for example, a normative approach would mean someone would take the medication provided the benefits outweigh the risks. Descriptive theories of decision making, such as the Dual-Process theory and Prospect theory (two of the foundational theories supporting Dan Kahneman’s 2002 Nobel prize in economics), demonstrate that humans are subject to cognitive biases that cause decision-making to deviate from the normative or rational. The Dual-Process Theory of decision making 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. 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.” A technology-delivered nudge should positively influence individuals’ behaviors through the use of non-intrusive education, social norm setting, and reciprocity expectation.

There are three types of nudge interventions that are strongly supported by prior literature that could be feasibly implemented as text messages within the context of medication adherence:

1) Communicating social norms. Social norms can activate and guide behavior in positive ways when a message normalizes positive behaviors, such as medication adherence, placing non-adherence outside the definition of typical behavior. In other contexts, social norms have been shown to improve healthy food choices, physical activity, everyday health behaviors (e.g. using the stairs vs. elevators) and even reduce home energy use. However, little or no research has tested the influence of social norm communication via text messaging to improve medication adherence.

2) Behavioral commitments. A behavioral commitment is something like committing to filling one’s prescription. Prior research has demonstrated a strong desire among individuals to act consistently with

their prior commitments, and eliciting commitments to engage in a specific behavior has been shown to be effective at improving a range of behaviors, including judicious use of antibiotics among clinicians. Commitments to fill one's prescription could be elicited via text messaging and may lead to greater concordance between individuals' commitment and their behaviors.

3) Narrative Stories: Narrative stories are increasingly recognized as an important way to increase vividness and comprehension of medical outcomes. One issue underlying medication non-adherence is likely a failure to recognize or understand the potential negative consequences the behavior, e.g., stroke, heart attack, or even death. Narrative interventions—particularly ones that describe stories of negative outcomes—may be particularly effective at helping patients concretely understand potential risks of non-adherence, spurring them to take action (improving medication adherence) to prevent negative outcomes.

Although text messaging has been used with positive effect to influence medication adherence,[1,2,4] such messages are not theoretically informed to influence social norms, behavioral commitment and/or use narratives.

APPROACH

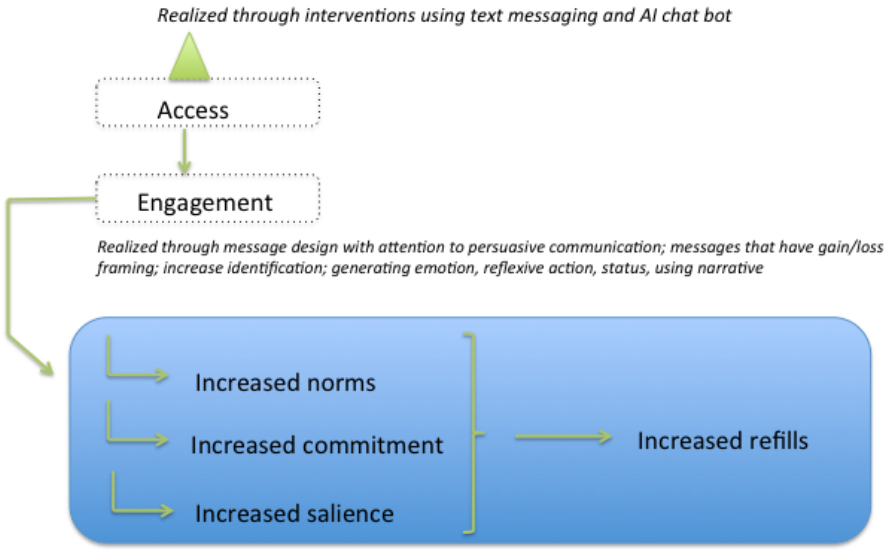
In the proposed study, we plan to develop and program a theoretically informed technology-based (a) nudge message library and (b) chat bot content library using multiple and iterative N of 1 within subject studies to optimize content for a range of diverse patients and convening a Stakeholder Panel to provide input on the messaging and study process.

