

## COMIRB Protocol

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

**Co-Principal Investigators:** Larry Allen, MD; Sheana Bull, PhD, MPH

**VA PI:** Meg Plomondon, PhD.

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Up to 50% of patients do not take their cardiovascular medications as prescribed, resulting in increased morbidity, mortality, and healthcare costs. Interventions to improve adherence, such as patient education, reminders, pharmacist support, and financial incentives, 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 framing choice 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 from 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<sup>1-3</sup> offer an intriguing and as of yet untested opportunities to adapt behavioral ‘nudges’ using ubiquitous cell phone technology to facilitate medication adherence.

The objectives of our two-part, multi-center study are as follows over the course of 4 years:

**Aim 1:** Conduct a pragmatic patient-level randomized intervention across 3 HCS to improve adherence to chronic CV medications. The primary outcome will be medication adherence defined by the proportion of days covered (PDC) using pharmacy refill data. Secondary outcomes will include intermediate clinical measures (e.g., BP control), CV clinical events (e.g., hospitalizations), healthcare utilization, and costs.

**Aim 2:** Evaluate the intervention using a mixed methods approach and applying the RE-AIM (reach, effectiveness, adoption, implementation, and maintenance) framework. In addition, assess the context and implementation processes to inform local tailoring, adaptations and

modifications, and eventual expansion of the intervention within the 3 HCS more broadly and nationally.

## 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 20% to 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, over a quarter (28%) of patients were non-adherent to dabigatran, a direct oral anti-coagulant that 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 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 - this technology is increasingly used 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 50.0% (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 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,<sup>1-4</sup> such messages are not theoretically informed to influence social norms, behavioral commitment and/or use narratives.

## **PREVIOUS WORK**

Throughout 2018, we established the procedures and start-up necessary to initiate this four-year study successfully with an informed approach (COMIRB #18-0630). We have developed a message library, and vetted and developed through a series of N of 1 trials and stakeholder panel input. IT infrastructure has been developed across three healthcare systems (see below for additional details).

We have also piloted and refined our patient identification procedures, opt-out methods, and the text messaging intervention through a pilot study (in progress at this time).

## **SETTING**

The proposed study setting includes Denver Health, UCHealth, and the Denver VA healthcare systems (HCS).

## **APPROACH**

Over the next four years, we propose conducting a patient-level, randomized pragmatic trial testing a variety of strategies “nudging” patients through text messages to encourage medication adherence to already-prescribed cardiovascular medicines.

**Inclusion & Exclusion Criteria**

Programmers will identify eligible patients based on the presence at least 1 of the cardiovascular conditions listed in **Table 1** and with a prescription for at least 1 of the classes of medications to treat the cardiovascular conditions listed in **Table 1**. Participants must be patients at UHealth, Denver Health, and the VA. Patients must have had a fill for a medication of interest within the 100 days prior to the cohort build date.

There will be minimal exclusions criteria: 1) patients who have neither a landline or cellphone; or 2) enrolled in hospice or palliative care; or 3) Non-English or Spanish speaking; 4) residing out of the state of Colorado.

Patients with a refill gap of at least 7 days within the past year utilizing pharmacy refill data will be eligible to receive nudges. We will specifically target patients from the following patient groups: 1) Age > and <= 65 years of age; 2) Male and female patients; 3) one versus multiple cardiovascular condition of interest; and 4) English and Spanish speaking patients.

**Table 1.** Inclusion criteria for the study based on cardiovascular conditions and medications classes of interest

<b>Condition</b>	<b>Classes of medications</b>
Hypertension	Beta-blockers (B-blockers), Calcium Channel Blocker (CCB), Angiotensin converting enzyme inhibitors (ACEi), Angiotensin Receptor Blockers (ARB), Thiazide diuretic
Hyperlipidemia	HMG CoA reductase inhibitor (Statins)
Diabetes	Alpha-glucosidase inhibitors, Biguanides, DPP-4 inhibitors, Sodium glucose transport inhibitor, Meglitinides, Sulfonylureas, Thiazolidinediones, and statins
Coronary artery disease	PGY-2 inhibitor (Clopidogrel, Ticagrelor, Prasugrel, Ticlopidine), B-blockers, ACEi or ARB and statins
Atrial fibrillation	Direct oral anticoagulants, B-blockers, CCB

**Opt-out Consent Process**

Programmers will develop identical study databases within each HCS to store potential participants. All data will be stored on secure, separate servers or on RedCap.

We will use this pool to send opt-out consent letters to potential participants. An opt-out consent packet will be sent to all eligible patients prior to randomization. The packet will contain an introductory letter with information about the study, an opt-out form, and a self-addressed, stamped envelope. An opt-out survey will also be included. This opt-out survey aims to gauge the reason for patients opting-out. The survey is optional.

All materials will be available and sent to patients in both English and Spanish for UHealth and Denver Health patients. If they have previously specified in their contact preferences that they prefer English or Spanish, we will send materials in their preferred language. As is standard, materials will be sent in English only at the VA. All materials will be sent on letterhead and branding appropriate and specific to each HCS. The letter will be signed by either the primary care provider for the patient or the site principal investigator.

Should an opt-out packet be returned by the United States Postal Services (USPS) due to an incorrect address, etc, a member of the study team will call the potential participant no more than two times to verify their address; should they not hear from the participant the patient will not be included in the study. Upon the deadline for response to the opt-out consent has expired, patients that have not opted-out will be randomized accordingly. Signed and returned opt-out forms will be securely stored in a locked filing cabinet (returned opt-out forms for VA patients will be securely stored at the VA).

