Behavioral Economics to improve Antihypertensive Therapy Adherence (BETA)

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PROTOCOL SUMMARY

Purpose and Knowledge to be Gained	• The purpose the research is to determine the rates of undiagnosed and uncontrolled hypertension at a population level, as well as changes in clinical practice following the introduction of the new ACC/AHA Hypertension Guidelines, develop new metrics to assess blood pressure control and to test the validity and responsiveness of those metrics in a pilot study. • Results from this work will further our understanding of the size and characteristics of the undiagnosed and uncontrolled hypertensive population. Such information is vital to developing systems to adequately engage these individuals in care, the first step in controlling their disease. Further, understanding how long it takes for these individuals to be connected with an appropriate provider and have their hypertension controlled lays the framework for future work to help decrease delays and minimize variation. A pilot study will offer vital insight into the responsiveness of our newly created care measures and provide pilot data for a proposed larger study. • Additionally, a separate pilot study and interviews will provide important information regarding potential interventions to increase adherence to blood pressure medications. These findings will further our understanding of the types of interventions that can be best utilized in addressing uncontrolled hypertension.
Research Procedures	• The primary research procedures for Aims 1, 2 and 3A are a retrospective review of blood pressure levels for outpatients in the Cedars-Sinai system before and after the introduction of the new clinical guidelines. • Aim 3B is a pilot study to assess the use of home blood pressure monitoring linked to the electronic medical record. This is a prospective intervention of an already approved device, which is compatible with the Cedars-Sinai electronic medical record system and promoted on the Cedars-Sinai website. Study participants for this feasibility study will only include patients already under the care of the PI. • Aim 4A involves conducting interviews discussions to understand the feasibility and implementation of an intervention to increase medication adherence. Participants in the interviews will include current patients who are taking hypertension medications as well as clinic staff. • Aim 4B is a pilot study to evaluate the feasibility, acceptability, and efficacy of an intervention to increase medication adherence involving text message reminders and small incentives for adherence to pill-taking routines.
Subject Population	• For Aims 1-3: All patients seen at least twice in a 12-month period at any Cedars-Sinai outpatient facility • For Aim 4A: All patients with hypertension currently taking hypertension medication and clinic staff • For Aim 4B: All patients with hypertension taking hypertension medication

Duration	• For Aims 1, 2 and 3A, all data is retrospective, using already available data collected during routine care. The data to be utilized was collected as part of clinical care from 1/1/2012 through 3/30/2019. • For Aim 3B, prospective data collection will occur during a 9 week period, beginning at the time of patient enrollment. • For Aim 4A, interviews will last one hour on regular clinic days. • For Aim 4B, prospective data collection will occur during a 9 month period, beginning at the time of patient enrollment.

GENERAL INFORMATION

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1.0 BACKGROUND, RATIONALE

Routine ambulatory care visits with diverse clinical specialists represent critical missed opportunities to identify and treat patients with undiagnosed or under-treated hypertension. Hypertension is one of the most important cardiovascular risk factors in both its prevalence and the severity of its consequences.[1] Decades of laboratory and clinical studies have demonstrated a clear link between hypertension and devastating cardiovascular events including stroke, myocardial infarction and renal failure.[2-8] Despite the clear risk, half of hypertensive individuals have blood pressures that exceed current standards for control (<130/80), including nearly 20% of hypertensive individuals who have not yet been given a diagnosis.[1, 9] The high rates of undiagnosed and uncontrolled hypertension appear largely due to lack of recognition or insufficient action by clinicians and health systems, rather than lack of access to care: 82% of individuals with uncontrolled hypertension have a routine place of care and nearly two thirds had at least two ambulatory care visits in the past year.[10] Blood pressure is routinely documented during most ambulatory visits, even in specialty clinics like ophthalmology and orthopedics. Moreover, electronic medical record systems (EMRs) have been widely adopted in outpatient clinics,[11] and EMR data that is routinely recorded during clinical encounters can accurately identify patients with undiagnosed or uncontrolled hypertension.[12-16] This means that health systems already have the data and technical expertise needed to identify patients with undiagnosed and undertreated hypertension. However, few health systems leverage these resources, probably because the feasibility and benefits of doing so have not been demonstrated.

As such, our proposed research program will leverage the capabilities of the EMR to in the detection and treatment of uncontrolled hypertension. Via a future NHLBI-funded K23 Career Development Award, we will achieve two long-term goals. First, we will demonstrate how health systems can use the EMR for the surveillance and detection of undiagnosed and under-treated hypertension. Second, we will develop and test health system-based interventions aimed at reducing the time that hypertensive patients spend without a diagnosis, intensified treatment, or optimal control. We plan to use

the Cedars-Sinai Health System as a laboratory for this research, including both the Medical Delivery Network and the offices of private practitioners who use the Cedars-Sinai EMR.

Additionally, we will perform a pilot study to assess the feasibility of using the EMR to decrease delays in obtaining blood pressure control. Obtaining optimal blood pressure control has linked to a higher number of in-person clinic appointments.[17] With the expansion of wearable devices, the ability to track blood pressure outside of the clinical setting has increased, creating the potential to eliminate this barrier.[18, 19] Cedars-Sinai allows for clinical data, including blood pressure, to be uploaded directly to the medical record, making this information instantly visible and actionable for providers. We will conduct a pilot study using EMR linked remote blood pressure monitoring devices, in conjunction with clinical pharmacist interventions to assess for a decrease in the time to blood pressure control.