Dr. Sheana Bull will lead the work to develop a nudge message and AI chat bot library. She will work with staff in the mHealth Impact Lab that she directs, established in 2014 in response to the burgeoning industry of innovative yet largely unproven digital and mobile solutions offered to address health behavior and health outcomes. The digital and mobile health industry has criticized the biomedical community for their research trial processes that are lengthy and cumbersome, which for digital health innovations may result in evidence to support technologies that have become obsolete. The mHealth Impact lab is dedicated to building rigorous scientific evidence for digital and mobile solutions, yet on a rapid and responsive timeline. They have experience in supporting the design, development and evaluation of text message, social media and mobile application (or apps) to support diverse interventions for chronic and infectious illness and primary and secondary prevention.

Message Development

There is a growing consensus that mobile and digital interventions for health promotion must motivate to pay attention, act on and derive the intended benefit from messages. Dr. Bull and colleagues have explored how persuasive message design with tailoring and personalization can impact program effects. Outcomes from this work include a theoretical framework, the *Integrated Theory of mHealth*, that suggests careful attention to technology message design must be integrated into existing theoretical and conceptual frameworks to increase engagement with messaging and in turn maximize effects.[8] We will adapt this framework **(Figure)** to guide development of content. Persuasive communication strategies with demonstrated efficacy for engaging participants in the social media realm include: 1) messages that increase sender status, 2) evoke emotions, 3) trigger a reflexive response, 4) increase identity with a group or community, and 5) use a narrative structure. [38] Health communication theory further considers the importance of framing messages with a positive or negative outcome (gain/loss framing) and of helping people process messages so they become more identified with the outcome. [39,40] Critical to this process is the consideration of message design to maximize access, which 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.

Figure: Integrated Theory of mHealth



We will generate multiple options for text message content related to 3 types of messages: 1) increasing norms for adherence, 2) commitment to medication adherence and 3) salience of messages related to adherence in order to increase medication refills.

As optimized text messages are being developed, we will program our text message delivery system to ensure automated text message and chat bot message delivery. Specifically, we will utilize the commercially available Upload Mobile Messaging (Upland Software, Austin, TX) to develop a system to send text messages. Telephone numbers and associated usernames are programmed through a Customer Relationship Management (CRM) database and then linked to a message library for Upland Mobile Messaging to execute. The AI chat bot arm is an intervention designed for delivery on the phone using algorithms to help users identify barriers to medication refill and adherence; strategies to overcome these barriers; and a plan to enact these strategies. Chat bots are designed to simulate actual human conversation based on prescribed inputs. This process is similar to that one might experience through an online customer service interaction.[2] The AI chat bot will be programmed using an existing commercial product, called Textit, which is an Application Program Interface (API) that you create automated, artificial intelligence (AI) chat.[3] We will rely on a CRM system to develop a database of all eligible study participants and will program this system during this time as well. We will set up the message schedule and branching algorithms within the CRM platform and convey to Upland Mobile Messaging and Textit for distribution once messages have been finalized. Dr. Bull has developed these text and interactive message response systems similar to the chat bot in prior studies and will be able to leverage these experiences in the development of The Nudge study messages.