### **Patient Identification Process**

From this pool of candidates, patients will be followed forward and those identified to have a gap of at least 7 days in one of the CV medications at any time during the two-year monitoring period will be randomized to one of the four study arms. For patients who are prescribed multiple CV medications, eligibility for randomization will be triggered by the first 7-day gap for any medication.

We have already developed algorithms that queries pharmacy data for a defined medication refill gap based on the date that the medication was supplied and the number of medication days supplied. This algorithm is in use for a medication adherence study currently. We will apply this algorithm across the 3 HCS to identify non-adherent patients.

Pharmacy data from UHealth and Denver Health will be accessed through both hospital-specific pharmacy data and Surescripts, a network with existing relationships with both HCS that provides pharmacy refill data from over 95% of US pharmacies. Daily pharmacy data via Surescripts is currently available at Denver Health, and is projected to become available at UHealth in the fall of 2019.

Every 3 months for up to two years, we will assess whether there are new patients who have met entry criteria in the interim, based on existing patients who now meet the eligibility criteria or new patients to the clinic. These patients will be sent an opt-out package and provided a reasonable timeline to return the opt-out form. We will continue to add new patients until months 24 following the start of the pragmatic study at each site to allow for at least 12 months of patient follow-up to assess for non-adherence.

### **Mobile Messenger**

Mobile Messenger (Upland Communications, Austin, TX) is an online platform specializing in text message transmission. Three separate accounts have been created to ensure each HCS data are stored separately; protected health information (PHI) between sites will never be combined. Each account will have a separate login and password. To access the Mobile Messenger account for the VA, Nudge study team members must be signed in behind the VA firewall.

A trained member of the Nudge study team will upload phone numbers, first name, medication class, and first three digits of the zip code. First, the researcher will identify the patient has a listed cell phone. Upon confirming the phone number, the patient will be entered into the appropriate study arm. Message schedules and example messages (attached) are available in this application packet.

The program will allow patients to STOP if they would like to opt-out of the study, or indicate DONE if they have filled their medication or if their physician has cancelled the medication of interest. There will also be an option to receive messages in Spanish.

### **Message arm descriptions**

The study will randomize at the patient level. Once randomized, patients will remain in the same study arm for the entire study whether or not they have subsequent refill gaps.

- 1) Usual Care:** This group will not receive an intervention. We have included a usual care group to demonstrate the impact of the text messaging interventions above and beyond usual care given that many prior medication adherence interventions have demonstrated small to negligible effects.
- 2) Generic nudge:** A generic reminder text will be delivered to patients to refill their medication at days 1, 3, 5, and 9 after they been labeled as non-adherent. During aim 1, we will further assess the optimal timing for delivery of these messages. We have put in the specific days to provide an example. In the day 1 text message, patients will have another opportunity to opt out of the study with text such as “text STOP if you wish to withdraw from this study.” The texts will stop once a patient has filled their medication.
- 3) Optimized nudge:** A behavioral nudge text will be delivered to patients to remind them to refill their medications at days 1, 3, 5 and 9 after they have been labeled as non-adherent. During aim 1, we will further assess the optimal timing for delivery of these messages. We have put in the specific days to provide an example. In the day 1 text message, patients will have another opportunity to opt out of the study with text such as “text STOP if you wish to withdraw from this study.” The texts will stop once a patient has filled their medication. The content of the behavioral nudge text messages will vary with each text and will be derived from the text message library built during the pilot year (COMIRB #18-0630)
- 4) Optimized nudge plus AI Chat Bot:** A behavioral nudge text will be delivered to patients to remind them to refill their medications at days 1 and 3 after they have been labeled as non-adherent. In the day 1 text message, patients will have another opportunity to opt out of the study with text such as “text STOP if you wish to withdraw from this study.” The texts will stop once a patient has filled their medication. If the patient has not filled their medication on days 5 and 9, an AI will conduct interactive chat via a chat bot to assess barriers filling the medication as described in Aim 1 above.

The AI Chat bot will assess for common barriers to medication adherence 1) socioeconomic factors, 2) provider-patient/health care system factors; 3) condition-related factors; 4) therapy related factors and 5) patient-related factors using a developed script that we are currently employing in a medication adherence study. Communication about all of these barriers will be pre-programmed to use as algorithms in the chat bot automated program. For each barrier, the AI Chat bot will problem-solve with the patient and identify commonly used successful approaches to overcome barriers, and will ask patients to choose and enact one solution to improve medication adherence. The AI chat bot library will include algorithms to support specific strategies to circumvent the adherence barriers responsible for each instance of a medication refill gap. For example, patients would be queried to determine if they have difficulty remembering what medications to take and when to take them; those that do would be asked if using a medication diary, involving a caretaker, or setting an alarm on their phone would help. Patients would be asked if they would like to try one of these strategies; for those that agree and identify a strategy, the AI chat program will include an algorithm to check in one week later to see how this strategy is going. Those who do not agree and/or identify a strategy will be offered other options and the process repeated until they do. If there are issues that arise that are not pre-programmed into the AI chat bot library, the AI Chat bot will refer the patient to the study pharmacist at each site for consultation and assistance with the issue. For example, a patient may have stopped taking his medication due to a side effect. The AI Chat bot will document this information through interactive chat then refer the patient to a study pharmacist to see if there are alternative medications. Dr. Bull has programmed libraries very

similar to this AI Chat bot approach and utilized them for behavior change in prior interventions.