Finally, we will perform an additional pilot study to assess feasibility, acceptability, and preliminary efficacy of daily text messages and incentives to support hypertension medication adherence. Medication non-adherence contributes to suboptimal blood pressure control and increased cardiovascular risk over time.[20, 21] Routines determine over 40% of all behavior and supporting their formation may offer an effective, low-cost and novel way to increase hypertension adherence. One successful routinization intervention is to anchor, or pair, a new behavior to an existing routine, such as brushing teeth or eating breakfast.[22-24] However, existing routinization interventions typically target participants with high intrinsic motivation.[25-29] Behavioral economics (BE) suggests that small rewards and reminders can support routinization for all patients, including those with low motivation.[30-32] We will conduct a pilot randomized controlled trial (RCT) using daily text messages and small incentives to evaluate potential improvements in medication adherence, and will conduct interview discussions to determine feasibility and acceptability of these incentives.

2.0 STUDY OBJECTIVES

The objective of the currently proposed study is to provide pilot data for this longer-term research program. In preparation for this K23 application, we must achieve the following aims.

***Aim 1: Determine the cross-sectional prevalence of undiagnosed and uncontrolled hypertension within the Cedars-Sinai Health System, as well as the patient, physician, and clinic characteristics associated with these outcomes*.** This will document the presence and extent of problems at this institution and reveal which populations and settings are most affected, providing insights that can be used to develop and implement future interventions.

Aim 2: Develop and pilot test new time-to-care and time-to-control measures. These measures will evaluate (1) how long it takes from when evidence exists in the EMR that patients meet criteria for hypertension before clinicians document a diagnosis and initiate treatment, (2) how long evidence exists that control is suboptimal before clinicians intensify treatment, and (3) how long each of these conditions exists before goal blood pressures are achieved. We plan to use these new measures in our future work because we expect them to be more responsive to changes in care than cross-sectional measures of control would be, and because they include both care processes (i.e., did clinicians do the right things) and outcomes (i.e., were clinical goals achieved), making it possible to distinguish whether suboptimal control is due lack of recognition, lack of action (e.g., clinical inertia), or insufficient action (e.g., suboptimal adjustment of antihypertensive medications).

Aims 3A and 3B: Aim 3A – Assess the validity, responsiveness, and potential utility of the new time-to-care and time-to-control measures. To assess validity, we can examine whether performance on the new measures is associated with performance on cross-sectional measures of blood pressure control. To assess responsiveness and potential utility, we can examine how performance changes with clinical practice. For example, the introduction of the 2017 ACC/AHA guidelines represented a marked change in the standard of care for hypertension in terms of criteria for diagnosis and blood pressure goals. If the

prevalence of undiagnosed and uncontrolled hypertension at Cedars-Sinai is high, slow uptake of these new standards may be one explanation. However, another potential explanation is the much greater level of effort needed to attain the lower blood pressure goals. If clinicians are recognizing uncontrolled hypertension and initiating or intensifying treatment, we would expect the time-to-care measures to exhibit stable performance after 2017 while performance on the time-to-control measures and cross-sectional control rates would decline.

We will also examine how performance on the time-to-care and time-to-control measures varies based on the setting in which blood pressure is measured. If we find that that performance on these time-to-care and time-to-control measures as well as control rates are better in Primary Care, Internal Medicine, Nephrology, or Cardiology clinics than in other specialty and subspecialty clinics, this would suggest the EMR may be a useful for the screening and detection of patient populations that would benefit from efforts to make a diagnosis and initiate or intensify treatment.

Aim 3B – We will perform a pilot study of the new time-to-control measure's responsiveness to more intensive blood pressure monitoring and intervention. This pilot will provide a subset of uncontrolled hypertensive patients with home blood pressure monitors linked to the EMR at Cedars-Sinai. This information will be monitored and acted upon weekly, allowing for a more rapid titration of medical therapy. A decrease in the time-to-control measure of blood pressure management would be a preliminary finding consistent with measure responsiveness.

Aims 4A and 4B: Aim 4A – We will conduct interview discussions to explore feasibility and acceptability of text message reminder and incentives for blood pressure medication adherence. These interview discussions will involve both patients and providers and will allow for a better understanding of existing routine behaviors that support pill-taking, appropriate messaging for text message reminders, and how to best implement the intervention.

Aim 4B – We will perform a pilot study to measure the feasibility, acceptability, and efficacy of interventions designed to increase blood pressure medication adherence. This pilot RCT will include a subset of uncontrolled hypertensive patients who will receive daily text messages and/or a small incentive related to blood pressure medication adherence, depending on the intervention group, with MEMS-cap devices to allow for automated electronic assessment of patient medication use. A subgroup of participants will document their experience with taking medication using a secure video platform.

3.0 STUDY POPULATION

3.1 SELECTION OF THE STUDY POPULATION

1. For Aims 1, 2 and 3A, data for patients will be obtained from the Cedars-Sinai electronic medical record.
2. For Aim 3B, a sample of 10 patients seen in the Hypertension Center or Women's Heart Center clinic, who meet the pre-defined criteria for uncontrolled hypertension at the time of data procurement, will be selected.
3. For Aim 4A, a sample of 20 patients seen in the Hypertension Center or Women's Heart Center as well as 7 medical providers will be selected to inclusion in interview discussions.
4. For Aim 4B, a sample of 60 patients hypertensive patients taking antihypertension medications will be selected.

