THE BLOOD PRESSURE LOWERING IN DIALYSIS TRIAL (THE BOLD TRIAL)

Sponsored by:

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PROTOCOL AGREEMENT

In my formal capacity as investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number: 1.1

Protocol Title: **The BOLD Trial**: Blood Pressure Lowering in Dialysis Trial

Protocol Date: February 5, 2018

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Investigator Signature *Date*

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Print Name and Title

Site # _____

Site Name _____

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LIST OF ABBREVIATIONS

Add all other abbreviations referenced in the protocol and delete any not referenced in the protocol.

AE	adverse event
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CRF	case report form
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
ESRD	End stage renal disease
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HD	Hemodialysis
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	informed consent form
IDH	intra-dialytic hypotension
IRB	Institutional Review Board
IV	intravenous
mEq	milliequivalent
PI	Principal Investigator
PHI	Protected Health Information
RAAS	renin-angiotensin-aldosterone system
SAE	serious adverse experience
SBP	systolic blood pressure

PROTOCOL SYNOPSIS

TITLE	The BOLD Trial: Blood Pressure Lowering in Dialysis Trial
PIs	Chi-yuan Hsu, MD, MSc Nisha Bansal, MD, MAS
FUNDING ORGANIZATION	NIH-NIDDK and Satellite Healthcare
NUMBER OF SITES	2
RATIONALE	Treating home blood pressure may be better than treating dialysis unit blood pressure to improve outcomes in patients on maintenance hemodialysis
STUDY DESIGN	Randomized controlled trial
PRIMARY OBJECTIVE	• To determine the feasibility of and adherence to a strategy of dry weight adjustment and anti-hypertensive medication titration to achieve home systolic blood pressure <140 mmHg vs. a pre-dialysis systolic blood pressure <140 mmHg over 4 months. • To test the safety and tolerability of an intervention to achieve home systolic blood pressure <140 mmHg.
SECONDARY OBJECTIVES	• To determine acceptability of a Bluetooth-enable home blood pressure monitor in dialysis patients • To determine whether the strategy of targeting home systolic blood pressure versus in-center pre-dialysis systolic blood pressure leads to differences in blood pressure levels
NUMBER OF SUBJECTS	50 (or 25 in each of the two arms)
SUBJECT SELECTION CRITERIA	Inclusion Criteria: 1. Provision of signed and dated informed consent form 2. Undergoing in-center, thrice weekly hemodialysis for treatment of end stage renal disease 3. Greater than 3 months since initiation of dialysis 4. Aged 18 years or above 5. Able to obtain a brachial blood pressure at dialysis and at home Exclusion Criteria: 1. Pregnancy, anticipated pregnancy, or breastfeeding as this will require increase to more than three time a week dialysis and/or preclude use of some classes of blood pressure medications 2. Incarceration or institutionalized living which may prohibit measurement of home blood pressure 3. Participation in another intervention study that may affect blood

	pressure 4. Patients in whom systolic blood pressure is not measurable (e.g. those with left ventricular assist devices) 5. Hypotension: average pre-dialysis systolic blood pressure <100 mmHg over last 2 weeks prior to screening while not taking any blood pressure medications 6. Life expectancy <4 months 7. Anticipated living donor kidney transplant within 4 months
INTERVENTION	• Dry weight and anti-hypertensive medication adjustment to target home systolic blood pressure vs. in-center pre-dialysis systolic blood pressure <140 mmHg
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	The total duration of the study is expected to be 24 months
PRIMARY ENDPOINT	• Feasibility of intervention • Adherence to intervention • Safety • Tolerability
SECONDARY ENDPOINTS	• Of the home BP participants, we will determine the modality they choose to transmit their home BP readings • Differences in blood pressures between treatment groups as assessed by blood pressure at dialysis and 44-hour intra-dialytic ambulatory blood pressure
STATISTICS **Primary Analysis Plan**	• We will quantify the screen: enroll ratio • We will report the proportion of participants in the home BP arm that complete the training, percent of home BP readings completed over the study period, and mean time from home BP measurement to transmission to the study team. • We will quantify rates of completion and drop out in each treatment arm. • We will report rates of hypotension and hypertension in each treatment arm. • We will quantify rate of intra-dialytic hypotension and symptoms related to intra-dialytic hypotension in each treatment arm.
Rationale for Number of Subjects	This pilot study is designed to test study logistics and optimize study interventions within the confines of a pilot study budget, not to find statistically significant differences between the two arms.