Patients will be followed for up to 24 months. They will remain in the same study arm for the duration of the study and receive the same intervention for subsequent episodes of non-adherence.

### **Plan for responding to text messages from patients**

- a) If a patient texts “stop” to unsubscribe, the patient is automatically withdrawn from receiving the intervention (messages). Patients may also text misspellings of the word “stop” (such as “tsop,” etc.), or send a message indicating the patient would like to be removed from the study. We will continue to view already-collected, standard of care data from these patients.

In the initial version of the consent form, we described a “stop” response as a way to “fully withdraw” from the study. These patients were opted out from the study entirely, and data are no longer being collected on these patients. In v.12.3.19 of the info sheet, the language was amended. For patients that have hit “stop” in the original cohort, researchers will call the patients (please find script) to obtain verbal consent to collect their data moving forward. If patients do not consent or cannot be reached after two attempts, we will continue to treat the patients as fully opted out and we will not view their data moving forward. Patients from this original cohort that hit “stop” in the future will be flagged and the calling process will be implemented.

- b) Should a patient respond “done” to indicate they have already filled their prescription or a physician has cancelled their medication, we will stop sending patients any further text messages about refilling the medication in which they had a delay until their medication is again due for a refill (i.e. 30 – 90 days in the future). We will immediately remove the patient from further text messages for this instance of medication non-adherence.

Misspellings of “done” or messages indicating they have already filled their prescription or that a physician cancelled their medications will be treated as if they responded “done.” If a physician has stopped their medication, we will no longer monitor for medication refills for that specific medication. For other medications, we will resume following the other medication refills. If the patient has a refill gap for the same or for other medications again, we will start delivering text messages within the same arm that they had been previously randomized to.

- c) Patients may request Spanish messages at any time via text. We will start to deliver Spanish language texts following the request. If the patient meets additional criteria for texts during the duration of the study, they will receive Spanish language texts.
- d) There will be text messages that do not fall into any of the categories above. A Research Assistant will monitor these responses and will triage the messages depending on the content of the messages. In our pilot study, some patients sent responses to the text messages that (a) requested additional information about the study and/or (b) requested more detail on the specific medication that required a refill, even though the text message they were responding to did not solicit this information. For these types of unsolicited messages, the Research Assistant will respond with a link to our study webpage where we will post information about the study, sponsors, participating institutions, and a contact number they can call for more information. This webpage will include a “Frequently Asked Questions” (FAQ) about the Nudge Study,

and we will post responses to anticipated questions (e.g. Does my provider know about this study?; How did you get my cell number?; What if I don't want to participate?; etc.).

We anticipate that patients may text unsolicited information about a side effect or adverse event related to their medications. In these cases, we will have the site study pharmacists call the patient to find out more about the issue. We will also have the pharmacist contact the patient's PCP to make them aware of the issue.

Other responses, such as questions about the intervention or requests for information about their medication, will be triaged and responded to by a research assistant, pharmacist, or physician, as deemed appropriate. A call script for the research assistant is included. We will catalogue the messages that we receive from patients and if there is a theme, we will develop a FAQ and place information on the study website. In cases where the patient still has not refilled their medication after 5 days of their reply "done", a research assistant on the study team will first confirm that the medication refill has not been completed. If the medication has not been refilled after chart review, they will then contact the patient to see if he or she is having issues with refilling the medication and try to resolve any issues with the patient.

In addition, we will update the patient's care provider on a regular basis about medication gaps and other medication issues of their patients. The frequency and mode of contact will be based on their indicated preference, which we will solicit at the start of the study during our clinic presentation. If the provider did not indicate a preference, we will send this information via email on a weekly basis.

## **Quantitative Analysis**

The study will be a randomized controlled study with four treatment arms. When patients are identified through pharmacy refill data to have a 7-day gap in any prescribed CV medication refills, they will be randomized to one of four arms, described in Intervention below. Randomization will be stratified within each of the eight clinics, and within strata defined by number of other CV medication classes that are prescribed at randomization (1-4), using blocks of 4 patients to ensure balance within clinics over time. Thus, within each clinic and number of other medication stratum, each set of 4 consecutively enrolled subjects will be randomized to the four study arms. Treatments will be initiated immediately upon randomization, in response to the 7-day gap.

The primary outcome is adherence to CV medications as measured by 12-month proportion of days covered (PDC). There are several complications in using this outcome, including a) a need to account for periods when subjects are not at risk of depleting their medication supply (see below for details), b) defining PDC when considering five medication classes (antihypertensives, statins, oral hypoglycemics, antiplatelets, and anticoagulants), c) accounting for number of other prescribed CV medications (more opportunities to miss days, and more opportunities to receive reminders), d) modeling the non-normal bounded distribution of PDC, and e) a desire to express results on a PDC difference (not risk ratio or odds ratio) scale. Analyses accounting for these complications are described below. Secondary outcomes include clinical events (e.g., event times for stroke, MI, mortality), utilization of care (e.g., hospitalizations or clinic visits for CV-related reasons), and costs of the interventions and of medical care. Given survival, subjects will be followed for at least 12 months following randomization to assess these secondary outcomes. 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 outcomes.

### ***Ascertainment of Outcomes***

Data for the primary outcome PDC will be obtained using pharmacy records from each of the healthcare systems during the 365-day follow-up. To address complications a and b above: a) The assessment will be based on the number of outpatient days a patient has a medication available, among all days they were at risk of depleting that medication. At-risk days will be days during which a patient was prescribed the medication and should have depleted their supply, and will exclude days following death. Inpatient days will not be considered in the calculation. Note that at-risk days is medication specific, as medications may change during the one-year assessment period. b) We will consider three definitions of PDC: i) Medication-specific PDC: calculate PDC for each class of medication a patient is prescribed, ii) All-medication PDC: calculate PDC requiring all prescribed and at-risk medications be available on a day, and iii) Average PDC: calculate the average PDC across medications the patient is at risk of depleting on a day, and average over all days when at risk of depleting at least one medication.

