Study Protocol and Statistical Analysis Plan
Project Title:
Self-Management of Blood pressure for Hypertensive Veterans
NCT ID (NCT03224624)
March 2, 2018

MANUAL OF PROCEDURES

Self-Management of Blood Pressure for Hypertensive Veterans (SMART)

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Chapter 1. Background and motivation.

1. Hypertension: a chronic condition ready for patient-centered self-management. Hypertension is the most common medical problem among US Veterans, with nearly 50% of the 5.5 million VA patients receiving health care services in 2006 having elevated blood pressure. Hypertension is the most common risk factor for stroke, cardiovascular disease, and kidney failure,[1] and the leading modifiable contributor to global disease burden.[2] The VA has been a leader in the study of hypertension and its outcomes for decades[3] leading both landmark clinical trial and cohort studies demonstrating that hypertension is a clinically significant and treatable risk factor.[4–7] *Translating our knowledge into effective treatment demands that we reassess the decades-long status quo of physician-driven blood pressure management and consider other health delivery methods.*

2. Current standard-of-care blood pressure management is inadequate in reaching treatment goals. The long-time clinical practice standard for treatment of hypertension involves intermittent, office-based measurement of blood pressure and adjustment of blood pressure medications. This approach has been recognized as inadequate for several reasons. First, therapeutic inertia,[8] or failure to initiate or increase medication despite poor control of blood pressure, is a major factor, exacerbated by infrequent office visits and reliance on in-clinic blood pressure measurements. Recent trials directed at reducing the behaviors associated with clinical inertia have not been successful in lowering BP.[9] Second, in-office blood pressure readings are not always reflective of out-of-clinic blood pressures and may not be as trusted by patients or even providers. Third, initiation of and adherence to newly-prescribed blood pressure regimens are fraught with opportunities to delay or avoid treatment, and are affected by issues of cost,[10] trust,[11] denial, and perceived efficacy[12] despite overwhelming evidence of the efficacy and cost-effectiveness of antihypertensive treatment.[13]

3. Home blood pressure monitoring is increasingly recognized as critical and more predictive of events, but not routinely integrated into clinical practice. Blood pressure is a continuous, and continuously variable, physiological parameter. There has long been debate about how well clinically measured blood pressures reflect the underlying physiology in any given individual. In the 1940s Smirk[14] demonstrated the correlations of 'basal' (e.g. morning rest) BP and 'casual' (e.g. randomly measured BP) and described the substantial variability of the 'supplemental' pressure – e.g. the amount of variability that could be expected surrounding a given basal pressure. Ambulatory blood pressure monitoring (ABPM) recordings – readings taken generally every 20 minutes throughout a day-night cycle – confirmed differences between in-clinic and out-of-clinic blood pressures and has also demonstrated that these various measures of blood pressure are not equal in terms of their implications for cardiac risk, with ABPM showing stronger relationships with cardiac risk than in-clinic blood pressure.[15]

In practice, however, while devices allowing self-measurement of blood pressure have been available for years, data from these devices has been slow to influence prescribing and treatment patterns despite guidelines.[16] Concerns raised by

physicians have included device inaccuracy, patient misuse or misreporting, and difficulties integrating data from home with clinic.[17]

Despite these concerns, multiple studies have demonstrated that patients are not only capable of home monitoring but that monitoring itself has a positive impact on hypertension care.[18] Including a blood pressure monitor in a hypertension care plan improves self-efficacy, and in many circumstances improves blood pressure as well. At the VA, while blood pressure monitors are available and often issued to patients, the integration of data from these monitors is accomplished in a haphazard, clinic-by-clinic fashion. To our knowledge, no formal VA study has attempted to allow patients to self-monitor and self-manage their blood pressure medications.

4. Patient-centered care for chronic medical conditions is increasingly valued and accepted in other domains. Home-based measurements of blood pressure are clearly emerging as clinically relevant and necessary for appropriate treatment. From a health services standpoint, moving to self-monitoring and self-management of blood pressure medication would involve a paradigm shift in medical care for a condition traditionally considered the domain of physician-dominated prescribing and treatment. Per the Institute of Medicine (IOM), an essential component of quality medical care is patient-centeredness, a component that, until recently, has been both underappreciated and underutilized.[19] The IOM issued ten rules for redesigning health care,[20] with several specifically related to patient-centered care. These included the patient as a source of control of that care; shared knowledge and the free flow of information; care based on a continuous healing relationship; and customization of care based on patient needs and values. Patient-centeredness includes both (a) the patient's experience of, and contribution to, medical care, and (b) the presence of an effective partnership between clinician and patient (i.e., the clinician as a "*collaborator*").

An effective plan for patients to self-manage their blood pressure must move toward patient-centered care without compromising safety. While medication management in diabetes, for example, has long been accomplished in collaborative fashion, with patients being empowered to use "sliding scales" for adjustment of different forms of insulin and different doses, the same is not true of hypertension, with conventional wisdom being that physician involvement would be required to adjust hypertension medications appropriately. However, acute hypo- or hyper-glycemia is at least as dangerous as low or high BP, and glucose monitoring and insulin adjustment is far more complex than the single medication changes proposed here.

5. Blood pressure self-monitoring and self-management in the TASMIN studies: promising, but not yet ready for VA practice.

The two major trials in the UK were the Telemonitoring and Self-Management in Hypertension 2 (TASMINH2)[21] trial and the Targets and Self-Management for the Control of Blood Pressure in Stroke and at Risk Groups (TASMIN-SR)[22] trial. These targeted, respectively, a general population with hypertension in general practitioner practices in the National Health Service, and a more restricted population with at least one major risk factor (stroke or transient ischemic attack, diabetes, stage 3 chronic kidney disease [CKD], past history of coronary bypass surgery, or history of myocardial infarction or angina). In each of these studies, participants in the

intervention arm were instructed in the use of a self-monitoring device and told to self-monitor for at least a week each month. If their BP was out of a pre-specified range, they were able to activate a step in a 2 or 3 step self-management plan. If BP was concerningly high or low, they were instructed to contact their general practitioner. The primary outcome was in-clinic BP change at 12 months. Each study found significant improvement in blood pressure in both groups, but more so in the intervention (self monitoring / self titration) group -- a between group difference of 5.4 mm Hg, (95% CI 2.4-8.5) in TASMINH2, and 9.2 mm Hg (95% CI, 5.7-12.7) in the TASMIN-SR trial, in comparison to a group receiving usual, clinic-directed care, without an increase in serious adverse events (SAEs). These blood pressure differences are not only statistically significant, but also extremely clinically significant. Even very small BP changes on the order of 3-5 mm Hg averaged over populations have been demonstrated in large modeling studies to have dramatic effects on public health in terms of decreases in cardiovascular events and early mortality.[23] Thus, the potential benefit of demonstrating that an intervention like this can be delivered through VA, ***even to a subset of its large hypertensive population***, is tremendous.

VA HSR&D agreed and has funded us at VA San Diego to complete just such a study, in collaboration with VA SF, addressing the question of self-management in 400 US Veterans.

