The PCORnet Blood Pressure Home Monitoring (BP HOME) Study
Protocol

Project Summary
The PCORnet Blood Pressure Home Monitoring (BP HOME) Study is a patient-level randomized controlled trial that will compare the effectiveness of home blood pressure monitoring (HPBM) with versus without a linked Smartphone application ("app") for helping patients with uncontrolled hypertension achieve a reduction in systolic blood pressure. The trial will be conducted within the National Patient-Centered Clinical Research Network (PCORnet), which supports a research network that enables distributed querying of EHR data in a common data model. It will also use the Eureka Research Platform, an online research platform hosted by UCSF that supports eConsent, online surveys, and data collection from devices such as HBPMs. Data from these two data sources will be used together to accomplish the study aims. Given that HBPM is the guideline-recommended standard of care (without specification of Smartphone linkage), the HPBM devices and the app are all commercially available and currently in use, and that clinicians, with input from patients, will maintain full control of how BP is clinically managed, we believe participation in the project poses minimal risk to participants.

Background and Significance
Uncontrolled BP is the leading preventable cause of death in the US after smoking, causing nearly 400,000 deaths per year[1]. While effective medications are available to control BP, multiple rounds of medication adjustment and intensification are typically required, and BP control is often not achieved[2,3]. The usual configuration of healthcare delivery – periodic and relatively infrequent office visits with a physician – is not ideal for achieving BP control quickly and efficiently[4,5]. One promising approach to enhancing clinic-based BP management is to support home BP monitoring by patients[6]. Home BP monitoring technology has advanced substantially in recent years particularly in terms of linkage with Smartphones via Bluetooth, which enables use of associated Smartphone applications. Smartphone applications enable a wide variety of functions potentially useful for BP goal attainment, including reminders to measure BP, recording and displaying measurements, interpretation of measurements (e.g., goal attained, BP dangerously high, etc), and facilitating communication of measurements with treating clinicians. It is unclear, however, if this technological advancement helps patients achieve BP control. The PCORnet Home Blood Pressure Monitoring (BP HOME) Study is an individual-level randomized controlled trial that will compare the effectiveness of Smartphone-linked versus standard HBPM cuffs for helping patients with uncontrolled hypertension achieve a reduction in systolic blood pressure.

Aims
1) To compare the effectiveness of Smartphone-linked versus standard home BP monitors for helping patients with uncontrolled hypertension achieve a reduction in SBP.
2) To assess patient-reported outcomes including satisfaction with the HBPM device and various aspects of BP management
3) To assess the outcomes within subgroups based on age, sex and race/ethnicity.

Hypotheses
Patients with uncontrolled hypertension who receive a Smartphone-linked HBPM will have a larger average reduction in SBP at 6 months compared to those who receive standard HBPM, and will be more likely to promote use of the device to a friend.

Study Design
We have designed a patient-level randomized controlled trial that will compare the effectiveness of Smartphone-linked versus standard HBPM for helping patients with uncontrolled hypertension achieve a reduction in their SBP, and patient satisfaction with the device. We aim to enroll 2000 patients who will be randomized in a 1:1 ratio to receive a Smartphone-linked or standard HBPM. We will use data from the electronic health record (EHR), an online patient portal, and the home BP monitor (in the Smartphone-linked arm) to collect outcome data for a period of at least 6 months (for the primary outcome), and up to 18 months (for secondary outcomes, depending on enrollment date). The primary BP control outcome will be reduction in SBP, by clinic measurements, at 6 months. The primary patient satisfaction outcome will be the Net Promotor Score[7,8], derived from self-reported likelihood of recommending the device to a friend, at 6 months.

Study Subjects
Target population
Adults receiving medical care who have uncontrolled BP

Accessible population
Adults receiving medical care at a participating PCORnet institution who meet inclusion criteria, are willing to enroll in the study, and complete baseline surveys.