3.2 INCLUSION CRITERIA

1. Patients seen at any Cedars-Sinai outpatient clinical (including OB/GYN) from 1/1/2012 thought 3/30/2019.
2. Age >18 years at any time during the study period
3. Patients with blood pressure recordings in the EMR

4. At least 2 outpatient clinic visits in a 12-month period
5. Additional inclusion criteria for Aim 3B only:
   -Patients must be seen in the Hypertension Center
   -Patients must have a smartphone compatible with My CSLink, the Cedars-Sinai mobile health application (any smartphone running iOS or Android operating software)
6. Additional inclusion criteria for Aim 4A only:
   -Patients must be currently prescribed hypertension medication.
   -Providers and clinic stuff must have been employed at clinic for 12 months.
7. Additional inclusion criteria for Aim 4B only:
   -Patients must be initiating or already taking antihypertension medication.

3.3 EXCLUSION CRITERIA

1. Patients only seen in inpatient, surgical, Emergency Department or Urgent Care settings
2. Patients with no blood pressure recordings in the EMR
3. Extra exclusion criteria for Aim 3B only:
   -Patient unwilling to sign up for My CSLink mobile health application
   -Inability to use a home blood pressure cuff
   -Patients only seen in OB/GYN settings
4. Additional exclusion criteria for Aim 4B only:
   -Patients not mentally fit to understand consenting procedures or do not own a cell phone

3.4 SUBJECT SCREENING AND ENROLLMENT

Subject screening applies only to Aim 3B, Aim 4A, and Aim 4B.

Aim 3B:

a. Patients to be included in Aim 3B will be identified by physicians in the Hypertension Center, as part of his clinic panel.
b. Eligible patients must have diagnosed hypertension but are not yet controlled (SBP<130 and DBP<80). Patients may already be on medications for hypertension.

Aim 4A:

a. The research coordinator will monitor the clinic schedule for potentially eligible patients. The nurse manager of the clinic will be notified of the offer for physicians and nurses in the clinic to participate in interviews. Recruitment will occur for staff via institutional email.
b. Eligible patients must currently be on hypertensive medication. Eligible staff must have been employed at the clinic for 12 months.

Aim 4B:

a. The research coordinator will monitor the clinic schedule for potentially eligible patients together with clinic providers and staff. We will consent and enroll 1-2 patients/day during the 3-month recruitment period.
b. Eligible patients must have hypertension and be initiating or already taking antihypertension medication.

3.5 SUBJECT RECRUITMENT

Subject recruitment applies only to Aim 3B, Aim 4A, and Aim 4B.

Aim 3B:

1. The Hypertension Center physicians will identify patients in his clinic who meet criteria for uncontrolled hypertension.
2. If the patient is agreeable, the clinical pharmacist will be contacted to complete enrollment. Enrollment will be completed during the same clinic visit at which the patient was identified, above. Informed consent will be obtained at that time. Further details of the enrollment process are detailed in Section 4.0, under 'Intervention.'

Aim 4A:

1. The research coordinator will identify patients with hypertension that meet inclusion criteria via the clinic schedule. Clinic staff, including physicians and nurses, will be contacted via institutional email to offer participation in interviews. All emails will be internal and not used for contacting patients.
2. If the patient is agreeable, the research coordinator or physician will be contacted to complete enrollment. Enrollment will be completed during the same clinic visit at which the patient was identified, above. Informed consent will be obtained at that time.

Aim 4B:

1. The research coordinator will identify patients with hypertension initiating hypertension treatment via the clinic schedule.
2. All patients will receive written consent materials explaining the purpose and contents of the study. All interview members will also receive written consent materials explaining the purpose and contents of the study. We will explain clearly that participation in a specific intervention group is not a choice but based on random assignment (the Human Subjects Protection document elaborates on IRB-related issues). We will show all potential participants the MEMS device and explain its purpose. Each will receive $50 USD for participation in each study assessment (baseline, month 1, month 2, month 3 and month 9).
3. Participants who are randomized into the incentive cohort and comply to greater than 80% medication adherence will be eligible to participate in a drawing every month for the first three months of intervention. The drawing will include a prize of either $0, $25, or $50.
4. All participants will receive a parking validation.

Participants who are not consented during the clinic visit will have the option to telephone consent or to receive a unique link to an electronic REDCap consent form that then leads to a standardized REDCap e-Questionnaire (which will be administered electronically for the majority of participants but also accessible via mailed hard copy or telephone administration for participants with limited electronic access and/or expressed preference for a non-digital format).

4.0 STUDY DESIGN AND METHODS

Achieving these objectives and aims will involve an analysis of existing data from ambulatory care visits at clinics affiliated with Cedars-Sinai Medical Center from January 1, 2014 through March 30, 2019. Via a detailed study protocol, we will establish patient eligibility criteria, specify study variables and measures for extraction from the EMR, and specify descriptive and multivariate regression analyses

related to Aims 1-3. An Advisory Board consisting of local and national experts in EMR systems, population health, hypertension, and the implementation of quality improvement interventions will provide guidance and feedback on the protocol and after we have obtained preliminary data.