1 INTRODUCTION

1.1 Background

Blood pressure (BP) is a powerful and modifiable risk factor for cardiovascular (CVD) events and death in the general population.[1-4] Observational studies document a progressive increase in risk of BP-related end-organ damage as systolic BP (SBP) rises above 115 mmHg.[1-4] Lowering of SBP to less than 140 mmHg had been the conventional target for treatment of hypertension.[5] Recent data from the SPRINT trial showed that targeting even lower SBP targets (<120 mmHg) lowered rates of CVD events and death in an at-risk population with or without moderate maintenance kidney disease.[6]

End-stage renal disease (ESRD) patients on maintenance maintenance hemodialysis (HD) have high rates of CVD events and death.[7-9] Approximately 2 million ESRD patients worldwide are treated with HD.[10] Reported CVD mortality rates are 10 to 30 times higher in HD patients compared with the general population.[7] Hypertension is present in >90% of patients at the initiation of HD[10] and persists over time in more than two-thirds.[10] Improved management of BP in this high risk population could potentially yield substantial benefits.

Management of BP in HD patients is in dire need for better evidence to guide management. The management of BP in HD patients has long presented a conundrum for physicians.[11-14] Differing from the general population, observational studies have repeatedly shown that HD patients with SBP measured prior to the dialysis treatment (pre-dialysis SBP; also referred to as dialysis-unit SBP) of <140 mmHg experience higher risk of mortality than those with SBP >140 mmHg (U-shaped association).[11-24] And patients with pre-dialysis SBP of 150-179 mmHg appear to be at similar, if not lower, risk for death compared to those with pre-dialysis SBP of 140-149 mmHg, even accounting for differences in patient characteristics. Nevertheless, practice guidelines have continued to promote treating pre-dialysis SBP.[25-29] For example, a pre-dialysis BP goal of <140/90 mmHg is recommended by Kidney Disease Outcomes Quality Initiative (KDOQI), despite the acknowledgement "it is unclear which blood pressure reading should be used as the guide for therapy."[30]

2 STUDY RATIONALE

We propose that solving this conundrum requires physicians to measure and treat out-of-dialysis-unit SBP rather than dialysis-unit SBP. We base our hypothesis on newly generated observational data from a NIH-sponsored multi-center cohort of incident HD patients (the Maintenance Renal Insufficiency Cohort [CRIC] study). We confirmed a "paradoxical" U-shaped association between *dialysis-unit SBP* and risk of all-cause mortality (**Figure 1 left panel**), but also showed a linear stepwise association between SBP *measured outside of the dialysis-unit* and risk of mortality (**Figure 1 right panel)**, in a pattern similar to that in the general population.[24]