Secondary outcomes for clinical events and utilization of care will be captured from the electronic health records (EHRs) at each of the three health care systems. Several sources of cost data will be used. To capture costs of development, implementation and maintenance of the intervention, we will develop instruments (e.g. time logs) 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. Intervention costs will be the long-term average cost of implementing the intervention excluding research and development costs. Medical care costs will be estimated using a resource-based method previously developed to assign costs to encounter data. Inpatient utilization will be measured using diagnostic-related groups (DRGs), outpatient utilization using relative value units (RVUs), and cost of pharmacy utilization using the midpoint between the Federal Supply Schedule (FSS) and the National Average Drug Acquisition Cost (NADAC). 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 as the median between the FSS and NADAC.

### **Planned Analysis**

Analyses will be based on the intent to treat principle, using all patients who were randomized.

### ***Descriptive analyses***

Descriptive analyses will be used to describe the cohort and to check for balance across study arms within strata (clinics and number of other medications prescribed). Primary outcome PDC will be calculated during the one-year period following treatment initiation. Simple descriptive estimates of each patient's PDC on each medication will be used for descriptive analyses.

### ***Modeling PDC***

Formal analyses will be based on daily data, using a binomial-type model with logistic link for the number of days covered by medication, which will be 365 but excluding days not at risk of depleting as described above. We will model the three definitions of PDC described above:

*i) Medication-specific PDC:* For a given medication class, the model will include fixed effect terms for treatment arm, clinic, patient covariates, and number of other CV medications the patient is prescribed, and a random subject effect for a subject's tendency to have higher or lower PDC compared with other subjects. Covariates to be adjusted for will be selected a priori based on clinical considerations and covariate data quality, the latter assessed after we have enough pilot and baseline data to make the assessment but before examining outcome data. All covariates included in outcome models will also be included in imputation models (see

below). The analysis will be carried out using daily data to account for the differing numbers of at-risk days across patients, and the possibility that the number of other prescribed CV medications may change during the one year PDC modeling period. The parameter being modeled is the probability that a given day is covered, conditional on fixed and random effects. This approach will account for complications a) varying numbers of at-risk days for different patients and different medication classes, b) defining PDC when considering multiple medication classes, c) adjusting for number of other CV medications prescribed, and d) the non-normal bounded distribution of PDC. Due to non-independence of days for a given subject, the binomial assumption will not hold and inference will need to be carried out using bootstrap or Markov chain Monte Carlo (MCMC) methods as described below.

*ii) All-medication PDC:* Each day for each subject will be coded as whether they have all prescribed and at-risk medications available or not. The same modeling process described above for medication-specific PDC will be used.

*iii) Average PDC:* Medication-specific PDC models will be estimated as described above, and will be used to calculate estimates of average PDC using the standardization methods described below.

### **Treatment comparisons**

Discussions with clinicians have indicated expressing results on a linear scale (PDC differences), as opposed to odds ratios or risk ratios, will be most appropriate for interpretation. Several such modeling approaches exist including Modified Binomial using robust standard errors, Additive Binomial using maximum likelihood, and standardization using counterfactual methods. We plan to base primary analyses on the standardization approach, which allows flexibility in estimating treatment comparisons and provides population average estimates that are parallel to simple proportion estimates of PDC. In this approach a mixed logistic regression model will be estimated using maximum likelihood, and the estimated model is used to calculate probabilities that each day is covered for each subject and each medication. Quantities of interest are estimated from the relevant averages of probabilities. For example, the estimated probability of medication availability for a given medication on a given treatment is the average of all estimated probabilities for all exposed days across all subjects assuming they received the specified treatment and were prescribed the specified medication, regardless of which treatment they actually received and which medication(s) they were actually prescribed. Contrasts of interest are formed from these estimates. Primary hypotheses involve pairwise comparisons between each of the four study arms, and will be conducted using the pairwise contrasts. Standard errors and confidence intervals will be calculated using bootstrap methods, since the binomial assumption of the model will not hold. Bonferroni adjustments will be used to correct for the 6 pairwise treatment comparisons.

The secondary outcomes of clinical events, care utilization and cost will be analyzed using similar approaches but based on appropriate models, e.g. Cox survival models for time to clinical event or rehospitalization, generalized gamma regression for cost, etc. Similar standardization methods allow results to be expressed on interpretable scales such as risk difference. Data will be analyzed using SAS (SAS Institute Inc., Cary, NC) and R software.