Inclusion Criteria
- Age ≥ 18 years
- At least one ambulatory visit in one of the participating study sites during the past year
- SBP > 145 mmHg at most recent clinic visit (may be treated with BP meds already or not), as reported by the participant
- A self-reported commitment to "work on lowering your blood pressure by 10 points or more to reduce your risk of heart attack and stroke"
- Owns a Smartphone (Android or iOS) and has an email address
- Willing to receive text messages from the study
- Can read/write English well enough to use English-based Smartphone apps and fill out online surveys in English

Exclusion Criteria
- Has an arm circumference <22 cm or >42 cm
- Owns a functioning HPBM and has used it in the last 3 months

Recruitment Plan

Participating sites will recruit patients via 2 basic methods.

1) *"High-Touch Methods":* Clinical or research staff at participating clinics will interact with patients directly to assess eligibility and interest in participation. IRB-approved study materials will be available to support the patient interaction. The materials will invite participants to register on the online portal, and they will be invited to enter their own special recruitment invitation code ("Golden Ticket Number") to enable subsequent linkage between their EHR data and their data collected by the online portal. Although those materials will be designed to be self-explanatory for patients, clinical or research staff can assist patients as they sign up on the portal. Clinic staff will keep a list of interested and apparently-eligible patients to whom a Golden Ticket was provided, with their associated Golden Ticket Number, to enable EHR data linkage for patients that eventually enroll and consent to participate in the study. This option requires active participation by the patient's treating clinical staff (though we hope it will be low-burden). We are also planning follow-up calls to patients who were provided a Golden Ticket Number but who did not end up enrolling in the study, to remind them about signing up and provide any technical support they might require. Our Phone Script is included in Attachment A.

2) *"Low-Touch Methods":* Patients appearing to meet criteria for enrollment according to their EHR data will be mailed, emailed, or otherwise contacted personally with an invitation to participate. The invitations will include the Golden Ticket Number to enable linkage, as above. Participating sites will have their own approved methods and procedures to facilitate this recruitment approach (Attachment A), otherwise they will use only the in-clinic recruitment method. This option does not necessarily require contacting of the patient's treating physician; these issues will be governed by local policies and rules and addressed at each participating site. These patients may also be called for follow-up (see Phone Script).

Attachment A describes site-specific recruitment procedures and materials.

<u>Determination of Eligibility</u>

Eligibility will be checked:

1) Preliminarily, by clinical or research staff and patients, using Recruitment Option 1 above;
2) Preliminarily, by EHR data review, using Recruitment Option 2 above;
3) Finally, with confirmation from patients, when they enroll through the online portal

<u>Consent Process</u>

We will use the Eureka Research Platform to deliver an electronic consent process that consists of a landing page, a simple "pledge" page that outlines responsibilities of the study (e.g., keep your data safe) and the patient (e.g., completing follow up surveys), a more traditional informed consent form (with a link to the Eureka Privacy Policy and Data Security Measures), and an invitation to participate in the study. All participants will also provide an electronic signature (collected via Docusign using our Eureka Research Platform) on a HIPAA Authorization form that will allow us to obtain their EHR data and link it with the other data collected via the platform. Participants in the Smartphone-linked arm of the study will also be taken through a "device consent" in which they will be instructed to download the Smartphone app associated with the device, and link their device account to their study account.

Attachment B describes the online portal, eligibility check and enrollment procedures that all participants responding to recruitment efforts will use to register and consent to participate in the study.

Study Interventions

Overview: Participants enrolled in the study will be randomized in a 1:1 ratio to two study arms distinguished by the type of HBPM device they receive. All participants will receive guideline-based instructions on HBPM.

Intervention arms: Participants will be randomized in a 1:1 ratio to:

- *Arm 1*: Smartphone-linked HBPM with associated Smartphone app
- *Arm 2*: Standard HBPM

Attachment C describes the specific devices used in each arm of the study, and the Smartphone app used in Arm 1.

Randomization plan: Randomization tables with stratification (by clinical site) and blocking (with randomly varying block sizes) will be generated and stored in the Eureka Research Platform. Participants meeting eligibility criteria, consenting, and completing baseline data collection will be automatically assigned the first previously non-assigned randomization code, and will be notified immediately of their assignment (i.e., no blinding).