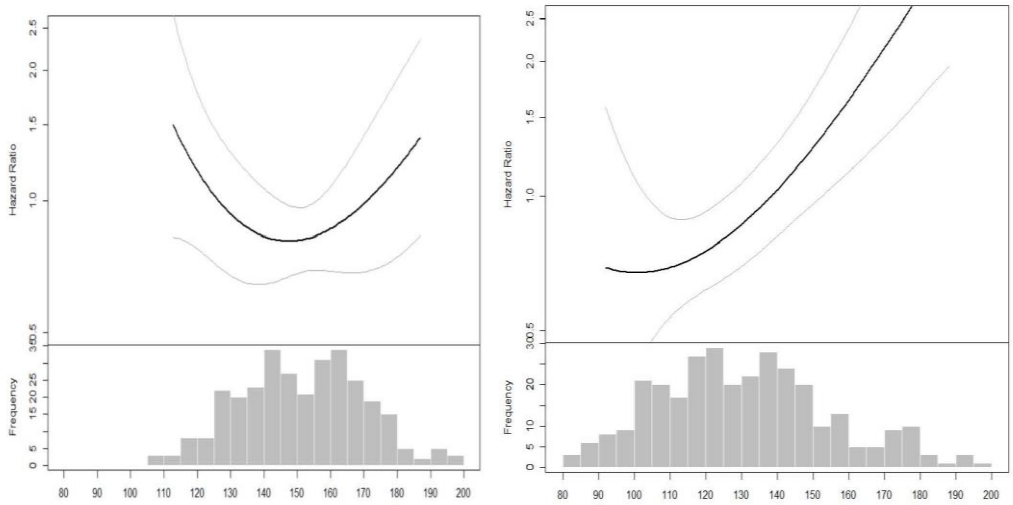
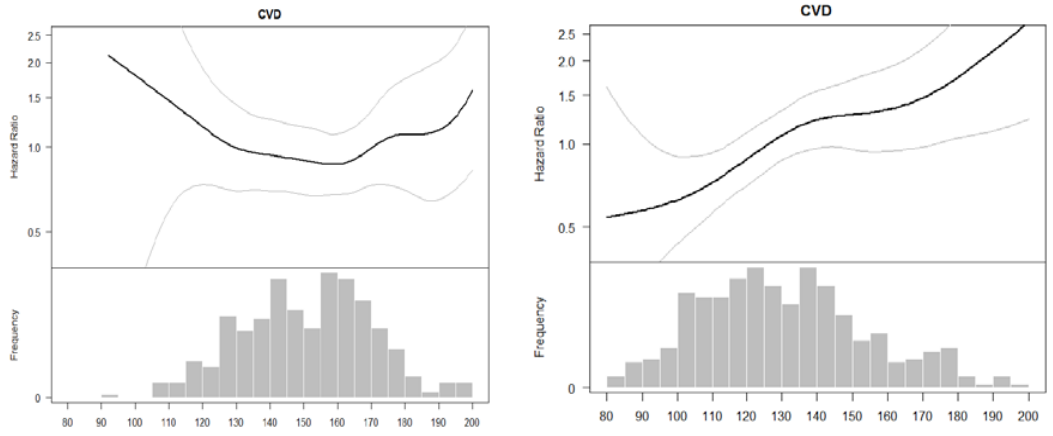


Figure 1. Association of pre-dialysis SBP (left panel) and out-of-dialysis-unit SBP (right panel) and risk of all-cause mortality (Bansal…Hsu, *Hypertension* 2015)

Our data are consistent with prior single-center studies.[15,31-33] We have since investigated adjudicated cardiovascular (CVD) events, which is novel as all-cause death is more commonly available as an outcome in dialysis epidemiology studies. Similar to all-cause mortality, there was a U-shaped association between dialysis-unit SBP and risk of CVD events (defined as a composite of heart failure, myocardial infarction, ischemic stroke, and peripheral artery disease events)(**Figure 2 left panel)**. In contrast, there was a linear stepwise association between out-of-dialysis-unit SBP with risk of CVD events **(Figure 2 right panel)**.[34]

Figure 2. Association of pre-dialysis SBP (left panel) and out-of-dialysis-unit SBP (right panel) and risk of cardiovascular events (Bansal…Hsu, *Hypertension* 2017)



Since these associations were observed in the *same patients*, they refute prior hypotheses that the reason for the U-shaped association between dialysis unit SBP and adverse outcomes is due to inclusion of "sicker" patients (such as those with severe systolic heart failure)[35,36] or due to physiological state unique to HD patients.[11,37] Instead, we hypothesize the inability to mount an elevated BP in response to fluid accumulated between HD sessions—reflected in the dialysis-unit BP documented at the start of each HD session—is an adverse prognostic marker. In short, dialysis-unit BP may reflect mostly the transient effect of inter-dialytic volume expansion, rather than being a good overall indication of BP load as it relates to end-organ damage. Alternatively, perhaps some type of "white-coat hypertension/effect" particular to HD patient is operative here. But regardless of the exact pathophysiologic mechanism, these data strongly suggest that the focus should be on measuring and *treating out-of-dialysis-unit BP, rather than dialysis-unit BP*, which will be a significant change from current practice.