*Missing data:* Patients with missing data in covariates, treatments (unlikely) or outcomes will be retained in the intent to treat analyses and their missing values imputed using multiple chained equation methods. The imputation model will include all covariate, exposure and outcome variables used in the outcome model. If patients are randomized but later opt out or drop out, their outcome data will be collected up to the point that they leave, and will be used as a variable in the imputation. When outcome data cannot be obtained, every effort will be made to

document reasons for these missing observations. 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 analyses of primary outcome:* We will consider several sensitivity analyses. First, an alternate estimation approach using MCMC instead of maximum likelihood will be considered. This approach would eliminate the need for bootstrapping, and would also allow imputation during the model estimation by treating missing covariates and outcomes as parameters in the Bayesian model and estimation. Second, we will fit mixed linear regression models to the binary 0/1 daily medication coverage outcome. Treatment differences will be on the PDC difference scale. Robust sandwich estimators will be used in the estimation, and bootstrap will be used for inference. We expect results of these sensitivity analyses to be similar to the primary analysis results. We will also use the methods described above to conduct several secondary analyses evaluating a) predictors of patients having an initial gap of at least 7 days, using the initial pool of candidate patients, to identify types of patients or prescription characteristics for patients at highest risk for non-adherence; b) predictors of subjects having a gap of at least 7 days while enrolled in the study; c) PDC for the individual medication that triggered enrollment in the study, to allow analyses of heterogeneity of treatment effect (HTE) by drug class; and d) analysis of alternate definitions of primary outcome, including time to first gap, PDC below 0.8, and number of 7-day gaps, during the one year follow-up. We will also carry out an analysis to estimate possible HTE between the three health care systems, using an interaction of treatment arm with health care system.

*Health system costs:* This analysis will examine intervention costs and incremental medical costs associated with the intervention. Cost data will be analyzed using the same methods described above with factors for study arm and health care system/clinic strata, using generalized Gamma regression, which include as special cases lognormal, Gamma and Weibull. The primary dependent variable will be healthcare cost, in total and separated into inpatient, outpatient, and pharmacy cost buckets. The primary independent variable will be the intervention arm the patient was randomized to. Results will be stratified by healthcare system.

### **Power Assessment**

We first estimated sample size required to achieve 80% power for the desired change in the primary outcome, then used current data to show we will be able to achieve this sample size.

*Power and sample size:* Required sample size was estimated for the primary outcome PDC during the 12 months following randomization. Preliminary data from the VA were used for these estimates. We made the following assumptions: a) Significance using two-sided level 0.05 tests, b) Power at least 80%; c) Difference between treatments in PDC of 10 percentage points; d) Bonferroni adjustment for the 6 pairwise comparisons among the 4 study arms, resulting in adjusted level 0.05/6; e) Analysis stratified by health care system; and f) Within-system and within-treatment residual standard deviation of 12 month PDC equal to 0.247 (mean 0.771), obtained by analysis of 594,466 veterans during the period 01/01/2010 – 09/30/2012 who were prescribed CVD medications. The large SD is due to a highly left-skewed PDC distribution. (We base sample size estimation on t-tests rather than the proposed binomial models since we do not have estimates of quantities needed to carry out power simulations. We may be able to obtain data for the PDC outcome for a set of baseline patients, in which case we will consider a refined power analysis.) Using these assumptions and estimates, and comparing any two treatments using a linear model with the above residual standard deviation of PDC, we estimate using sample size functions in R that we will need N=154 subjects per treatment arm, total

across the three health care systems, for a total of 616 subjects to be randomized across the three health care systems.

*Available sample sizes:* We obtained data from each of the three health care systems on the number of patients at the eight specific clinics (VA, 2 clinics; UCHHealth, 4 clinics; DH, 2 clinics) to be included in this study. Figure 1 below shows estimated numbers of patients seen, numbers with CVD conditions and prescribed CVD medications, and numbers with 7 day gap. These patients will be invited to participate, and assuming 80% agree to participate, and 90% of those yield usable outcome data, we expect to have usable outcome data for about 4,364 patients, or about 1,091 per treatment arm. Thus, we expect to have ample subjects (about seven times as many as needed) to achieve the necessary power for the primary analysis of PDC. Additional subjects will provide power for secondary analyses, and for analyses of secondary outcomes.

## **Exploratory**

### ***Covid Messaging***

On April 6, 2020, the Nudge Study started to send Covid messages to patients enrolled in the study (Amendment PAM006-1, approved March 18, 2020).

This study plans to scale the concept of the Nudge Study to other applications in the future. We propose pulling data regarding Covid testing of patients sent messages after April 6, 2020 to compare with Arm 1 (non interventional arm).

### ***Comparing opt out vs opt in demographics***

There is a growing interest in learning more about who is opting out of our study, as well as who is opting in.

Our study plans to compare the demographics of patients (race, age, ethnicity, gender) that have opted in vs opted out of our study. This requires pulling data from Electronic Health records to compare both cohorts.

We propose (12/1/20) to retrospectively pull demographic data from the EHR for patients that have opted out of the study (race, age, ethnicity, gender) to compare these data with patients that have opted in to the Nudge study. Moving forward, we will include a statement in the opt out packet (**Information Sheet, v 12/1/20**) to inform potentially-eligible patients that receive an opt out packet that demographic information will be drawn.

### ***Examining Social Determinants of Health (SDoH) on cardiovascular medication adherence***

Few studies focus on how SDoH interact cardiovascular medication adherence. Thus, we aim to explore the relationship between socioeconomic factors broadly as well as neighborhood-level resources with cardiovascular medication adherence. One measure of neighborhood-level resource is called area deprivation index (ADI). ADI has previously been shown to be correlated with outcomes such as readmission rates and adherence to retinal screening in diabetes. It has also been used to advocate for health policy change. To our knowledge, ADI has not been studied in the context of cardiovascular medication adherence more broadly.

We propose that all available participants from all 3 HCS will be included in this sub-analysis. The following data will be used:

- residential address
- 5-digit zip code
- study arm designation

Residential addresses will be geocoded to provide Federal Information Processing System and 9-digit zip code. Publicly available data maintained by University of Wisconsin School of Medicine and Public Health at <https://www.neighborhoodatlas.medicine.wisc.edu/> will be downloaded as an excel file and will be similarly saved on appropriate servers. Using excel functions, FIPS code or 9-digit zip code will be used to assign each residential address an area deprivation index score, national and state rank.