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Chapter 2. Study overview.

1. Study design overview. We plan a 400 participant, randomized, controlled, non-blinded, two-center study of patient-initiated self-management of blood pressure medication vs. usual care over a one-year study period, with planned post-study cohort follow-up via medical records. The primary outcome is the absolute change in in-clinic systolic blood pressure after 1 year.

The design of this study is informed by that of the published TASMIN trials of self-management, to capitalize on the foundational work of those investigators, while adding critical modifications to the intervention to best serve the VA system and allow a full assessment of this delivery mechanism in clinics at a VA hospital and CBOCs. Approximately 350 patients will enroll at VA San Diego; this value includes attrition. 30% of consented subjects are estimated to fail the screening process, therefore approximately 250 participants are expected to enter the follow-up period at this location. At VA San Francisco, approximately 200 patients will enroll and 150 will follow the full course of the study.

2. Description of the study population, sampling frame, and inclusion/exclusion criteria. We plan to enroll Veterans receiving healthcare through either (a) one of the VA San Diego Healthcare System's primary care clinics or area CBOCs (Chula Vista, Mission Valley, El Centro, Imperial Valley, Oceanside, covering an area from the Mexican border north to Orange County, and east to the rural desert and mountain communities) or (b) the VA San Francisco's primary care clinic who have a clinical diagnosis of hypertension and who are not currently at their in-clinic goal blood pressure, able to provide independent informed consent and expected to be in the area for at least 12 months. The figure gives an overview.

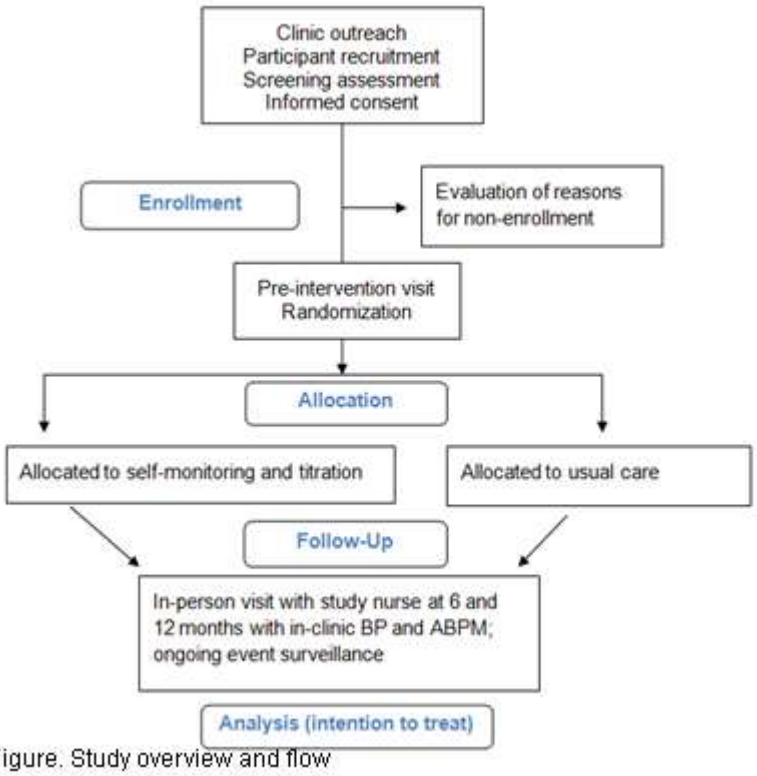

Figure. Study overview and flow

HIPAA Waiver and patient identification.
In the same manner as we have used in the past to recruit from primary care clinics for the SPRINT study, we have a partial HIPAA waiver to access the Computerized Patient Record System (CPRS) to identify hypertensive patients in primary care clinics and CBOCs; patients can also be identified through review of weekly clinic lists with providers. Specifically, we will use PHI to identify potential subjects in the VA San Diego Healthcare System (including the CBOCs) based on limited data in the medical record, including the Computerized Patient Record System (CPRS) concerning patients with hypertension meeting the basic criteria below (e.g. taking 1 or fewer antihypertensives and with blood pressure above clinical goal). The purpose of this is to enable the study team to identify patients in order to be able to tell appropriate patients about the study and obtain verbal permission from the patient so that study staff can be notified of the patient's interest in the study. Additionally, study staff may approach patients during their clinic sessions and invite them to learn more about the study. Recruitment letters may also be used instead of verbal contact during the course of providing medical care. Following introduction, study staff will communicate with interested individuals and set up a screening visit. Once study staff has discussed the study with the interested patient they will consent the participant and obtain full authorization for enrollment.

Exclusion criteria are designed to limit serious comorbidities and complex cases of hypertension while still permitting a large fraction of those with hypertension to be included in this study. Therefore, it is important to thoroughly investigate the patient's history and clearly document inclusion and exclusion criteria. Medical record review can be used for prescreening. Study staff should obtain Institutional Review Board's approval for these activities, as mandated by local practices. Local laboratories will be used for lab tests to determine screening eligibility. The maximum time between lab tests and screening eligibility will be 90 days.

Centers also need to keep a listing of why the participant who was told about the study decided not to participate. These reasons are recorded on "The Reasons Why Participants who are Approached and do not Consent" tally sheet. This evaluation of reasons for non-enrollment and chart-based outcomes of non-enrollees is key to planning for dissemination of this technique within diverse VA sites and populations.

Criteria for exclusion will include:

- Active prescriptions for > 1 antihypertensive agent (excluding chronic agents prescribed primarily for other purposes, such as alpha blockers for prostate disease or PTSD);
- Known allergies to 2 or more antihypertensive agents;
- Specific reasons for a blood pressure target different from in-clinic target of 130/80, or a corresponding home management goal of 120/80
- Currently not primarily in charge of his/her own medication administration (e.g. those living in institutions or with dementia or other limitations making self-medication care not possible);
- Life expectancy of < 12 months;
- Blood pressure at screening visit > 180 mm Hg systolic or > 110 diastolic, or < 130 systolic; screening cognitive function (Montreal Assessment of Cognitive Function, MoCA)[50] score less than 25;
- eGFR < 25 ml/min /1.73m^2 or end-stage renal disease (ESRD);
- Inability to use a standard home blood pressure cuff;
- Known secondary cause of hypertension that causes concern regarding safety of the protocol, in the opinion of the site investigator;
- Cardiovascular event or hospitalization for unstable angina within last 3 months;

- Symptomatic heart failure within the past 6 months or left ventricular ejection fraction < 35%;
- Pregnancy or planned pregnancy, or of child-bearing age not using birth control;
- Current participation in another clinical trial;
- Major factors judged to be likely to significantly limit comprehension of or adherence to interventions including dementia, psychiatric disease, or substance abuse.
- Cancer treatment within the last year

Primary care physicians and study staff will be able to exclude participants based on their judgment of the patient's capability to undergo the intervention.

Screening Procedures. The screening procedure involves blood pressure measurement at the time of a **primary care clinic visit** followed by review by study staff of other inclusion/exclusion criteria obtainable prior to consent. Participants must then complete a MoCA test (commonly used in primary care to screen for cognitive dysfunction) after completing the consent procedure for the study.