In our recent study, dialysis-unit SBP was generally higher than out-of-dialysis-unit SBP and the correlation was weak between the two measures (p=0.34). Nearly two-thirds (166/269=62%) of patients in this study with dialysis unit SBP >140 mmHg had out-of-dialysis-unit SBP <140 mmHg (**Table 1**). Thus, targeting dialysis-unit SBP may be leading to BP overtreatment in a substantial number of dialysis patients (those with high dialysis-unit but low out-of-dialysis-unit SBP), which may cause intra-dialytic hypotension, myocardial stunning and adverse cardiac remodeling.[38-40] Concurrently, other patients may be undertreated (those with low dialysis-unit SBP but high out-of-dialysis-unit SBP), which may result in end-organ damage.

Table 1. Cross-tabulation of dialysis-unit vs. out-of-dialysis-unit SBP in the CRIC study (N=377) (Bansal…Hsu, Hypertension 2017)

2.1 Risk / Benefit Assessment

This trial proposes to target an out-of-dialysis-unit SBP <140 mmHg vs. dialysis-unit SBP <140 mmHg among maintenance HD patients by adjusted estimated dry weight and anti-hypertensive medications. The algorithm will adjust RAAS inhibitors, beta-blockers, calcium channel blockers and other anti-hypertensive medications. The doses that will be prescribed will be within the scope of FDA approved doses. Potential risks of the study medications include: hypotension and bradycardia and associated symptoms such as dizziness. Subjects will be monitored for these potential risks closely through direct contact with the study coordinators. There is also a small potential risk of loss of confidentiality.

Blood pressure is one of the most important risk factors for cardiovascular disease and death in the general population. HD patients are at greatly increased risk of cardiovascular disease and death. So optimizing BP control in HD patients could potential yield substantial benefit. The proposed study is a pilot clinical trial test to test the feasibility and safety of treating dialysis-unit versus out-of-dialysis-unit blood pressure in dialysis patients. This will be most useful to practicing physicians, patients and public health planners.

Since the value of the findings is potentially large, we believe the proposed study's benefits outweigh the risks.

3 STUDY OBJECTIVES

3.1 Primary Objectives

The primary objectives of the BOLD Trial are:

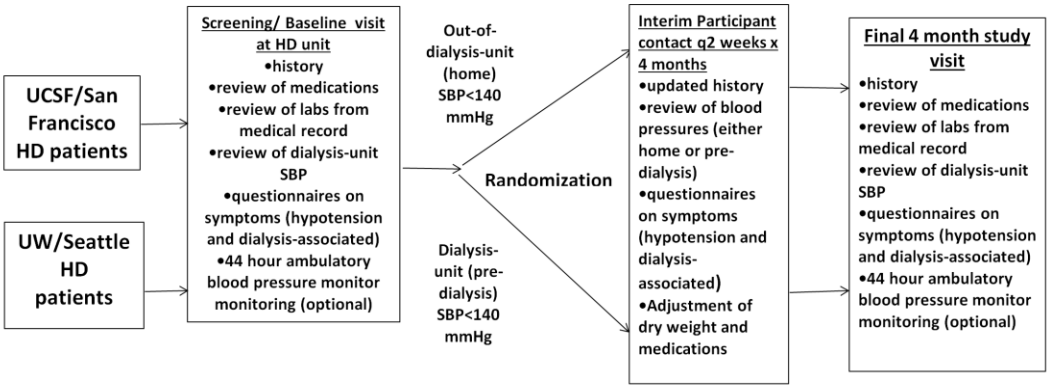
To determine the feasibility of and adherence to a strategy of dry weight adjustment and anti-hypertensive medication titration to achieve home systolic blood pressure <140 mmHg vs. a pre-dialysis systolic blood pressure <140 mmHg over 4 months.