Delivery of study devices and instructions: After randomization, UCSF-based study staff will confirm contact information and ship the assigned device to participants free of cost, and follow up via electronic survey, text message and/or phone calls to make sure the device is received. Upon receipt of their device, participants in Arm 1 (Smartphone-linked) will be asked to connect their device account to their study account, which will enable the study to receive BP measurement data from their device. Participants in both arms of the study will be provided guidelines for HBPM (using publicly-available materials developed by the American Medical Association and American Heart Association for their Target: BP Program), and told to continue interacting with their treating physician as usual for BP medication management, etc.

Measurements

Overview: Measurements will be obtained via online survey through our online portal, from the participant's EHR accessed via PCORnet, and from the Smartphone-linked HBPM device for participants randomized to Arm 1. *Online survey data* will be elicited at pre-specified time points; participants will receive a variety of reminders to complete surveys, possibly including but not limited to email, text, and personal phone calls. EHR data will be extracted for enrolled participants using PCORnet queries, and analyzed to evaluate baseline medical conditions and outcomes. All available BP measurements, encounter data and other EHR data from those queries, along with all BP and heart rate measurements extracted from Smartphone-linked HBPM for participants in Arm 2, will be used in analyses as per outcome definitions described below.

The following table describes the measurements we plan to obtain on enrolled participants:

	Baseline	1m	3m	6m	12m	18m
Online survey data						
Baseline BP and eligibility	X					
Basic demographics	X					
Subjective Social Status Scales[9]	X					
HBPM use		X	X	X	X	X
HBPM satisfaction		X		X		
Net Promoter Score[7,8]				X		
Satisfaction with BP management	X			X	X	X
Quality of shared decision-making[10]				X	X	X
Patient Activation[11]				X		

Attachment D provides the text of the online surveys we will administer.

EHR data (all available data through end of follow-up will be extracted in the following domains)
Basic demographics
Diagnoses
Encounter characteristics
Provider characteristics
Blood pressure
Medications
Lab results
Death indicator

The EHR data analysis section, below, provides additional detail.

HBPM device data (all available measurements made during follow up, for Arm 1 only)
Blood pressure
Heart rate

Primary BP control outcome: The following pre-specified outcome will be used for the primary test of comparative effectiveness:

1) Reduction in SBP at 6 months. Reduction is defined by the absolute difference between the eligibility SBP (collected from the patient at the time of eligibility assessment), and the SBP measured at the most recent outpatient clinical encounter 6 months after enrollment. If more than 1 measurement is recorded during a single clinical encounter, the lower/lowest will be used.

Primary patient satisfaction outcome: The following pre-specified outcome will be used for the primary test of patient satisfaction:

2) Net Promotor Score. This score is assessed by asking a single question about likelihood of recommending the device to a friend, with options from 1-10 (10 being extremely likely). As per published methods[7,8], persons indicating 9 or 10 are considered "Promotors"; persons indicating 7 or 8 are "Passives"; and persons indicating 1-6 are

"Detractors". The score is calculated by taking the percent of Promotors and subtracting the percent of Detractors, yielding a score for each group ranging from -100 to 100. Note that an identical score could theoretically be produced for a group with either a relatively high proportion of Promotors and Detractors, or a relatively low proportion of both.

Exploratory outcomes: The following pre-specified secondary outcomes will also be measured and analyzed. These include alternative measures of BP control, other patient-reported outcomes, and process measures intermediate along the causal pathway to BP control.