Table. Measures to be completed during the study

Category	Measures	Screen	Baseline	6 mo.	12 mo.
Screening	Cognitive screen (MoCA)	X			
	Blood pressure (primary care clinic)	X			
	Review for exclusion/inclusion	X			
Clinical Data					
	Demographics/comorbidities	X			
	Study clinic BP		X	X	X
	Ambulatory BP		X	X	X
	Home BP		Per protocol		
	Medications review	X	X	X	X
	Chemistry panel	X		-PRN-	X
	Urine albumin/creatinine	X			X
	Unscheduled clinic visits/ER visits/admissions		Ongoing review		
	Serious adverse events		Ongoing review		
Other data		**To complete once during Screen OR Baseline Visit**		**6 mo.**	**12 mo.**
Patient-centered	Rapid assessment of health literacy -SF	X			
	Patient-practitioner orientation scale	X			X
	Lifestyle change survey	X			X
Medication related	Morisky medication adherence scale	X			X
	Medication possession ratios (Chart Review)			X	X
HRQOL	European Quality of Life 5-D	X			
Social-Cognitive	Hypertension self-efficacy scale	X			X

Process-acceptance	Program Evaluation Survey		X	X
Chart follow-up	***Clinically available blood pressures***			***X+1yr***
	Clinically available events			***X+1yr***

3.Description of the baseline intake visit. After screening, both groups will complete a series of intake questionnaires on general health, demographics, and questions related to hypertension chronic management including health literacy, health-related locus of control, adherence, and quality-of-life questionnaires (Table 2). We have chosen the Rapid Assessment of Health Literacy (REALM-SF), Patient-Practitioner Orientation Scale, the adherence metrics in the Morisky Medication Adherence Scale, and the European Quality of Life scale.

In addition to these widely known measures, we have adapted two surveys (attached in appendix) to quantify patient self-efficacy and satisfaction and lifestyle modification in relation to hypertension.

During the screening or baseline study visit, all participants will receive training to appropriately check blood pressure at home using study-issued home blood pressure monitors. A baseline chemistry panel and assessment of albuminuria will be ordered, if not completed clinically within 3 months of the study visit.

Both groups will complete an initial study visit with the study team and physician and complete a 24-hour ABPM session. The ABPM session can be done prior to training for the intervention participants.

4. Random allocation and blinding. Randomization will be 1:1 intervention/control. Randomization will be done by a central system, stratified by degree of hypertension at initial visit (> 160 systolic or below) and block-randomized by clinical sites using the centralized randomization tool through the Health Services Research Center data servers. The study participants and personnel will be unblinded. The research assistant in charge of checking blood pressures at the initial, 6-month, and 12-month visits may be aware of treatment allocation but will use standard procedures and an automated Omron cuff, using the SPRINT study blood pressure measurement protocol (5 minutes of quiet rest followed by 3 automated blood pressures at one-minute intervals, averaging last 2 to determine in-clinic BP), to ascertain blood pressures to avoid digit preference and bias.

5. Follow-up study visits: Participants in both randomization arms will then return for 6-month and 12-month study visits at which times blood pressure will be checked by a research assistant, and participants will complete questionnaires similar to those obtained at baseline, blood and urine studies for kidney function and albuminuria (as part of routine clinical care) at 12-month visit, and repeat ABPM at both 6 and 12-month visits.

6. Usual care and intervention protocols. Both groups will be issued a home blood pressure cuff with data recording capabilities identical to that in the active arm of the study, (Microlife BP, Microlife USA Inc), will meet the study physician and have questions answered, and will be instructed to record and share results with their primary care physician at routine clinic visits. The patient's and provider's willingness to titrate to a clinical goal of 130/80 (home goal of 120/75) will be confirmed.

Usual care: For those in the **usual care group**, further hypertension care and laboratory monitoring will be assumed by the primary care physician at intervals chosen by that physician in terms of frequency of follow-up or testing, and patients in this study arm can be referred for any support plan that is part of usual care, including nurse visits, home telehealth, or pharmacist visits. Participants will return to the study visit at month 6 and 12 to complete the same study measures summarized above including ABPM measures. Blood pressure will be recorded at these visits but medication changes will not be part of these visits so as not to affect blood pressure treatment in the usual care group. We will track medication changes in the usual care group via chart review.

Intervention: The **intervention group** will be issued a home blood pressure cuff with data recording capabilities, identical to that in the control group, and instructed in its use. As part of the initial study visit with the study physician and study nurse they will learn about and review the blood pressure action algorithm **(see Figure)** and its use. Goal blood pressures in the home action algorithm are lower than in-clinic targets; it has been consistently demonstrated that home SBP is on average 10 mm Hg lower than in-clinic BP in most patients, so if the primary care clinician's stated target for a given patient is 130/80, the home target corresponding to this is 120/75.

The patients in the intervention group are provided with extensive training on how to write down their blood pressure readings, when to initiate a change, and how to track their medications using a Participant Training Standard Operation Procedure (attached in Appendix.) They are instructed to call their PCP with side effect issues, as would be done for normal medication changes. They are further instructed to call with issues related to self-monitored low or high blood pressure, per the color-coded charts provided. A training reinforcement call will also be made by the study coordinator to each of the participants in the intervention group after the training visit to ensure that each participant is fully confident in carrying out all aspects of the study.

Patient handouts and assessments:

1. Training Exercises
2. Patient Training Notes
3. Action Sheet
4. Contact Information Sheet
5. Weekly Reading Logs
6. Medication Change Details Forms
7. Color Coding Chart for patients
8. Final Training assessment

After the training session for the intervention, each patient will be individually assessed by study staff, to satisfy the research team that they are capable of self-managing their blood pressure. For those patients who do not successfully satisfy all areas of the assessment, an additional training session will be arranged after discussion with the study physician.

If patients are unable to successfully learn to self-monitor their blood pressure, it will be explained to them that they will be unable to participate in the active arm of the study and that they will return to their usual routine care. The reason for their withdrawal from active self-management will be recorded. They will be followed in an intention to treat fashion and will complete 6 and 12 month visits.

Intervention safety checking: The goal of the study is that the at-home group does not get routine in-person or telephone assessment prior to initiating a new medication. Indeed, if we did such assessments it would fundamentally negate the intervention. One training reinforcement phone call will be made to the participant after the baseline training session to answer any final questions the participant may have before beginning self-management protocol. At the 6 month visit, we will have an opportunity to review patients' blood pressures in clinic and if they have changed their medications according to the protocol. Participants' self-monitoring logs will be reviewed at the 6 month visit and graded according to whether they performed the self-titration procotol (a) correctly and (b) safely over the first 6 months. However, we will not conduct in person or telephone reassessment of patients at the time of each patient-initiated medication change. Protocol violations will be reviewed as they are reported and patients unable to continue with self-management will be withdrawn and returned to usual care, based on the judgement of the site investigator (with continued analysis by intention to treat). Patients calling to review the protocol or with questions about self-management will be reassessed by phone and study staff and physician will note whether they are able to continue.