Patients will need to have at least two years of data available in CS-Link to be included in the study (defined as two or more clinic visits at least two years apart and occurring within the study dates). We will include ambulatory care visits with faculty, medical delivery network, and private physicians in all specialties if they use CS-Link. We will exclude care in the emergency department, urgent care, and hospital settings because blood pressure may be temporarily elevated due to acute illness. For eligible visits, we will obtain the recorded blood pressure values, whether the blood pressure was assessed manually or automatically (if available), and the physician identity (coded).

We will define blood pressure control based on the 2017 ACC/AHA guidelines (blood pressure <130/80). In sensitivity analyses, we will also consider control based on the JNC-7 guidelines (blood pressure <140/90), due to the recent change in the standard of care.

We will create three time-to-care measures: time-to-diagnosis, for patients who qualify for new diagnoses; time-to-initiate, for the same patients; and time-to-intensify, for patients with established diagnoses. We will create two time-to-control measures, one for patients with new and one for patients with established diagnoses. The new time-to-care and time-to-control measures will be based on the 2017 ACC/AHA guidelines. We will define undiagnosed hypertension as two ambulatory blood pressures >= 130/80 without an ICD-9/10 code for hypertension in the preceding year; uncontrolled hypertension will be defined using the same blood pressure criterion but patients will have an ICD-9/10 code for hypertension. A new diagnosis of hypertension will be defined as an ICD-9/10 code for hypertension without a prior code or antihypertensive medication use in the preceding year. We will define treatment initiation as the first prescription for an antihypertensive medication following a new diagnosis of hypertension. Treatment intensification will represent the addition of another antihypertensive medication, an increase in the dose of an existing antihypertensive medication, and a change from one antihypertensive medication to another. We will access the 2017 guidelines and other standard sources to develop a list of antihypertensive medications. Time to care will be calculated as the number of days from the last blood pressure above goal to the documentation of the diagnosis or the initiation/intensification of treatment. Time to control will be calculated as the number of days from the last blood pressure above goal to the first blood pressure at goal.

From the EMR, we will extract the following patient characteristics to use in descriptive analyses and for adjustment in multivariate models: age (all subjects over age 89 will be grouped into one category titled ">89"), gender, self-reported race/ethnicity, zip code, primary and secondary healthcare payer, comorbidities associated with or exacerbated by hypertension (diabetes, chronic kidney disease, atherosclerotic heart disease, stroke, heart failure, etc.). We will also extract the following clinic and physician characteristics for each visit by an eligible patient during the study period: physician identity (coded), clinical specialty (e.g., internal medicine, cardiology, orthopedics), zip code, affiliation (faculty, medical delivery network, private practice), number of ambulatory care visits per year documented in CS-Link (a measure of clinical volume).

As a test of the responsiveness of the new time-to-control measure, we will perform a pilot study of the use of home blood pressure monitoring linked to the Cedars-Sinai EMR. The pilot would include 10 randomly selected uncontrolled hypertensive patients identified in Aim 1 and provide them with a CSLink compatible home BP cuff (Withings BPM) and training on how to link the device to their medical record. **The home blood pressures readings will be reviewed weekly for each patient by a clinical pharmacist (already part of the Smidt Heart Institute and Hypertension Center of Excellence care team) who will titrate blood pressure medications, in accordance with published guidelines, over the phone with the patients, under the supervision of a clinical cardiologist (JE). Enrolled patients will already be under the care of the supervising clinician. The clinical pharmacist already sees and**

manages patients as part of the Hypertension Center of Excellence. As such, these steps represent continuation of already provided care. Monitoring of home BP measurements will occur for a total of 8 weeks from enrollment. We hypothesize that patients in the study will achieve a shorter time-to-control measure than the overall population, as measured in Aim 3.

Aim 3B Pilot Study Intervention (Only applies to Aim 3B):

1. Subject identification and recruitment will be completed as described in Sections 3.4-3.5.
2. Each of the 10 enrolled subjects will be evaluated in-person at the time of identification by the PI in clinic
    - At this visit, the patient will complete informed consent (Supplement 1). Informed consent will be obtained by the clinical pharmacist.
    - If consent to participate is given, the clinical pharmacist will confirm that the patient is enrolled in the My CSLink mobile application. If they are not, they will complete the signup during the visit.
    - Next, the patient will be provided with a home blood pressure cuff and instructed in its use. The device will be linked to the patient's medical record at this visit, via their smartphone and the My CSLink application. A test blood pressure will be performed in the room and upload of this information into the patient's record confirmed by the clinical pharmacist.
    - The patient will be educated on proper checking of home blood pressure, as described in the 2017 ACC/AHA Guidelines (Supplement 2).
    - The patient will be instructed to check their blood pressure and upload it once daily.
    - To assist with compliance, the patient will be provided with an informational document outlining the appropriate method to check blood pressure and reminding them of how to upload their measurement each day (Supplement 3).
3. The clinical pharmacist will ensure complete documentation of the following at time of enrollment: history and physical, review of past medical history, allergies, current medications, vitals and prior testing. If information is missing, the treating physician (JE) will be informed and return to complete this documentation.
4. One week after the initial visit, the clinical pharmacist will review the patient's uploaded data, as well as medical record for any new events that could alter blood pressure measurements or therapy. Following this, the clinical pharmacist will contact the patient by phone to review the readings.
5. If the patient has missed $\geqslant$3 days in a 1-week period, the clinical pharmacist will ask the patient about barriers to completing data collection/upload. Specific identified problems will be directed to the PI.
6. Based on patient blood pressure readings and in concordance with the 2017 ACC/AHA Guidelines, the clinical pharmacist will titrate blood pressure medications, as clinically indicated. The clinical pharmacist may order, review and act upon laboratory testing, as indicated. These processes will be done under the supervision of a cardiologist (JE).
7. Steps 5-7 will be continued for a total 8 weeks (ending 9 weeks after the in-person appointment). At that time, the clinical pharmacist will remind the patient at the end of their final phone call that they will no longer be reviewing their blood pressure or titrating their medications.
8. If at any time during the study, a patient's blood pressure is considered out of range (SBP<90 and patient symptomatic; DBP<40 and patient symptomatic; SBP>190 or DBP>115, regardless of symptoms), if the patient develops symptoms consistent with either significant hypotension or hypertension, has critical lab values (Na<125 or >150, K<3.0 or >5.5) or has any other concerning clinical finding, they will be instructed to seek care at the nearest Emergency Department.