This data will be reported in aggregate in multiple forms: mean, frequency, mode of state decile rank of the ADIs in total and by each study arm. Maps of the geospatial data will be created to visually depict the distribution of state decile ADI in the study populations. Additional analysis of geospatial patterns and subgroup analysis based on low, medium, and high area deprivation index will be performed to understand if neighborhood level resource is an effect modifier for primary outcomes in the Nudge study.

A similar process was previously undertaken and approved in the following: COMIRB 20-1021.

## **Qualitative Analysis**

### ***Assessment of patient perspectives***

In year 5, after the intervention and follow-up period has ended, we will survey patients via text message and Nof1 telephone interviews. We have conducted similar interviews with patients following adherence interventions. These interviews will help inform further refinement of the interventions<sup>65</sup> as we plan for broader dissemination of the intervention (if demonstrated to be effective) to more clinics and patients with other chronic conditions.

#### *Text message survey*

We will randomly sample 150 patients across the three sites to participate in a voluntary survey about their experience with the intervention over the University-hosted Qualtrics platform ([https://ucdenver.co1.qualtrics.com/jfe/form/SV\\_5jBlah5rV7tcSoK](https://ucdenver.co1.qualtrics.com/jfe/form/SV_5jBlah5rV7tcSoK)). The survey will not collect or solicit any PHI (see Attachment – Satisfaction Survey v 9.23). The sample will be stratified evenly across patients who received one of the three intervention arms.

#### *Mailed survey*

If the response rate of the text messaged surveys is below 20%, the surveys will be mailed out to patients who previously received the survey via text but did not respond. A \$2 incentive will be included in the mailed packet to encourage responses. An information sheet will be included to explain the survey and incentive to the patient (Attachment – Information Sheet v2.23).

#### *Nof1 Interviews*

In a random sample of up to 50 patients who respond to the survey and indicate they would be interested in participating in an additional interview, we will contact them via telephone to get more in-depth feedback through qualitative interviews on the intervention (Attachment - Nof1

interview guide, v. 9.23). No deeply personal information or PHI will be solicited. Interviews will take place over Zoom, Cisco Jabber (DH/UCH), and secure hospital phone lines (VA). Interviewers will utilize detailed notetaking with an interview guide, and interviews will be recorded to be transcribed (at DH and UCH only). Interviews will cease once information saturation is reached. Nof1 participants will receive an electronic gift card of \$30. A postcard consent will be read to the patient prior to the commencement of the interview (Attachments – Satisfaction Postcard Consent v9.30 (for DH/UCH), Satisfaction Postcard Consent v5.23 (for the VA)).

### ***Assessment of provider and health systems leaders perceptions***

We will conduct key-informant interviews with up to 2-3 providers (6-9 across the 3 HCS) from each setting whose patients have received the intervention to get their feedback about the intervention and the intervention effects on their patient’s medication taking behavior. For some providers, they may have received a note from the study team informing them that their patient did not refill their medications and we will also interview the providers on their perceptions of that process. 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 and gauge their reaction to the findings. With any indication of positive outcomes, we will ask participants to describe their likelihood to maintain the system within their setting, and to discuss any barriers to maintenance and specific actions needed to overcome these barriers.

### **Study Evaluation**

The study will be evaluated using the Practical, Robust Implementation and Sustainability Model (PRISM) and RE-AIM framework components of Reach, Effectiveness, Adoption, Implementation and Maintenance. We will also develop tools and a sustainability plan to broadly disseminate the intervention, if effective. PRISM considers important implementation concepts from Diffusion of Innovations, the Chronic Care Model, the Model for Improvement, and the RE-AIM framework and highlights four components that influence implementation success: 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. These four elements will be assessed in a formative manner and will be critical to understanding how to further disseminate the intervention if demonstrated to be effective. PRISM also identifies a set of important outcomes from the RE-AIM model (i.e., Reach and Effectiveness, Adoption, Implementation, and Maintenance) for evaluation. We will incorporate the assessment of the 4 components that influence implementation success into our evaluation and this will be further discussed in the implementation evaluation section below (Table 2).

**Table 2.** RE-AIM measures

RE-AIM Domain	Domain Description	Measure	Data Source
Reach	Degree to which target population is impacted.	1.Number of eligible patients. 2.% of patients who did not opt out. 3.% patients with 7-day gap 4.Representativeness of participants	Study database derived from EHR clinical and pharmacy data

<b>Effectiveness</b>	Success of the intervention to change outcomes.	1.Improvement in medication adherence (PDC) and reduction in utilization/clinical outcomes/costs	Study database
<b>Adoption</b>	Degree to which interventions are taken up by organizations.	1.Clinics approached and willingness to participate in the intervention	Study database
<b>Implementation</b>	Degree to which interventions are implemented as intended.	1. Among patients with gap, how many interventions were delivered per patient 2. Proportion reached and by method 3. Among patients in arm #4, Proportion where AI chat bot was used and the barrier identified 4. Barriers and facilitators to implementation 5. Budget impact/ Cost of the program and replication costs 6. Qualitative interviews 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.	1. Qualitative interviews 2. Study database
<b>Maintenance</b>	Can the program be sustained over time?	1. Identifying barriers to maintenance at the end of the study. 2. Intent to continue intervention following grant support 3. Can intervention be extended to other patient populations with different conditions	1. Post-implementation qualitative interviews 2. Study database