The study research staff will be responsible for teaching the participant randomized to the intervention arm on appropriate use of the home cuff and how to record readings. Using standard techniques of adult learning theory, the team will assess the individual participant's understanding and readiness to learn; will gear the education to the participant's skills and knowledge; and will approach initial errors in a non-judgmental fashion. The study team and physician will assess whether the learning session has adequately prepared the participant to self-manage by using 5 pre-set scenarios that lead down each of the potential pathways (e.g. blood pressures too low, too high, appropriate, not enough data to make a change, see training appendix) and asking the patient to describe their actions based on those scenarios. If there are concerns about the patient's readiness after a single session, an additional session will be scheduled to facilitate maximal comfort with the algorithm (maximum 2 sessions). The number of training sessions needed per participant will be noted in the study database. The participant will be provided with paper log books to track their self-monitoring and medication changes, as well as any symptoms or notes they wish to make. The study team and physician will be available by phone for questions throughout the study period; these calls will be noted in the study database. If a participant in the intervention group does not feel comfortable with the algorithm after 2 training sessions, he or she will be returned to usual care, but as the participant has been randomized, his or her data will be handled as though self-managing, to follow the intention-to-treat protocol.

The **default** stepped medication self-management algorithm (**Figure**, similar to protocols used successfully at the Kaiser healthcare systems) will be reviewed and, if necessary, customized by the study physician, to include information about when laboratory tests should be done. Unless there are compelling reasons to continue current medication, participants already taking one medication will be switched to the first step medication in the study protocol. If participants are not willing to change to the study medication, or have specific indications for their current medication (e.g. beta-blocker for atrial fibrillation, ACE inhibitor for diabetes) a personalized self-management plan including their current medication will be developed by the study physician. Concerns such as medication allergies, specific indications or contraindications, will be discussed on an individual basis based on the initial study visit, the self-management plan will be modified as needed, and the final self-management plan will be shared with the primary care physician via co-signature-requiring notes in CPRS.

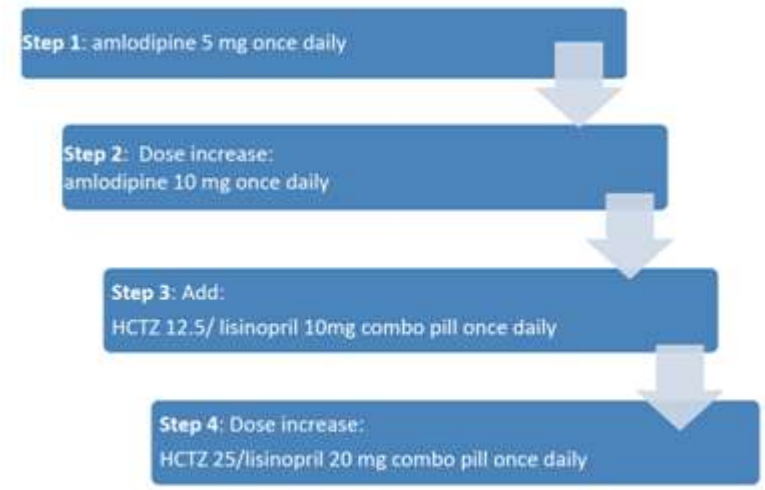

Figure. Standard medication change algorithm.

All study prescriptions will be entered by the study physician in 'suspended' status at the initiation of the study. The pharmacy system allows medications to be ordered in this status and then activated at an appropriate interval, as for for medications intended for a forthcoming procedure. Prescriptions in this mode cannot be activated without the involvement of a physician or designated pharmacist. The patient will be able to activate the steps in the protocol by calling the SMART study phone line, the study team will alert the study physician to activate the next medication. The study physician, team pharmacist, or coordinator, in turn, will alert the primary care physician to changes via mandatory co-signature and approval on notes in the medical record. This will alert the physician of an impending medication change. The primary care physician will still be the first point of contact for any in-person visits related to hypertension; any interval calls to the study team regarding blood pressure symptoms will also be routed to the primary care physician.

The primary care team will be able to stop, start, or alter the doses of medications based on new clinical information. All study-related prescription fills and use of antihypertensive medications outside the scope of the study will be tracked. Some safety issues will be monitored in this fashion as well: If a patient (for example) attempts to activate 2 steps in the course of a week (which would violate the monitoring protocol, which specifies a longer interval of home monitoring prior to a new medication) that will be considered a potential safety violation related to the self-management protocol. We note that we cannot capture via pharmacy records all instances of medication mismanagement or non-compliance by patients either in the self-management or the usual care arm.

Follow-up laboratory testing for electrolyte abnormalities (basic chemistry panel) will be triggered by any request by a patient for Step 3 or Step 4 medications. The initial instruction manual for self-management will clearly indicate that laboratory tests must be done after adding a medication with electrolyte effects. Participants will be reminded of the need for laboratory testing by specific labeling on the new medication bottle. Those who do not report for the required laboratory test within a two week window will receive a phone call from study staff reminding them to do so. These laboratory studies will be routed primarily to the study team, with additional mandatory notification to the primary care team; ***any action on abnormal labs will be primarily managed by primary care, with oversight by study physicians to ensure safety***. Between-visit contact with the study will be limited to patient-triggered calls to issue blood pressure medication according to the algorithm. All other care will be handled by the primary care team. Patients who require all 4 steps of the algorithm and are not at blood

pressure target will be considered to have exhausted the self-management algorithm and will then be treated at the discretion of their primary care physician. Follow up will continue by protocol to allow analysis of data by intent-to-treat.

After completion of the 12-month study, all patients will be followed in a cohort phase of the study which will involve chart review for further blood pressure measurements done as part of clinical care and for safety outcomes and events over the following 12 months, and then for long-term outcomes (e.g. blood pressure control, CVD events, mortality) over another 8 years. We will complete this cohort phase, which is a low-cost follow-up protocol, because of concerns about transience of study effect in prior clinical trials; this will allow us to evaluate whether any blood pressure differences we detect are long-lasting or transient, and allows us to conduct long-term outcomes based analyses.

7. Outcome measures.
Primary blood pressure outcome: in-clinic blood pressure change. The primary blood pressure outcome measure for the study will be between-group change in in-clinic systolic blood pressure, defined as difference between the averaged blood pressure at the baseline visits vs. the averaged blood pressure at the scheduled final study clinic visit. This outcome measure is the standard in BP treatment studies, optimizes power, and allows comparison between our results and those of other studies. Measurements will be made by an Omron automated blood pressure cuff 3 times 1 minute apart after 5 minutes of rest; the average of the 2nd and 3rd BP will be used to define primary outcome BP.
Secondary blood pressure outcomes: Secondary blood pressure outcome measures will include change in ABPM over the course of the study and percentage at goal blood pressure based on the in-clinic readings.