Schedule of Procedures

Activity	In-Person Visit	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8
Medical History/Exam	X								
Phone Call to Patient		X	X	X	X	X	X	X	X
Medication Titration	†	†	†	†	†	†	†	†	†
Laboratory Testing	†	†	†	†	†	†	†	†	†
Discharge from Study									X

X = Completed † = Completed, as clinically indicated

Specific Protocols for Aims 4A and 4B Only:

We will also conduct interview discussions and a pilot RCT study of the use of text messaging and incentives to increase blood pressure medication adherence. Interview discussions will include 20 randomly selected patients currently taking hypertension medication and 7 clinic staff who have been employed for at least 12 months. We will conduct eight 1-hour interviews with patients recruited on a regular clinic day and one interview with providers & clinic staff to inform the intervention content (total of 27 participants). Open-ended questions will be asked before more closed-ended, probing questions so as not to bias responses and allow for exploring new leads and related topics, and to generate rich narratives. Answers to such questions will indicate the areas most important to respondents—which may, or may not, conform to our expectations. Standard probes, such as verification and compare and contrast questions, will be used. Based on the standards set by the CSMC IRB, all patients will receive $30, while the providers and clinic staff will not receive payment. Findings from the interview discussion will be used to inform the pilot study intervention in Aim 4B.

The pilot RCT study would include 60 randomly selected hypertensive patients on hypertension treatment who may receive text message reminder and/or incentives, depending on the treatment group to which they are randomly assigned. Participants will be randomly assigned to one of three treatment groups: the control group (receives care as usual plus information on importance of establishing pill-taking routines), the message group (receives daily text messages for 3 months reinforcing information on importance of establishing pill-taking routines), or the incentive group (in addition to the same daily text messages as the message group, has a chance of winning small, intermittent rewards for taking medication in accordance with established pill-taking routine). The intervention period will last for 3 months and data monitoring will occur for an additional 6 months post-intervention totaling 9 months. Participants randomized into the incentive cohort will be eligible for a drawing only if they achieve greater than 80% medication adherence. The drawing will take place once a month for the first three months of participation with a chance to receive $0, $25, or $50. Outcome measures include electronically measured medication adherence, hypertension control, adherence to established pill-taking routine, and feasibility and acceptability of intervention. We hypothesize that patients in the message and incentive groups will have higher medication adherence and hypertension control compared to the control group, and that patient in the incentive group will show greater adherence to established their pill-taking routine compared to the message and control groups.

Among participants in Aim 4B, 30 (10 from each group) will be selected to provide real-time feedback on their experiences with medication and medication taking. We will seek to enroll the first 10 participants from each group. Participants will document their experiences in real-time using a secure video platform (Medallia LivingLens). Participants may decline to participate in real-time feedback and remain in study. The submitted video diaries will be used to evaluate the feasibility, acceptability, and efficacy of interventions. In-the-moment qualitative data from participants can enhance our understanding of why trials succeed or fail, but are challenging to gather. Geography, language barriers, time constraints, and participant literacy can undermine such efforts. Instant video recordings can address this: they are immediate, and also tend to be frank and comprehensive. In recording their real-time opinions, research participants are unfettered by the need to type out their experiences - a more time consuming and (for many) difficult way to record their immediate reaction to events. To address this, we will collect in-the-moment video data from participants about their daily experience with taking medication. Diaries can focus on any aspect of their experience with the trial, including success stories or reasons for failing to take medication. The video content will provide crucial data about participants' body language, emotional state, and practical aspects of their life, such as how their home environment factors into their adherence. This will help us understand why such interventions succeed or fail.