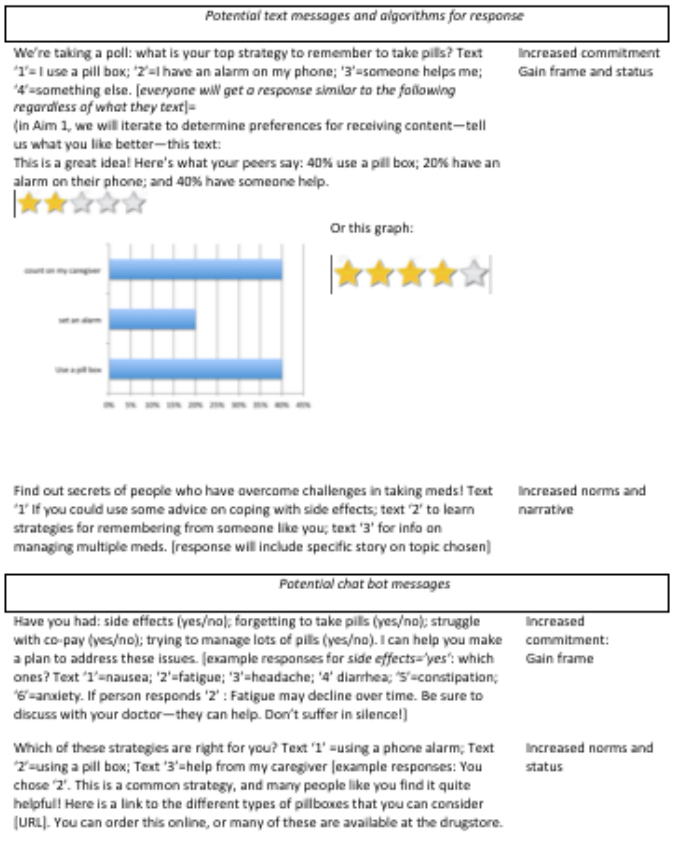
Interactive voice response (IVR) telephone messages

We will also voice record the content of the text messages and program the branching algorithm into an interactive voice response (IVR) telephone system. IVR is a technology that allows a computer to interact with humans through the use of voice and/or input via the telephone keypad. IVR systems can deliver prerecorded messages and ask patients questions with responses recorded via voice or input via the telephone keypad. Patients often interact with these systems in their daily activities such as calling the airlines to purchase a plane ticket or calling a credit card company to inquire about purchase transactions. IVR systems can handle large call volumes and can deliver outbound calls. We have used IVR to deliver short messages to patients for many of our prior and current medication adherence interventions. In addition, we have also used inbound (patient initiated) calls and outbound (automatic calls to patients) to collect patient reported health status. Finally, we have used IVR across several health systems to improve blood pressure control. We will program the messages and the algorithms using the Aspect Prophecy commercially available software. We have used this software and IVR for the past 7 years for many of our projects.

N of 1 Interviews

We plan to enroll approximately 20 (up to 30) N of 1 interviews. We plan to enroll a diverse group of male/female, younger/older patients, those with one vs. more chronic conditions and those speaking primarily English vs. Spanish. We will create an *a priori* library of various versions for messages in both English and Spanish for each of these arms and will send out different versions of messages to each participant over a four- week period. 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 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 final library that are less popular. We depict this below **(Figure)** by showing that the graph has received more stars than text to convey popular strategies to facilitate medication management. For the IVR messages, we will ask participants to rate the clarity of the spoken messages, engagement, and persuasiveness using a star system on the telephone keypad akin to the text messages. We will sort and rank messages utilizing a comparative approach, asking participants to select a preferred message from among 2-3 options that convey the same idea. Working iteratively, we will refine messages to convey content that utilizes the content and structure with the most stars and repeat this process at least two times until we have a library of messages that includes highly ranked content and structure, such that it is highly readable, easily navigable, engaging and likely to persuade action. We will do the same for the IVR messages. We understand that it will be unlikely that there will be uniform agreement on message engagement and persuasion given the subjectivity of these concepts. Thus, our libraries will include diverse options for different demographic groups.

Figure: Potential optimized messages and AI Chat bot messages and related theoretical constructs



Stakeholder Panel
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. Dr. Matlock 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 that will meet monthly during the first 9 months of the study.