The ABPM gives multiple different 24-hour parameters to be examined. In our work we will focus on 24-hour average systolic and 24-hour average diastolic blood pressures, rather than examining diurnal patterns. The reason for this choice is that these 2 metrics essentially give more precise characterizations of two variables (systolic and diastolic blood pressure in clinic) at the 3 timepoints at which they are obtained than clinic blood pressures do. They also allow characterization of participants as having ‘white coat’ hypertension (higher in-clinic than ABPM) vs. ‘masked’ hypertension (higher ABPM average than in-clinic) vs ‘true’ normo- or hyper-tension.

8. Safety metrics. We will assess SAEs both by active chart surveillance for ER or unscheduled clinic visits for enrolled veterans as well as by interview at the study visits. The CPRS system allows automated notifications to study physicians and staff for all patients enrolled in the study, so that admissions and ER visits can be reviewed on an ongoing basis; we will compile these quarterly. Every time a new medication is requested, a chart review by study staff will be triggered to confirm that medications are not being requested too frequently (protocol violation) in the intervention arm. Participants with significant safety violations in the intervention arm, identified either through interval contact or through log reviews at the 6 month visit, will be considered to have failed self-management and will be returned to usual care. Participant-reported side effects and adverse events will be actively collected at the 6- and 12-month visits in both groups.

Potentially study-related SAEs and all hospitalizations and major events will be reviewed locally by the study physicians. An un-blinded DSMB consisting of 3 experienced nephrologist-epidemiologists and a general internist, all working in the VA system and assisted by the study statistician, will review SAEs and in clinic BP data in both groups at the point where 100

participants reach the six-month time point, and every time an additional 100 participants reach six months. Any major interval SAEs or concerns will be communicated to the lead member of the DSMB who will have the option to ask for a full review.

9. Patient oriented metrics.
The Patient-Practitioner Orientation Scale has been used in prior hypertension studies at VA and assesses patients' preferred role orientation (patient- vs. provider-centered) in their clinical encounters.
Acceptability: Acceptability of the intervention will be measured using research study retention rates, patient satisfaction questionnaires including both quantitative and qualitative ratings, and adherence measures described below. We will assess participant satisfaction using 10 questions developed by the investigators. Similar questions have been used by Dr. Groessl in other studies. (See Appendix 1). Clinicians with at least 2 intervention participants in the study will be surveyed with two simple Likert-scale questions regarding their opinion of the intervention and whether they would want future patients to use a similar plan.
Adherence: Adherence to the intervention protocol will be measured using data on patterns of use of the home blood pressure cuff in comparison with the recommended schedule of monitoring, and self-reported and pharmacy-confirmed medication requests in response to blood pressure results. We will issue medications for all participants enrolled in this study as 30-day refills, to best estimate medication possession ratios over the 12 month study. The Morisky medication adherence scale will be used to assess participants' medication adherence behavior at each study visit.
Self-efficacy: Self-efficacy for hypertension self-care reflects levels of confidence in the ability to perform basic self-care activities crucial to the intervention as well as confidence that these activities can be performed and be beneficial as a whole. The wording of the items has been adapted to be specific to hypertension self-care (see Appendix). The measure consists of 6 items, rated on a 10-point scale.
Health-related quality of life (HRQOL): We will administer the EQ5D questionnaires to assess HRQOL at baseline, to assess the impact of baseline health status in this population.

Chapter 3. Recruitment and Informed Consent

3.1 Best Practices for Recruitment
The different sites may require different approaches to recruitment. In our prior clinical trials recruiting from VA populations, we have had success via HIPAA waivers and chart reviews combined with letters/phone calls to potential participants; we have also been successful in recruiting in-person in the clinic setting, reminding clinicians of inclusion/exclusion criteria, using notecard-size handouts with study phone contact, etc.

Organizational approaches
On a weekly basis, each actively recruiting site should track:
* methods used to identify new participants
* number identified
* number of initial contacts
* number of screening visits scheduled/planned

Oversight
The clinic PI and coordinators will meet regularly during recruitment to review the past week's and month's (and recruitment period to date) recruitment productivity

(e.g., telephone screenings conducted, clinic screenings conducted, number of potential eligible, number randomized), the next week's schedule for screening and randomization visits, and the next month's schedule of recruitment activities (days on which practices or pharmacies will be visited, mailings will be disseminated, etc.)

3.2 Participant Screening within the Clinical Practice

Both sites should be recruiting from primary care practices (not hypertension specialty clinics, renal or cardiology clinics).

1. Direct contact

 Approach patients or doctors in the wards and clinics. Display posters and pamphlets in the clinics and wards.

2. Clinic chart reviews

 Performing a thorough clinic chart review can help to identify potential participants. Once potential participants are identified, a letter can be sent describing the study to the participant.

 If the participant agrees to come in for a screening visit, send a letter describing what the visit will entail, as well as what they can expect to happen once randomized into the study.

3.3 Informed consent.

Obtaining Consent from Participants

Consent must be obtained at a time and place when there is opportunity for:

 Giving a participant adequate information about the study;
 Providing adequate opportunity for the participant to consider all options;
 Responding to the participant's questions;
 Ensuring the participant has comprehended the information;
 Obtaining the participant's voluntary agreement to enter the study;
 Continuing to provide information as the participant or situation requires.

Who can obtain consent from potential participants?

The site PI and his or her designees can obtain consent. Local site procedures such as providing the participant a copy of the consent form and local research informational brochures should be done at this point in time.

Chapter 4. In Clinic Measurements and Administering Questionnaires

4.1 Inclusion and Exclusion Criteria

Criteria for inclusion:

Over 18 years of age
Clinical diagnosis of hypertension
Currently above clinical goal blood pressure (>130 or >80 in clinic)

C**riteria for exclusion**:
active prescriptions for > 1 antihypertensive agent;
known allergies to 2 or more antihypertensive agents;
currently not primarily in charge of his/her own medication administration (e.g. those living in institutions or with dementia or other limitations making self-medication care not possible at the discretion of site investigator);
life expectancy of less than 12 months;
blood pressure at screening visit > 180 mm Hg systolic or > 110 diastolic
Specific reasons for a blood pressure target different from in-clinic target of 130/80, or a corresponding home management goal of 120/75
Screening cognitive function (Montreal Assessment of Cognitive Function, MoCA)[50] score less than 25;
eGFR < 25 ml/min /1.73m^2 or end-stage renal disease (ESRD);
inability to use a standard home blood pressure cuff;
known secondary cause of hypertension that causes concern regarding safety of the protocol, in the opinion of the site investigator;
cardiovascular event or hospitalization for unstable angina within last 3 months;
symptomatic heart failure within the past 6 months or left ventricular ejection fraction < 35%;
pregnancy or planned pregnancy, or of child-bearing age not using birth control;
current participation in another clinical trial;
or major factors judged to be likely to significantly limit comprehension of or adherence to interventions including dementia, psychiatric disease, or substance abuse.
Cancer treatment within the last year.