5.0 DATA COLLECTION AND MANAGEMENT

5.1 DATA PROCUREMENT

- For Aims 1, 2 and 3A, Drs. Ebinger, Cheng and Nuckols will seek to obtain the data in Tables 1 and 2 (below) from the EMR with the assistance of the Research and Informatics Scientific Computing Core (RISCC)
- For Aim 3B, data will be collected by the clinical pharmacist directly from each patient's medical chart
- For Aim 4A, interview data will be digitally recorded during each session. Interviews will be conducted by a PhD researcher from RAND, specifically trained in qualitative research.
- For Aim 4B, medication adherence data will be collected electronically through the MEMS-cap device. Additional data will be collected via survey instruments administered by study staff during clinic visits.
    - Video Diary Sub-Study for Aim 4B: During the first 3 weeks, we will prompt participants once a week to submit video diaries, although they will be encouraged to submit whenever they want to share or document something. The video diary prompts will be combined with (preceded by) 1-2 survey questions asking participants to quantify their level of satisfaction with the intervention overall or specific intervention components. Prompts and video diaries will be sent and documented using Medallia LivingLens, a secure platform designed to document remote video recordings for qualitative research. Participants will download the Medallia LivingLens application to their smart phone, which will be used to record their video diaries. Storage and security details of video diaries are located in section 5.5.
    - For all aims, data will be collected via EHR or REDCap based questionnaires. All captured data will be housed in a HIPAA-compliant secure storage system, such as REDCap or Box, within the Cedars-Sinai network with access restricted to only approved members of the research team.

5.2 TIME PERIOD OF DATA UNDER REVIEW

- Data will be reviewed from between the dates 1/1/2012 through 3/30/2019. For patients enrolled in the pilot study described in Aim 3B, data will be collected during the 9 week period of their participation.

- Data for Aims 1, 2 and 3A will be collected retrospectively. For Aim 3B, data will be collected weekly starting on the date of their in-person appointment and will be collected prospectively during the 9 week period of monitoring for each patient, estimated between the months of June and November, 2019. For Aim 4A, data we be collected during the interview discussions. For Aim 4B, data will be once per month during clinic visits for the first 3 months, and then every 3 months until 9 months after enrollment.
- Information will be kept for a total of 2 years following the initiation of the study.

5.3 VARIABLES COLLECTED

- For Aims 1, 2 and 3A, please refer to Tables 1, 2, and 3 for variables that will be collected.
- For Aim 4B, please refer to Table 4 for variables that will be collected.

5.4 SOURCE DOCUMENTS

- For Aims 1, 2 and 3A, we seek to obtain the data in Tables 1 and 2 from the EMR with the assistance of the Research and Informatics Scientific Computing Core (RISCC)
  -Table 1 contains patient level data to be obtained at the visit level
  -Table 2 contains medications to be obtained at the patient level for each visit. Data is to include if the medication has been prescribed and if so, at what dose and frequency. The prescribing provider and providers specialty will also be acquired.
  -Zip Code will be used to estimate population level sociodemographic factors from census data
- For Aim 3B, patient medical records will be the source document for the information identified in Tables 1 and 2, as well as information outlined in Table 3
- For Aim 4B, survey instruments will be the source document for the variables outlined in Table 4. Video diaries will be obtained and stored, as detailed in section 5.5.

Table 1 (Data collected for all aims)

Blood Pressure readings at each outpatient clinic visit
Provider Name at each visit
Provider Specialty at each visit
Provider demographic
ICD-9/ICD-10 codes
Dates of each clinic visit
Patient insurance information
Patient date of birth
Patient ZIP Code
Patient age
Patient gender
Patient ethnicity
Patient BMI at each visit
Primary Care Physician Name and Practice Location
Patient glomerular filtration rate at each clinic visit
Highest A1C level during study period

Table 2 (Data collected for all aims)

ACE-Inhibitors/Angiotensin Receptor Blockers	Beta-Blockers	Diuretics	Calcium Channel Blockers	Nitrates	Other
Lisinopril	Metoprolol	Hydrochlorothiazide	Amlodipine	Imdur	Hydralazine
Benazepril	Bisporolol	Chlorthalidone	Diltiazem	Isordil	Clonidine

Captopril	Carvedilol	Metolazone	Verapamil		Aliskiren
Enalapril	Propranolol	Lasix	Felodipine		
Fosinopril	Nadolol		Isradipine		
Ramipril	Atenolol		Nifedipine		
Perinodopril	Labetalol				
Losartan	Nebivolol				
Valsartan					
Candesartan					
Irbesartan					
Telmisartan					
Azilsartan					
Eprosartan					
Olmesartan					

Table 3 (Data collected for Aim 3B only)

Initial Visit (Week 0)	Baseline blood pressure
	Current medications (names, doses and frequencies)
	Laboratory values (basic metabolic panel, TSH and A1C)
Weekly Phone Call (Weeks 1-8)	Record all uploaded blood pressures in the EMR
	New/updated laboratory values
	Current medications (names, doses and frequencies)
	Changes to medications (names, doses and frequencies)
	Patient reason for missing or absent blood pressure data, if applicable

*Note, baseline demographic factors for patients enrolled in Aim 3B will already have been collected as part of Aim 1.

Table 4 (Data collected for Aim 4B only)

Survey measures (initial visit, month 3 visit, month 9 visit)	Behavior economic measurements (biases, behavioral automaticity, intrinsic motivation measures)
	Demographic and socioeconomic data (age, gender, education, employment, insurance type, income, marital status and housing)
	Medical factors (baseline blood pressure, number of non-antihypertensive medications on at baseline, final number of antihypertensive medications at the end of the study and history of cardiovascular disease)
	Physical symptoms/side effects of medications
	Structural barriers to medication adherence (insurance status, patient distance to pharmacy)
MEMS-cap electronic data (automatically captured)	Date of bottle opening (for hypertensive medication)
	Time of bottle opening (for hypertensive medication)

5.5 DATA COLLECTION AND STORAGE

- The data for Aims 1, 2 and 3A will be abstracted from the EMR with the assistance of RISCC and stored in a CSMC supported Box file, accessible only to the study investigators