## Data Management

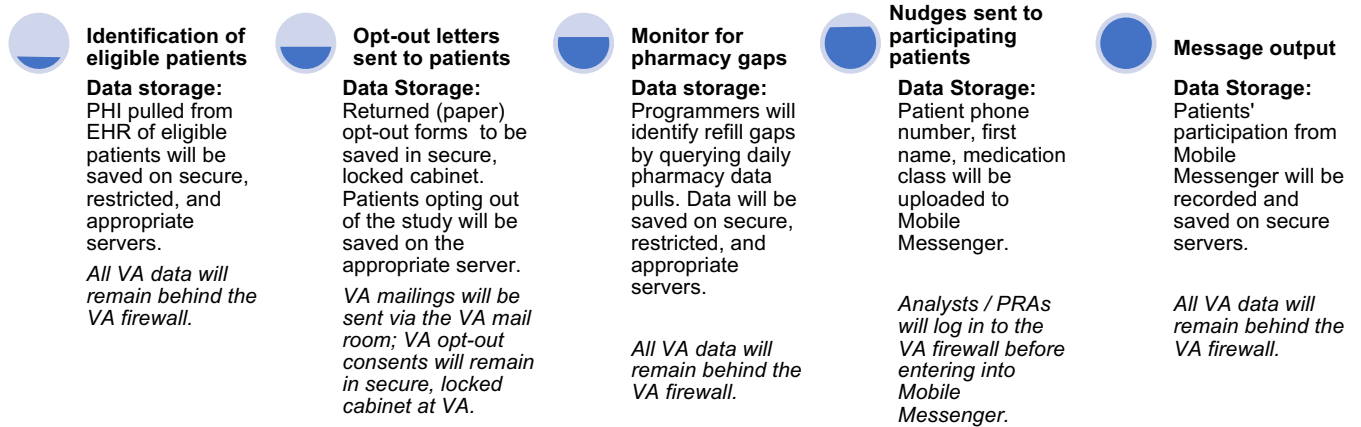
We will set up a distributed network across the 3 HCS and each HCS will manage their own data in the delivery of the study intervention. We will set up parallel processes so that each of the sites can monitor patients for gaps in medication refills and can deliver the intervention when needed. This will keep patient PHI within each of the HCS without the data leaving the HCS. We envision that this will be the process for other HCS that want to adopt the intervention if the intervention is demonstrated to be effective across the NIH Collaboratory sites.

At UCHealth and DH, pharmacy data is available for prescriptions filled within the HCS pharmacy as well as non-HCS pharmacy. Data for prescriptions filled at non-HCS pharmacy are automatically obtained at both UCHealth and DH as part of their routine clinical operations in the care of their patients through Surescripts. For example, we have all pharmacy data for UCHealth patients, which is derived from the following sources: ~15% from UCHealth pharmacy and ~85% from non-UCHealth pharmacy. Surescripts pharmacy data are available at the current time for Denver Health and will be estimated to become available in the Fall of 2019 for UCHealth.

## Data Movement

Programmers will upload data to the appropriate secure server in an appropriate format. All data will be kept separate from the data associated with the other affiliated healthcare systems. Data will be accessed by a centralized programmer from the Nudge Team via secure server to put into Mobile Messenger (**Figure 2**).

**Figure 2. Data Flow and Transfer for Proposed Trial**



## 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. In a previous study (COMIRB #18-0630), we developed a standing stakeholder panel. We will continue to convene the Stakeholder panel quarterly, as needed.

- **Participants:** The stakeholder panel consists of up to 5 people from each HCS: 1-2 of the following: patients, pharmacists, providers and persons involved in the leadership or operations of the health system from each HCS. Members previously recruited through relationships of the investigators will be welcome to join. New members will be identified through existing relationships / snowball recruiting.
- **Location:** The panel will meet in a central, secure location with ample free parking. Each member of the panel will be reimbursed \$50 per meeting.
- **Meeting content:** The Nudge study team will present the ongoing study progress to obtain feedback on the project, such as 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.
- **Payment:** Participants in the panel will receive \$50/meeting they attend, resulting in up to \$200 per year.

## Protection of Human Subjects

This research project involves human subjects recruited from three health care systems (HCS): 1) University of Colorado Health; 2) Denver VA Medical Center; 3) Denver Health and Hospital Authority. We will identify eligible patients from the 3 HCS using the electronic medical record system of each HCS. Patients must meet all of the following inclusion criteria to participate in the study: the presence of 1 or more of the following cardiovascular conditions (hypertension, hyperlipidemia, diabetes, coronary artery disease, and/or atrial fibrillation) and are prescribed 1 or more of the classes of medications to treat the cardiovascular conditions (b-blockers, calcium channel blockers (CCB), angiotensin converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARB), HMG-CoA reductase inhibitor (statins), thiazide diuretics, PGI-2

inhibitors (anti-platelets), direct oral anticoagulants, oral diabetes medications). These inclusion criteria are designed to identify a group of adults with suboptimal medication adherence who would benefit from the proposed intervention. Participants are not eligible if they meet any exclusion criterion: 1) patients who do not have either a landline nor cellphone; 2) enrolled in hospice or palliative care; 3) Non-English or Spanish speaking. We plan to enroll up to 100 subjects from each of the healthcare systems, resulting in enrollment of up to 300 patients total.

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. The goal of this study is to ensure that patients take their medications as prescribed.