- ***Participants:*** The stakeholder panel will consist of 4 people from UCH (2 patients, one pharmacist, and one person involved in the leadership or operations of the health system). Members will be recruited through relationships of the investigators. Dr. Matlock 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. At the first meeting, one of the patients will be selected by the group to be a co-leader of the stakeholder engagement core with Dr. Matlock.
- ***Location:*** The panel will meet in meeting space at the Adult and Child Center for Outcomes Research and Delivery Science (ACCORDS) where there is ample free parking. This is where Dr. Matlock currently runs his patient advisory panel. Each member of the panel will be reimbursed $25 per meeting.
- ***Meeting content:*** Dr. Matlock will train study team staff in the proper conduct of patient advisory meetings. During these two-hour meetings, the investigators of Nudge will present the ongoing text message development to obtain feedback both on the content. 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 the implementation challenges and brainstorm with the investigators strategies to mitigate these. This partnership between the study team and our stakeholders (patients, providers, and health system leaders) will help to make the intervention components and products more sustainable if a future study is implemented.
- ***Payment:*** Participants in the panel will receive $25/meeting they attend, resulting in up to $225.

Protection of Human Subjects
The study team believes that this project poses minimal risk to all subjects involved. There is no clinical intervention being proposed, and no deeply personal matters will be discussed.

In the proposed study, we plan to work with patients to develop, test, and refine the messaging of the text message intervention by enrolling patients in a series of N of 1 trials and convening a Stakeholder Panel. We will enroll approximately 20 patients in the N of 1 trial and 2 patients in the Panel. We will also enroll 2 individuals with clinical / health systems roles from UCH.

Study subjects will be identified using electronic data. We will request a waiver of documented consent from study subjects as this study is very low risk, our contact with participants will primarily take place remotely and we are concerned that the remote informed consent process would be overly burdensome to the patient. We also request a HIPPAA waiver as we are obtaining verbal consent from patients, often over the phone. We will provide all subjects a one-page description of the study and will allow for accurate time to review and discuss the objectives of the study, their participation, and the option to withdraw at any time. Consents will be obtained by trained members of the research team.

The study will be conducted according to Good Clinical Practice guidelines, the U.S. Code of Federal Regulations (CFR) Title 21 CFR (Part 50 – Protection of Human Subjects and Part 56 – Institutional Review Boards) and the Declaration of Helsinki.

Sources of Materials

Trained and certified professional staff will manage all data according to detailed study protocols. Data will be used specifically for research purposes. All materials will be created for low-literacy populations, and also be translated to Spanish for our Latino population. Materials will be reviewed by our Stakeholder Panel as applicable.

Potential Risks to Participants

We do not anticipate any substantial risks to be associated with participation in this study. As with any study involving participants with chronic disease, however, there is some risk of psychological discomfort related to discussing disease management. Participants will be informed that if they choose to discontinue the study at any time, this will not interfere with their usual medical care.

As with all research, there is also a slight risk of loss of confidentiality and/or anonymity, especially for participants in the Stakeholder Panel. A discussion on respect for others' confidentiality will start the first meeting. These procedures have been developed and used in many studies and we will adhere to these procedures for the proposed study.

We have standard operating procedures for data acquisition and data management designed to protect against data loss and maintain patient confidentiality. Computer files will be password protected. Files containing names, addresses, or other personal identifiers will have a separate password and will be accessible only to personnel who need to contact subjects.

Adequacy of Protection of Risk

To mitigate risk of psychological discomfort and/or time burden during key informant interviews, participants will be informed that they do not need to participate, and they will be reminded that they do not need to answer questions that make them uncomfortable, and they may choose to withdraw from the study at any time without losing any benefits to which they may be entitled. Interviewer notes will contain no direct identifiers other than a study-specific random identifier for focus group participants.

As is the standard, all staff participating in the project will complete compliance and human subject research training and all recruitment materials and consent forms will be approved by the Colorado Multiple Institutional Review Board (COMIRB).

Potential Benefits to Subjects

No claim is made that subjects will benefit from participation in this project. However, the results of the study may improve care to the extent that our study improves medication adherence.

Data Quality, Transfer, and Security

Designated study team members will oversee all Nudge Study data-related activities, including data quality monitoring and data security. All data will be stored on a secure server at each site. Designated research team members 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. Research team members will establish data use or business associate agreements for sharing data.

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