- Data for Aim 3B will be abstracted from the medical chart of each patient. Data will be recorded in an Excel file and stored in a CSMC supported Box file, accessible only to the study investigators
- Data for Aim 4A will be obtained via digital audio recording from interview discussions and will be stored in a CSMS supported Box file, accessible only to the study investigators
- Data for Aim 4B will be obtained via survey instruments and MEMS-cap devices. Data will be recorded in an Excel file and stored in a CSMS supported Box file, accessible only to the study investigators
- Identifying information will be kept for no longer than 2 years from study initiation.
- Identifiers will be stored in a separate file. A non-identifying code will be tagged to each patient and will serve as a 'key' to link identifying data. This key will only be available to the study investigators.
- Prompts and video diaries will be sent and documented using Medallia LivingLens, a secure platform designed to document remote video recordings for qualitative research. Participants will download the Medallia LivingLens application to their smart phone, which will be used to record their video diaries. Videos are then securely sent for review by the research team. All content is captured and stored in a secure Amazon S3 environment. All data at rest is AES-256 encrypted and encrypted in transit with HTTPS. All files in S3 are encrypted as well as all records/documents stored in databases and search indices. All communication to and from the data center is protected via SSL. API Authorization is protected by OAuth. SAML and OAuth are used for SSO integration. Data is backed up and fully redundant to ensure availability of our systems both real time and in the event of failure. Videos are stored with AWS. AWS has been audited and certified against the most stringent attestation standards and enables compliance with regulatory privacy requirements such as GDPR. AWS has been audited on the following standards: SOC 1/SSAE, 16/ISAE 3402 (formerly SAS 70), SOC 2, SOC 3, FISMA, DIACAP, and FedRAMP, PCI DSS Level 1, ISO 9001 / ISO 27001, ITAR, FIPS 140-2, MTCS Level 3.

5.6 CONFIDENTIALITY AND SECURITY OF DATA

- All data will be stored in a CSMC supported Box file.

6.0 DATA AND SAFETY MONITORING

6.1 DATA AND SAFETY MONITORING PLAN

- For Aims 1, 2 and 3A, as all data has already been collected as part of routine clinical care, there is no data safety monitoring plan for these aspects of the study.
- For Aim 3B, all clinical data for each patient will be reviewed by the patients' Cardiologist weekly following the phone visit performed by the clinical pharmacist. This process will specifically review:
    - Laboratory values
    - Blood pressure measurements
    - Adverse events reported to the clinical pharmacist
    - Indications for changes to medical therapy
- Adverse events will be handled by the patients' treating physician (JE)
- To ensure data integrity, a data analyst (PB) will review the charts of each of the 10 patients weekly and confirm the data points outlined in Table 3 have been correctly identified and recorded by the clinical pharmacist during their phone visit with the patient. Discrepancies will be brought to the attention of the PI.
- The independent cardiologist will record his/her activities and findings weekly in a report filed with the PI, which will be made available to the IRB at the end of the study period, or at anytime upon request.
- Describe the methods to be used to document the data monitoring activity.
- For Aim 4B

- A safety monitoring committee will be established for this study. This committee will consist of at least 2 experts with experience in conducting patient-oriented and physiology studies, and/or clinical trials focused on cardiovascular disease. The Clinical Endpoint Committee (CEC) members will include Dr. Susan Cheng, MD, MPH (Chair, CEC), Dr. Rose Tompkins, MD, and Dr. Janet Wei, MD. The mPIs will meet with the CEC as frequently as every month, and no less than every 3 months, to present study progress, protocol deviations, adverse events, and other participant related issues. The CEC will review each item or incident and conduct blinded adjudication according to pre-established protocols for end-point adjudication. For each adjudication, the CEC will reach a consensus agreement and then will provide the mPIs with a consensus recommendation on whether to continue the protocol and how to report each result to the institutional human and research ethics committee (IRB). A report will be generated following each meeting and the mPIs will submit this report to the IRB for review. The mPIs will be responsible for submitting all adverse events and protocol deviations to the IRB for review.

6.2 QUALITY CONTROL AND QUALITY ASSURANCE

- To ensure data integrity, a data analyst (PB) will review the charts of each of the 10 patients weekly and confirm the data points outlined in Table 3 have been correctly identified and recorded by the clinical pharmacist during their phone visit with the patient. Discrepancies will be brought to the attention of the PI.
- The data analyst will record his/her activities and findings weekly in a report filed with the PI, which will be made available to the IRB at the end of the study period, or at anytime upon request.