Among patients who fulfil these eligibility criteria, we will send them a letter outlining the study and include an opt-out postcard. Within the opt-out packet will include an introductory letter, information about the study, the opt out form, and a self addressed, stamped envelope. The envelope will be directed to a PRA within the Data Science to Patient Value (D2V) initiative, who will remove the participant from the potential list, and save the consent in secure, locked cabinet, as noted in the IRB application. Should an opt-out package be returned, a D2V PRA will call the potential participant no more than 2 times to verify their address; should we not hear from the participant, we will not include them in the study.

For patients who do not return the letter after the proposed deadline, we will include them in the study. Additionally, we will engage our stakeholder panel in designing, refining, and implementing the intervention. Stakeholder participants have been previously consented via postcard consent.

### **Study subject identification**

Study subjects will be identified using electronic data. For the Stakeholder Panel, we will continue to involve our existing Stakeholder Panel in the study, and recruit through existing relationships and/or snowball recruitment techniques as needed.

We will request a waiver of documented consent from study subjects as this study is very low risk and could not be reasonably completed without such. As described previously, we will provide all potential participants with a packet of information about the study, an opt-out letter, and a self-addressed stamped envelope. The text messages will also allow for opting out by texting STOP (as described above).

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 always a slight risk of loss of confidentiality. 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.

Behavioral incentives (nudges) will be administered to the participants as a method to reinforce the treatment plan prescribed by physicians that patients have already received. The nudges themselves will not prescribe medicines nor introduce new instructions/treatments. However, there is some risk that patients will interpret the text message information that is 'tailored' to them has been approved by their physician or that a computerized system is foolproof.

### **Adequacy of Protection of Risk**

To mitigate the above risks, the text message nudges will contain a secondary opportunity for opt-out, and will contain pharmacy contact information, should the patient decide to discontinue their participation or want to contact the pharmacist with questions or need more information about the intervention or their prescribed medications. Contact information for those opting out of the study will be maintained in a separate file and deleted as soon as recruitment is complete. The opt out consent will also state that the text messages are not from their doctor.

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, separate for 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.

### **Nof1 Addendum proposal (1/24/21)**

#### **Interview overview**

Trained qualitative researchers will conduct Nof1 (one-on-one) qualitative interviews to assess the usability and preference of a proposed research study that is being built off of the existing

Nudge Study. Interviews will be held over Zoom (Sample questions are available in **Appendix I**; sample messages are demonstrated in **Appendix II**). Meetings should not exceed 60 minutes and patients will be reminded they can stop at any time. Patients will be notified that the Zoom meeting will be recorded.

### **Patient population**

We will purposively sample diverse patients from each setting to gain a balance of older and younger; male, female and non-gender conforming; Spanish and English speakers; and persons who identify as Latinx and/or Black proportional to their representation as patients at Denver Health. Patients must reside in the State of Colorado, speak English or Spanish, own a cell phone, and have the ability to participate in a virtual Zoom interview.

### **Recruitment methods**

Nudge Study PRAs will recruit patients from a Denver Health cardiovascular clinic under the direction of Site PI Pamela Peterson, MD, MSPH. PRAs will recruit an estimated 20 (no more than 30) patients with at least one cardiovascular condition and prescribed at least one medication to treat the condition of interest. Due to the Covid-19 January surge, PRAs will recruit patients that would otherwise be recruited in person via the phone to reduce Covid transmission.

### **Consent**

Patients will be read a verbal postcard consent for this study over the phone as minimal risk is introduced in these interviews; no deeply personal matters will be discussed.

### **Compensation**

Patients participating in interviews will be offered a gift card for an online store valued at \$50 for their participation.

## **Assessment of healthcare professionals and health system leaders perceptions addendum proposal (11/13/2023)**

### **Interview overview**

We will conduct one-on-one interviews with up to 6-8 healthcare professionals to explore their perception of discussing, and/or recommending patient-focused mobile health apps. Interviews will be held over Zoom (Sample questions are available Appendix II). Meetings should not exceed 60 minutes and healthcare professionals will be reminded they can stop at any time. Participants will be notified that the Zoom meeting will be recorded.

### **Patient population**

We will purposively sample eligible healthcare professionals such as – providers, pharmacists, health system leaders, nurses, and public health practitioners. Additionally, snowball sampling recruitment strategies will be applied for participant recruitment and selection as well. Participants must speak English and have the ability to participate in a Zoom interview.

### **Recruitment methods**

Researchers will recruit an estimated 10 (no more than 12) participants who have familiarity with the Nudge study or experience using mobile health applications at their workplace.

### **Consent**

Participants will be read a consent form for this study over the phone and the consent form will be sent the via email prior to the interview as minimal risk is introduced in these interviews.

1. Gurol-Urganci I, de Jongh T, Vodopivec-Jamsek V, Atun R, Car J. Mobile phone messaging reminders for attendance at healthcare appointments (Review). *Cochrane Database of Systematic Reviews*. 2013(12).
2. de Jongh T, Gurol-Urganci I, Vodopivec-Jamsek V, Car J, Atun R. Mobile phone messaging for facilitating self-management of long-term illnesses (Review). *Cochrane Database of Systematic Reviews*. 2012(12).
3. Vodopivec-Jamsek V, de Jongh T, Gurol-Urganci I, Atun R, Car J. Mobile phone messaging for preventive health care (Review). *Cochrane Database of Systematic Reviews*. 2012(12).
4. Head KJ, Noar SM, Iannarino NT, Harrington NG. Efficacy of text messaging-based interventions for health promotion: A meta-analysis. *Social Science & Medicine*. 2013;97:41-48.