3) Documented attainment of a 10 mmHg reduction in SBP from baseline to 6 months, as defined above.
4) Documented attainment of a 10 mmHg reduction in SBP at 6 months, as in Outcome 1, but assessed using home BP measurements, when available. As per guidelines, a set of 12 or more home measurements (counting no more than 2 in the morning and 2 in the evening of each day) within any given 1 week time period will count as a completed Home Measurement Protocol[12]. The average SBP and DBP measurements within the most recent completed Home Measurement Protocol within 180 days of the index date (e.g., 6 months after enrollment) will then be used as the attained BP, regardless of subsequent clinic measurements or subsequent random home measurements. If no completed Home Measurement Protocol is available within 180 days of the index date, the most recent clinic measurement will be used. Note that a documented Home Measurement Protocol can only be attained in Arm 1, as home measurements will not be accessible in Arm 2.
5) Other BP Control outcomes defined as ((SBP<140 mmHg and DBP<90 mmHg) OR (SBP<130 and DBP<80) OR 10 mmHg reduction), assessed using the baseline measurement (self-reported OR last clinical measurement prior to randomization from the electronic health record) and subsequent measurements (clinical measurements OR clinical + home measurements) at a specified time-point (6 OR 12 OR 18 months) or using a time-to-control approach.
6) Patient reported outcomes including various aspects of satisfaction with the HBPM device and BP management, including quality of shared decision-making and patient activation.
7) Visit frequency. We will analyze the number of ambulatory care visits during the 6 month follow up period; we will also analyze the number of visits made before attainment of the first in-control BP.
8) Medication intensification. We will analyze the proportion of clinical visits with high BP (SBP>140 mmHg or DBP>90 mmHg) after which a BP medication was added.

Pre-specified subgroups: The following subgroups are pre-specified:

- Baseline Age: 20-44 vs 45-64 vs. 65+ years
- Sex: Male vs. Female vs. Other vs. Missing
- Race/Ethnicity: Non-Hispanic White vs. Non-Hispanic Black vs. Non-Hispanic Asian vs. Hispanic (any race) vs. Other/Multiple vs. Missing
- Subjective Social Status, measured through online survey at baseline, using MacArthur Scale for SES (not the "Community" version)[9]: Upper vs. Middle vs. Lower tertile, defined within our recruited sample of participants

Analysis Plan

Overview: Our primary analyses will test two independent hypotheses: that SBP reduction (outcome 1, defined above) differs by study arm, and that promotion of the HBPM device (outcome 2) differs by study arm. Subgroup analyses and exploratory outcomes will also be analyzed, as described below.

Primary BP control analysis: For analysis of this outcome, which is continuous (defined above), we will use a random effects linear model, including a random effect for clinic and a fixed effect for a 3-level variable that indicates whether the clinic is participating in a concurrently-running cluster-randomized quality improvement trial (Not participating vs. Full Support MAP intervention[13,14] vs. Self-Guided MAP intervention[13,14]).

Primary patient satisfaction analysis: The Net Promoter Score (NPS) is calculated from the proportions of Promoters and Detractors, as described above. To assess the influence of treatment assignment and other exposures on the NPS, we will first define the 3-level outcome classifying each participant as a Promoter, a Passive, or a Detractor, then fit a random effects multinomial logistic model for the independent effect of the exposure on this outcome. The model will include the same random and fixed effects specified for the primary BP control analysis. Expected proportions in each outcome group by treatment assignment will then be obtained using standardization. Finally, the NPS scores for each group, as well as the between-group difference in the score, with 95% confidence intervals for each, will be calculated as linear combinations of the adjusted proportions, and a p-value calculated assuming a null hypothesis of no between-group difference in the NPS.

Subgroup analyses: We will produce subgroup-specific analyses of the primary outcomes for each of the pre-specified subgroups, and test for heterogeneity by including the appropriate interaction terms in the models described above, with an omnibus test for each of the 4 grouping variables. Subgroups that include fewer than 100 study participants or with missing values for the subgrouping variable will be omitted from the omnibus test and results presentation. P-values for within-subgroup treatment effects will be reported only if the omnibus test is statistically significant at $P<0.05$.

Exploratory analyses: We plan to analyze many additional outcomes, including alternate methods of defining BP control, alternate time-points, and additional endpoints including patient-reported outcomes and BP control process measures. These analyses are not planned for testing of the primary hypotheses, but are important for describing the experience of BP control using the two different device types and for generating hypotheses for future study. Our general approach to these analyses will be similar to how we approach the primary and secondary analyses, but we may use other methods that are not pre-specified.

EHR data analyses: We plan to analyze the EHR data obtained from each partner site. Each partner's EHR information is standardized to the PCORnet Common Data Model (CDM) to collect data from the EHR systems. The PCORnet CDM is a HIPAA Limited Data Set and quality checks of the EHR data are performed using procedures and algorithms that PCORI established

for its clinical data research network sites. Among other things, it standardizes laboratory tests and results using LOINC for laboratory tests and medication data using RxNorm.