7.0 STATISTICAL CONSIDERATIONS

7.1 STUDY OUTCOME MEASURES

Analyses will test the following pre-specified hypotheses for each goal:

Aim	Hypotheses
1: Determine cross-sectional prevalence of undiagnosed and uncontrolled hypertension at CSMC, as well as the patient, physician, and clinic characteristics associated with these outcomes.	1) Cross-sectional rates of undiagnosed and uncontrolled hypertension at CSMC, based on the 2017 AA/AHA Guidelines, will be similar to national rates (20% and 50%, respectively). 2) Cross-sectional rates of undiagnosed and uncontrolled hypertension will be higher under the 2017 ACC/AHA Guidelines than the JNC-7 Guidelines. 3) Rates of undiagnosed and uncontrolled hypertension will be lower among patients with visits in Primary Care, Internal Medicine, Nephrology, or Cardiology clinics than for patients who only receive care in other clinics.
2: Develop and pilot test new time-to-care and time-to-control measures.	1) Data already collected in the EMR can be used to calculate these five new measures of hypertension care.
3A: Assess the validity, responsiveness, and potential utility of the new time-to-care and time-to-control measures.	1) Performance on the time-to-care and time-to-control measures will be associated with cross-sectional control rates at the clinic and physician level. 2) Following release of the 2017 ACC/AHA Hypertension Guidelines, performance on the time-to-control measures and cross-sectional control rates will worsen while performance on time-to-care measures will remain stable. 3) Performance on the time-to-care and time-to-control measures will be better for patients with visits in Primary Care, Internal Medicine, Nephrology, and Cardiology clinics than for patients who only receive care in other clinics.
Aim 3B: Pilot study of the new time-to-control measure's responsiveness to more intensive blood pressure monitoring and intervention	1) Use of home blood pressure monitors linked the EMR will allow for weekly intervention by a clinical pharmacist, with titration of antihypertensive therapy, according the to 2017 ACC/AHA Hypertension Guidelines 2) The time-to-control period with will be shorter for those enrolled in the pilot study than those in the general population, not provided with home monitoring and weekly clinical pharmacist intervention
Aim 4A: Interview discussions to explore feasibility and acceptability intervention to increase blood pressure medication adherence	1) This is an exploratory aim, designed to inform Aim 4B. No a prior hypothesis.
Aim 4B: pilot study to measure the feasibility, acceptability, and efficacy of interventions designed to increase blood pressure medication adherence	1) Medication adherence and hypertension control will be greater among treatment groups compared to control group 2) Patients in the incentive group will demonstrate greater routinization compared to both the control group and the message group

For Aim 1, we will use these data to conduct descriptive analyses of rates of blood pressure control among patients with ambulatory care visits at Cedars-Sinai. Next, we will conduct multivariate regression models using blood pressure control as the outcome variable and various patient, physician and clinic characteristics as the independent variables. We will examine how results differ between the 2017 and JNC-7 guidelines.

For Aim 2, we will apply the new time-to-care measures and time-to-control measures to the same dataset. This will involve an iterative process of refinements as we discover issues that warrant the exclusion of certain blood pressure measurements, types of visits, or patient populations. The result will

be both refined measures and descriptive data on the time-to-care and time-to-control for both undiagnosed and uncontrolled hypertension.

For Aim 3A, we will conduct unadjusted and then adjusted multivariate regression analyses assessing whether time-to-care and time-to-control measures are predictors of (i.e., associated with) blood pressure control rates at the physician level. We will perform these analyses at the physician and clinic levels because time-to-control rates are tautologically associated with the presence of control, and because many types of future quality improvement interventions would likely target individual physicians and clinics. We will compare performance on these measures and control rates between patients with visits in Primary Care, Internal Medicine, Nephrology, and Cardiology clinics than for patients who only receive care in other specialty and subspecialty clinics.

Next, we will perform interrupted time-series analyses of changes in the three hypertension measures after 2017 using multivariate regression models. These analyses will examine each hypertension measure (time-to-care, time-to-control, and control rates) as the dependent variable, using the quarter year as the independent variable. We will examine whether there is a change in intercept or slope during any quarter following the announcement of the ACC/AHA guidelines in 2017. We will then qualitatively compare such changes across the three outcome measures, to assess whether time-to-care is more responsive, as expected.

For Aim 3B, we will conduct unadjusted and then adjusted multivariate regression analyses assessing whether time-to-control measure was different between those enrolled in the pilot study and patients in the non-intervention group.

For Aim 4A, two independent coders will develop a codebook that details the inclusion and exclusion criteria, as well as typical exemplars for each topic or theme. Together, the coders will work to establish inter-coder reliability (evidenced by Cronbach's alpha $\geqslant .70$) with the goal to converge on a single, agreed upon meaning for each thematic area. For each topic, they will identify the range of themes mentioned, which were most and least salient, and which were discussed most and least frequently. This will produce research reports on specific topics describing the range, central tendency, and distribution of each theme, presenting segments of text as exemplars, which will be used to guide the refinement and implementation of the intervention in Aim 4B.

Finally, for Aim 4B, we will conduct unadjusted and then adjusted multivariate regression analyses assessing whether medication adherence, hypertension control, and adherence to pill-taking routine differ between treatment groups.

7.2 SAMPLE SIZE CONSIDERATIONS

There are over 150,000 patients in the Cedars-Sinai Medical Delivery Network. Based on initial estimates from EIS, we expect blood pressure readings from at least 75,000 different patients and over 500,000 clinic visits annually, totally over 2.5 million blood pressure readings during the study period. This volume of longitudinal data will allow for development of the proposed measures (Aims 1-2) and to assess their validity and responsiveness (Aim 3A). About 75,000 number of records will be accessed and analyzed as a part of this research (Aim 1-2 and 3A). The home blood pressure cuff study (Aim 3B) is designed to provide pilot data for a proposed K23 application. Enrollment of 10 individuals into this study will demonstrate feasibility and data upon which to complete a larger grant application. Aims 4A and 4B represent components of a R21 grant proposal, with the stated funding purpose of developing pilot data to support a future R01 study.

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