4.2 Visit Procedures

Screening Visit procedure

1. Verify participant's interest in study.
2. Obtain in person study consent and HIPAA authorization for main trial prior to randomization (randomization can also occur at time of screening visit if time allows)
3. Continue collection of screening information, including such items as contact information, additional eligibility information including BP measurement, concomitant medications, medical history, and MoCA. If time allows, questionnaires can be completed once at Screening or Baseline visit.

Baseline visit (Randomization Visit)

1. Reconfirmation that all inclusion/exclusion criteria were addressed at screening
2. Verification of participant consent and HIPAA authorization.
3. Verification of participant contact information
4. Completion of the study randomization procedure and baseline data collection
5. Issuance of home BP cuff (to all participants) and initial training session (for active self-management). Issuance of home BP cuff can also be done at Screening visit, if time allows.

4.3 Baseline/Randomization Visit Procedures

Measures as described in the table below are completed at each visit:

Table. Measures to be completed during the study					
Category	**Measures**	**Screen**	**Baseline**	**6 mo.**	**12 mo.**
Screening	Cognitive screen (MoCA)	X			
	Blood pressure (primary care clinic)	X			
	Review for exclusion/inclusion	X			
Clinical Data					
	Demographics/comorbidities	X			
	Study clinic BP		X	X	X
	Ambulatory BP		X	X	X
	Home BP		Per protocol		
	Medications review	X	X	X	X
	Chemistry panel	X		-PRN-	X
	Urine albumin/creatinine	X			X
	Unscheduled clinic visits/ER visits/admissions		Ongoing review		
	Serious adverse events		Ongoing review		
Other data		**To complete once during Screen OR Baseline Visit**		**6 mo.**	**12 mo.**
Patient-centered	Rapid assessment of health literacy -SF	X			
	Patient-practitioner orientation scale	X			X
	Lifestyle change survey	X			X
Medication related	Morisky medication adherence scale	X			X
	Medication possession ratios (Chart Review)			X	X
HRQOL	European Quality of Life 5-D	X			
Social-Cognitive	Hypertension self-efficacy scale	X			X
Process-acceptance	Program Evaluation Survey			X	X
Chart follow-up	***Clinically available blood pressures***				***X+1yr***
	Clinically available events				***X+1yr***

At the baseline visit, entry of demographic data, contact information, review for common comorbidities and chart review for history of past medical history can be completed prior to the visit and confirmed with the participant.

Participants should be instructed to bring all medications, prescription and nonprescription, to the baseline visit. It is especially important that they bring prescriptions or supplements not provided by VA so that study physicians are aware of other medications and potential interactions.

Participants should have a chemistry panel and urine testing ordered clinically, if not completed clinically within 3 months of the study visit, with agreement of the primary care physician.

After consent, at either screening or baseline/randomization visit, the participant will also initiate 24 hour blood pressure monitoring; they should be informed in advance of this and plan to wear a button-down shirt to facilitate placement of the monitor. They may need to adjust evening plans to allow them to wear the monitor continuously for the next 24hours.

Participants should also be advised that the training session for self-monitoring is potentially lengthy. If they cannot stay for ~ 3 hours, they should be scheduled for a second appointment at the same time as the baseline visit appointment, in anticipation of being randomized to the active treatment arm.

Training

For those randomized to the self-management arm, the first step is to undergo training in self-monitoring. Refer to Patient Training SOP (attached in appendix). Once the participant can reliably use the self-monitoring device, training on recording and responding to blood pressures can begin. If a single session is not satisfactory, an additional session should be scheduled before the participant makes any blood pressure adjustments on his or her own. Patients are also welcome to bring their spouse/partner along to the training sessions.

Learning Objectives

At the end of the training the patients will:

- Understand the justifications and requirements of the study
- Know who to contact and how, in case of questions, emergencies, queries and problems
- Demonstrate the correct assembly and use of the blood pressure monitor
- Know how often and when to measure their blood pressure
- Demonstrate how to record the readings correctly
- Understand the color coding system
- Correctly color code each day's readings
- Correctly color code each overall week of readings
- Correctly choose the action required to be taken at the end of each week
- Understand when and how to adjust their own medications
- Feel confident to be able to carry out the requirements of the study

The patients will then be asked to practice with the study staff.

Assessment- Each participant in the self-management arm will be individually assessed to satisfy to the research team that they are capable of self-managing their blood pressure.

The patient will be assessed on their ability to:

- Demonstrate accurate use of the blood pressure monitor and recording of results at home
- Demonstrate accurate use of the blood pressure monitor and recording of results in front of the assessor
- Demonstrate correct application of the color chart to readings

- Demonstrate good knowledge and application of the theory related to the required actions and medication changes

The theoretical requirements will be assessed using paper-based exercises, as well as verbal questions and answers based around case scenarios. A training form that includes details of the assessment scores will be completed by the trainer to ensure the patient has successfully satisfied all areas of the assessment. For those patients who do not successfully satisfy all areas of the assessment, an additional training session will be arranged after discussion with the study physician.

If participants are unable to self-monitor their blood pressure after 2 trainings, it will be explained to them that they will be unable to participate in self-management; they will continue in the study, in an intention to treat fashion, but will not self-manage. The reason for this will be recorded on the training form.

Making Medication Changes

Medication changes will only apply to blood pressure medication and will involve either:

- Increasing the dose of current medication, or
- Starting to take a new medication, usually in addition to the ones the patient already takes

During the final step in training, the participant will meet with the study physician to learn when and how to adjust their medication by learning the self-titration algorithm. (See attached Patient Training SOP)

Agents available for the self-titration algorithm

The preferred titration scheme is:
Amlodipine 5 mg
Amlodipine 10 mg
Amlodipine 10 mg plus HCTZ 12.5 mg/Lisinopril 10 mg (combination pill)
Amlodipine 10 mg plus HCTZ 25 mg/Lisinopril 20 mg (combination pill)

This 4 step plan was chosen for several reasons:

1) It starts with an agent that does not require monitoring of chemistry panels
2) It includes the 3 preferred classes of antihypertensive agents after step 2
3) It includes only 2 different physical pills

Although there is a preferred standard titration scheme, there will be participants for whom switching from current single medication to amlodipine is not feasible (or who are already taking larger doses of amlodipine); for whom prior history precludes use of one of these three agents (note that an ‘allergy’ is not the only reason to preclude use of a medication, e.g. chart must be reviewed for hyponatremia in setting of HCTZ in past); for whom there are reasonable expectations of drug interactions, etc.

For these participants, the study physicians at each site will choose a reasonable titration algorithm, also including two different drugs, and 4 titration steps as above.

Preferred medications are any VA formulary medication, to include in order of general preference:

- Sustained-release calcium channel blockers (CCBs)
- Thiazide-type diuretics
- Loop diuretics
- Angiotensin converting enzyme (ACE)-inhibitors
- Angiotension receptor blockers (ARBs)
- Beta-blockers
- Direct vasodilators
- Potassium-sparing diuretics
- Alpha1-receptor blockers
- Adrenergic inhibitors

To facilitate titration, combination pills are encouraged.