To test the safety and tolerability of an intervention to achieve home systolic blood pressure <140 mmHg.

4 STUDY DESIGN

4.1 Study Overview

This is a two center, placebo-controlled, randomized 4 month trial of 50 subjects. This will be a pilot clinical trial to test the feasibility, adherence, safety and tolerability of a strategy of targeting home SBP <140 mmHg vs. dialysis-unit (pre-dialysis) SBP <140 mmHg. These targets will be achieved using an algorithm of estimated dry weight and anti-hypertensive medication adjustment. Home BP measures will be recorded every other week and transmitted to the study team. We have chosen the same SBP target and the same algorithm for both arms so we can test the effect of the *setting* of BP measurement (rather than a specific BP target or medication). Participants will have contact with the study team every 2 weeks to obtain information on interim study outcomes (updated medical history, completion of study questionnaires) and adjust estimated dry weight and anti-hypertensive medications. A final study visit will occur at 4 months.



5 CRITERIA FOR EVALUATION

5.1 Primary Outcomes

Feasibility

- The study will determine how many eligible participants (and their nephrologists) agree to participate in the study (screen: enroll ratio)

Adherence

- We will determine what proportion of participants in the home BP arm successfully complete home BP training, perform home BP readings every other week and transmit data in a timely manner to the study team via any method.
- We will determine the drop out and completion rate in each arm.

Safety

- We will monitor for excessively low blood pressure readings (e.g. dialysis unit blood pressure readings of <90 mmHg) and dangerous consequences of excessively low blood pressure (e.g. syncope, falls).
- We will monitor for excessively high blood pressure readings (e.g. dialysis unit blood pressure readings of >200 mmHg) and dangerous consequences of excessively high blood pressure (e.g. flash pulmonary edema).

Tolerability

- We will review the dialysis record every 2 weeks to determine frequency of intra-dialytic hypotension, defined as SBP<90 mmHg during dialysis
- For symptoms assessment, we will contact participants (in both treatment groups) once every 2 weeks. Patients will be queried via interview (either phone or during dialysis) about adverse events noted during the immediate past HD session which will include symptoms of hypotension[92] such as cramping (yes/no), dizziness/lightheadedness (yes/no) and fatigue (yes/no).[92-94] We will

also ask patients "how long did it take you to recover from your last dialysis treatment."

5.2 Secondary Outcomes

- Acceptability of a Bluetooth-enabled home BP monitor: of the home BP participants, we will determine the modality they choose to transmit their home BP readings (e.g. via Bluetooth, manual log, phone, etc)
- Differences in blood pressures between treatment groups as assessed by: (1) pre-dialysis SBP and DBP; (2) post-dialysis SBP and DBP and (3) 44-hour intra-dialytic ambulatory blood pressure monitoring from beginning to theend of the study (optional)

6 SUBJECT SELECTION

6.1 Study Population

Subjects with ESRD on maintenance in center hemodialysis who meet the inclusion and exclusion criteria will be eligible for participation in this study.