Queries will be sent to the sites asking for the following data:
- Ambulatory Clinic information, including:
- Basic demographic and visit information
- Diagnoses
- Medication orders
- Blood pressure and pulse measurements
- Lab Reports relevant to blood pressure
- Vital Status

To obtain the information above, we will use the following tables from the PCORnet CDM:
- DEMOGRAPHIC
- ENCOUNTER
- PROCEDURE
- VITAL
- PRESCRIBING
- DIAGNOSIS
- LAB_RESULT_CM
- DEATH
- DEATH_CAUSE

Please note that the research team will NOT request release of information pertaining to drug and alcohol abuse, diagnosis or treatment; HIV/AIDS testing; genetic testing; or mental health diagnosis or treatment.

Attachment E summarizes the steps required for the OneFlorida Data Trust to obtain data for the queries.

Enrollment prediction modeling:
In response to PCORnet's emphasis on ensuring access to health care interventions for vulnerable populations, we plan an exploratory post-hoc analysis examining any disparities in enrollment in BP HOME, particularly by race and ethnicity. Black and Hispanic/Latinx patients are underrepresented in clinical trials and health care research generally, and specifically within hypertension research. This is particularly worrisome given that these subgroups experience disproportionate burdens of negative sequelae of hypertension, including coronary artery disease, stroke, and chronic kidney disease. Further, the interaction between social determinants of health (SDH), Black race and Hispanic ethnicity, and participation in interventional trials is not well understood.

We plan to study the interaction between self-identified race, self-identified ethnicity, and various indicators of social determinants of health, measured at both the census tract and individual patient level, to understand their effects upon enrollment in BP Home. To accomplish this, participating BP Home sites will analyze all persons invited to join BP Home

and analyze predictors of enrollment. BP Home sites will consider different predictors depending on their availability; e.g., OCHIN may consider social determinants of health they have specified based on patient address and also at the individual patient level, while other sites may have different types of predictors. Sites will generally keep individual-level data on non-enrolled patients local and do analyses through their honest broker teams, sharing only model results (aggregated).

Multiple hypothesis testing: The intervention will likely be regarded as successful by clinicians if it is shown to be both efficacious and acceptable (that is, both co-primary outcomes are positive), so no penalty for multiple testing is needed to support this conclusion. In any case, the results of both hypothesis tests will be reported. No formal penalization for multiple hypothesis testing is planned for the subgroup or exploratory outcome analyses, which will be treated as exploratory and hypothesis-generating.

Multiple imputation for missing data: Our general approach to missing data will be multiple imputation. While our primary BP control outcome is defined to minimize loss to follow up and missing data, it is still possible that follow up will be missing if EHR linkage fails. If this occurs (and in general for other analyses), we will use a multiple imputation strategy. This approach will be optimized by the requirement for completion of baseline surveys before randomization occurs. It is likely that our primary patient satisfaction outcome will be missing in a sizable proportion of patients, since it will require patients to log back into our system and fill out an additional survey. Again, we will handle this situation with multiple imputation. In addition to multiple imputation under the standard assumption that data are missing at random (conditional on observed covariates and outcomes), we will also implement sensitivity analyses using imputation under plausible missing-not-at-random scenarios.

Data and Safety/Interim Monitoring: Given the minimal risk nature of the intervention (both arms are considered standard of care), no formal interim monitoring is required. All study staff are CITI-trained, and will be on the alert for unanticipated adverse effects; if such effects are identified, UCSF study staff will notify our IRB and all study sites as needed to minimize risk for participants in the study.

Sample size justification: With 2000 patients randomized (1:1 ratio, 1000 standard vs. 1000 Smartphone-linked), we will have 80% power to distinguish very small standardized treatment effects of only 0.125 standard deviations (SDs). For example, if the standard deviation of SBP reduction is 8, we would have 80% power to distinguish a reduction of 11 mmHg from 10 mmHg in SBP reduction between the two groups. We have not attempted a power analysis for the Net Promotor outcome given the complexity of the calculated score.

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