Chapter 4.c Post Randomization Visit Procedures 6 mos and 12 mos

These visits should be scheduled at the time of the baseline visits. Participants should receive a reminder phone call 1-2 weeks prior to the visit to ensure that the date remains acceptable. Participants should bring all written logs of home blood pressure (both groups) for collection and copying (participants may return with their logs to home if they so desire).

At the 6 and 12 month visits, procedures and surveys should be completed per the table above and blood pressure recorded in the study visit. 24-hour blood pressure monitors will again be used so participants should be reminded ahead of time to plan for this, and reminded at the visit to mail the device back promptly.

At the 12 month visits, participants should be reminded to return the equipment issued for the study. This includes blood pressure cuffs as well as logs and notebooks. They should be seen by the study physician at this visit and reminded that their blood pressure care is fully managed by their primary care physician from this point forward.

Chapter 5. Retention, Adherence

Adherence and retention for a clinical trial are essential. In this trial, we foresee several potential barriers and solutions:

1) Disappointment with being in the ‘usual care’ arm leading to lack of follow-up for the 6 and 12 month visits

   Approach: make sure randomization is not set up as a ‘win/lose’ situation
   Remind all participants that the financial incentives are for completion of 6 and 12 month visits

2) Frustration/fear/anxiety about self-monitoring, leading to avoidance of the intervention protocol, repeated phone calls to study staff or PCP, etc

Approach: up-front support and extra training visits as needed; but need to avoid 'taking over' from primary care and over-supporting during period of test of self-monitoring. If participant calls frequently remind them about 6 and 12 month visits and alert their PCP, or alert study physician to contact PCP

3) Primary care 'burnout' from study burdens – confusion about response to participants in a blood pressure study

   Approach: repeated and patient education, for both physicians and PACT team

Chapter 6. Procedures for Inactive/Lost/Refused Participants and Missed Visits

During the course of the study, we may find that certain participants become disinterested or frustrated. Participants in the active arm of the study may fail that arm (because of increasing meds above study titration plan, failure to follow protocol, etc) but should stay in the study for follow up purposes in intention to treat fashion.

Potential status options for a participant are:

- Active status – a participant is considered to be active if following the assigned randomized treatment and in contact with the study.

- Inactive status – a participant is considered to be inactive if he or she is no longer self-monitoring/self-managing for any reason (but is still in contact with study).

- Lost status – a participant is considered to be lost-to-follow-up if he/she has missed more than a follow-up visit, cannot be contacted by any ordinary means (e.g., home phone, cell phone, mail, email, fax, etc.), clinic staff do not know the participant's whereabouts, and alternative contacts either do not know where the participant is or cannot be contacted themselves.

- Refused status – a participant is considered to be refused if he/she has withdrawn consent to participate in the study and refuses further contact for any reason.

To the greatest extent possible, we will attempt to complete follow-up visits for participants who are either active or inactive and to contact lost participants.

Chapter 7. Ascertainment of Study Outcomes

Blood pressure will be measured in the primary care clinic at the start of the study. We will use the clinically measured blood pressure as the blood pressure used for eligibility criteria, since primary care physicians may act on this blood pressure prior to the patient enrolling in the study.

Study clinic blood pressure will also be used to verify primary care clinic measurements and ensure that blood pressure is at least 130 systolic at baseline.

At the baseline, six-month, and twelve-month visits, the blood pressure will be measured by a research protocol (3 measurements with interval pauses as above). The blood pressure from the research study visit on the day of randomization will serve as the baseline study visit for this trial. The outcome blood pressure will be the similarly measured (research protocol) blood pressure at the 12 month study visit.

ABPM set-up will be done according to our previously used Spacelabs protocols from SPRINT study.

All study instruments will be administered by research staff in-person with patients at the baseline, 6 and 12 month visits.

Chapter 8. Safety Monitoring and Reporting

The main clinical adverse events that will be monitored during this trial are those related to over- or under-treatment of blood pressure. These were not different from usual care during the two studies of similar interventions in the UK, and only 3% of those in the intervention group deviated from self-titration protocols in those studies. Nevertheless, we plan to actively monitor for these issues by scheduled chart review for clinical or ER visits, hospitalizations, and potentially study-related serious adverse events (e.g. syncope, hypertensive urgency, stroke, MI, death). Other adverse events potentially related to the study will also be collected (e.g. medication side effects, abnormal laboratory findings including sodium < 130 or potassium <3 (for those on thiazide); potassium >6 for those on ACE; creatinine 50% higher than baseline).

We have assembled a DSMB for this study given the potential risks of self-management of blood pressure. This will consist of experienced nephrologist-epidemiologists and a general internist, all working in the VA system. Assisted by the study statistician they will review AEs and BP data in both groups at the point where each group of 100 participants have reached the six-month time point.

Real-time Safety Monitoring: The DSMB lead will be informed by formal written event reports and directly by teleconference within 24 hours of any serious adverse event (SAE) deemed by the investigators to be potentially study related. The chair will make preliminary recommendations and/or call a full ad hoc meeting of the DSMB. All other related AEs and unrelated SAEs will be reported to the chair at a frequency determined by him/her, and reviewed by the full DSMB at the mid-point meetings or earlier, at the discretion of the DSMB chair. Serious adverse events will be reported to VA IRB by the investigators as required.

Data Safety Monitoring Board: The DSMB will include 3 physicians from VA institutions with statistical expertise and clinical knowledge of hypertension as well as trial experience.

All lab tests in this protocol (renal function panel, urinalysis, urine protein, urine creatinine) are used in routine care and will be reported in CPRS to both the study team and primary care physician.

Chapter 9. Data Management, Quality Control, and Statistical Considerations

DATA MANAGEMENT AND STATISTICAL CONSIDERATIONS.

1. Data Management Overview. Data will be collected on paper forms and questionnaires. All forms will be coded to facilitate entry into quantitative computer database. The project coordinator and research assistant will monitor the quality of the data on a weekly basis so that prompt resolution of errors and omissions can be achieved. Coding and data entry will be done as data is collected. All data will be entered in the secure online data base, using study ID numbers. Links to identifiers will be saved internally at each site. Paper data forms will be stored in locked cabinets in the study office space.

2. Data analytic plan. Preliminary analyses will begin with an examination of the distribution of variables to assess their characteristics (means, standard deviations, medians, outliers), to provide descriptive statistics of the study population, and to allow assessment of randomization. Continuous measures will be tested for normality and non-normally distributed variables will be transformed to meet the normal distribution assumption for linear models. Randomization will be tested by performing a series of Wilcoxon rank sum test and Fisher's exact test to compare the two study groups on demographic and initial clinical variables. Randomization will be stratified by BP level at entry (at 160 systolic), and block (of 10) randomization will be done for each clinical site. We will pursue standard intention-to-treat analysis of the randomized group as a primary analysis, with the ANCOVA analyses as secondary approaches should randomization have failed on critical metrics. Blinded randomization should assure that the distribution of risk factors will not confound the associations of interest, however inclusion as covariates may reduce error variance and may therefore improve statistical power. In case of missing data, appropriate data analytic techniques will be used, which may include deletion, imputation, inclusion of an indicator of missing values, or pattern-mixture modeling. All analyses for the primary aims will use an intention-to-treat approach. Sensitivity analyses will consider the importance of missing data or loss-to-follow-up (last observation carried forward, vs. imputation of data from other sources such as clinic visits). Outcomes will be analyzed using open source statistical software R.[65]

For ambulatory blood pressure data, each individual 24-hour BP reading will be assessed for adequacy (defined as at least 14 daytime and 7 nighttime readings) and transformed into summary variables (e.g. 24-hour mean blood pressures). Home blood pressure data will be recorded in 2 ways: (1) the internal memory of the home BP device will be downloaded directly at the time of 6- and 12-month visits and (2) in the event of a memory failure, the participants' log book records will be reviewed and values entered. Questionnaire data will be entered and encoded along appropriate scales and scores on these questionnaires will be examined in univariate analyses to determine response distributions and coding.

Hypothesis 1a (primary hypothesis): Improvement in systolic blood pressure measured at clinic from baseline to 12 month will be greater in the intervention vs. the usual care group. The primary outcome is the absolute change of systolic blood pressure (SBP) measured in mmHg from the study clinic randomization visit to the month 12 visit. The primary statistical test for comparison for continuous outcomes is a simple t-test across the two randomized groups. As a secondary analysis, in case of issues with randomization for differences in baseline BP, an Analysis of Covariance (ANCOVA) model with intervention group as a main effect and baseline SBP as a covariate will be fitted to study the group difference in change of SBP from baseline to week 12. Baseline sociodemographic and other clinically important characteristics at baseline will be assessed for imbalance between the two study groups and their association with the outcome using a univariate analysis (Wilcoxon rank-sum test, Kruskal-

Wallis test, Spearman correlation coefficient or Fisher's exact test). These variables will be included as covariates in the ANCOVA model if found to be moderately associated ($p < 0.15$) with the outcome or unbalanced ($p < 0.10$) between groups. Purposeful model selection method[66] will be used to select the main effects in the final model, all covariates that are significant at $p< 0.10$ will be kept in the final model. To assess the difference in the effect of patient characteristics on the outcome between intervention and control group, we will study the interaction between treatment and patient characteristics in the final model, as appropriate. Pre-specified interactions will include analyses of effects in, older vs. younger participants (< 65), , African-American vs. other races, and initial BP level (> 160 vs. lower), and educational level (less than high school degree or more). We recognize the possibility of chance findings due to multiple comparisons by these strata, P-values for interaction will be evaluated conservatively, and data will be conservatively interpreted. If numbers in any of these subgroups are too small to allow a reasonable investigation, the subgroup analysis will be dropped. Forest plots will be constructed to assess whether subgroup effects are similar, in exploratory analyses.

Hypothesis 1b: Improvement in systolic blood pressure measured by ABPM from baseline to 12 month will be greater in the intervention vs. the usual care group. For SBP measure by ABPM, we will take an average SBP over the 24 hour measurements as the outcome measure. The change in average SBP between baseline and month 12 will be compared between two intervention groups using similar analysis methods as we described for Hypothesis 1a.

Hypothesis 1c: The proportion of blood pressure reaching the *130/80 goal* at month 12 in intervention group will be greater in the intervention vs. the usual care group. The outcome is a binary variable which measures whether the blood pressure was at goal. The Fisher's exact test will be used to compare the proportion of subjects with blood pressure reaching the individualized goal at month 12 between the intervention and the usual care arm. Multivariable logistic regression will be used to study the difference in outcome between two study groups with adjustment for baseline variables if randomization is unbalanced. Univariate analyses (Fisher's exact test, Wilcoxon rank sum test) will be used to assess the association between the baseline characteristics and the outcome first, then those variables that are moderately associated ($p < 0.15$) with the outcome or unbalanced ($p < 0.10$) between study groups will be included as potential covariates in multivariable model.

Hypothesis 2. Medication related SAEs and patient-reported outcomes will be similar in the two arms and there will be similar rates of ER visits and hospitalizations in the two arms. Descriptive statistics (mean, SD, median and range) will be used to summarize the number of medication related SAEs, patient-reported outcomes, number of unscheduled clinic visits, number of ER visits and hospitalizations over the 12-month study period. The difference in proportion of subjects with medication related SAEs, proportion of subjects unscheduled clinic visits, rates of patient-reported symptoms, proportion of subjects with ER visits and proportion of subjects with hospitalizations will be compared between two study groups using Fisher's exact test.

Hypothesis 3: End-of-study levels of acceptability of the self-management protocol will be high. Patient self-efficacy will be higher in the self-management arm relative to the usual care arm. End-of-study acceptability scores will be reported descriptively as percentages. For self-efficacy scores and other scores measured at multiple time points, the change in outcome from baseline to month 12 will be compared between two study groups, and we will use similar analysis methods as those used for Hypothesis 1a.

F4. Sample size and power. Power analyses were conducted for detecting the difference in mean change of SBP over 12 months between the subjects with intervention and subjects in control group (*Hypothesis 1a*) assuming a two-sided Type I error of 0.05 and an attrition rate of 20% at month 12, with sample size estimation based on a 2 sample t-test. Based on prior literature in hypertension, we assumed a standard deviation of individual change in BP over 1 year of 16 mm Hg (conservative estimate based on standard deviation of blood pressure measurement in multiple clinical studies,[40,41] and similar to that seen in our pilot data in older CKD patients[43]) and considered a difference of 5 mm Hg to be a clinically significant difference, a smaller difference than was seen in the TASMIN studies (which found differences of 5.4 and 9.2 mm Hg with similar sample sizes). With a 20% attrition rate, we need to recruit 200 participants per arm, or 400 total participants (total of 320 participants completing the study) to have 80% power to detect a minimum of 5mmHg (Cohen's effect size of 0.31) for the difference in mean change of SBP over 12 months between intervention and control groups.
Data Safety Monitoring. We will, in addition to proactively collecting adverse events, hospitalizations, clinic visits and protocol violations, collect blood pressure data from participants at the six-month in-person visit as they self-monitor during the study. At the point where 100, 200, and 300 participants cross the 6-month point, the DSMB will review the accumulated information both from the in-clinic blood pressure averages as well as the log reports from the home BP cuffs in both groups. Although TASMIN investigators reported a less than 3% rate of protocol violations in the self-management participants, we are interested in tracking this in our intervention arm as well at the midpoint of the study. Inappropriate requests for study prescriptions will be tabulated. DSMB members will be able to examine whether out-of-range readings led to appropriate participant behavior. If this rate is considered to be too high by the DSMB, they will have the option of halting the study due to safety concerns. They will also have the option of halting the study due to SAEs or other concerns.

Chapter 10. Data Security and database management

The database for this project is being managed by UCSD's Health Services Clinical Research Center, with data security as per their prior work with VA contracts. Forms will be completed on paper during visits and then entered into the data base using ID numbers only. Full identifiers will be stored on local secure drives in master log files and paper backup copies of records will be stored locally. Data integrity checks will be performed regularly by HSCRC and the study statistician.