6.2 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Undergoing in-center, thrice weekly hemodialysis for treatment of end stage renal disease
3. Greater than 3 months since initiation of dialysis
4. Aged 18 years or above
5. Able to obtain a brachial blood pressure at dialysis and at home

6.3 Exclusion Criteria

1. Pregnancy, anticipated pregnancy, or breastfeeding as this will require increase to more than three time a week dialysis and/or preclude use of some classes of blood pressure medications
2. Incarceration or institutionalized living which may prohibit measurement of home blood pressure
3. Participation in another intervention study that may affect blood pressure
4. Patients in whom systolic blood pressure is not measurable (e.g. those with left ventricular assist devices)
5. Hypotension: average pre-dialysis systolic blood pressure <100 mmHg over last 2 weeks prior to screening while not taking any blood pressure medications
6. Life expectancy <4 months
7. Anticipated living donor kidney transplant within 4 months

6.4 Strategies for Recruitment and Retention

- Target study sample size: Our target sample size is 50 participants (25 participants at UCSF and 25 participants at UW).
- Source of participants: outpatient hemodialysis units affiliated with UCSF and UW or where UCSF and UW faculty practice.
- We will use the Electronic Medical Record (EMR) or directly query dialysis healthcare providers at UCSF and UW to identify eligible participants. We may confer with the primary nephrologist prior to approaching the patient if there are concerns about the suitability of the patient to participate in a research study.
- Incentives: Participants will be provided $25-50 per month for participation in the study, depending on the visit number and the site.

7 STUDY TREATMENTS

7.1 Method of Assigning Subjects to Treatment Groups

Enrolled subjects, stratified by site, will be randomly assigned in a 1:1 allocation to one of 2 groups (25 patients at both sites): (1) home SBP<140 mmHg and (2) in-center pre-dialysis SBP<140 mmHg. Randomization will be in done via Redcap in random size blocks to minimize bias in randomization and to ensure balanced assignment at each site. Both groups will be followed in parallel.

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the subject or subject's legal representative. If appropriate, assent must also be obtained prior to conducting any study-related activities.

7.2 Blinding

Due to the nature of the intervention, the study will not be blinded to either the investigators nor the study participants.

7.3 Measuring Home SBP

We will use the Microlife WatchBP Home A BT device.

After appropriate training by study personnel, study participants will be asked to take their own BP at home every two weeks.

- Home BP will be taken on a non-dialysis day
- Participants will be instructed to obtain a BP measure in the morning on a non-dialysis day (3 consecutive BP measures obtained at one sitting)
- Participants will be instructed to obtain a BP measure in the evening on a non-dialysis day (3 consecutive BP measures obtained at one sitting)

Participants will have several options to share the home blood pressure readings with the study team.

- For participants with a smart phone, the BP readings can be automatically downloaded via Bluetooth to an app then to a secure cloud server.
- Participants can download the readings from the home blood pressure device via USB drive and shared with the study team.
- Participants can keep a paper log of home blood pressure readings to share with the study team.
- Participants can text,phone or email the results to the study team.

We will allow assistance from family members or other caregivers and work in other ways with study participants to minimize burden of data transmission.

7.4 Measurement of In-Center Pre-Dialysis SBP

Pre-dialysis BP will be taken by an automated BP device by dialysis unit staff using regular dialysis unit equipment.

We will educate the dialysis unit staff and participants to allow patients to relax (ideally a 5 minute rest) prior to BP being measured and that the BP cuff should be placed over bare arm or a thin garment.

The pre-dialysis BP will be reviewed by the study team every 2 weeks.

7.5 Treatment Adherence

Participants in both treatment arms will have regular contact with the study coordinator (scheduled approximately every 2 weeks), where they will be reminded/encouraged to take all prescribed anti-hypertensive medications and medication reconciliation will be performed. For participants in the home BP treatment arm, home BP readings will be reviewed and assessed for adherence.

7.6 Temporary Discontinuation

Temporary discontinuation will be allowed in the study protocol in the event of hospitalization, travel out of town or other unavoidable breaks. Participants will be re-evaluated at hospital discharge or return to regular maintenance dialysis unit and resume participation in the trial barring any clinical contraindications. This mimics how study intervention would be implemented in actual clinical practice.

7.7 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she fails to engage in participants contacts (either by phone or in the dialysis unit) of greater than 1 month and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to engage in contacts with the study team :

- The site will attempt to contact the participant and counsel the participant on the importance of maintaining the assigned contact schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant. These contact attempts should be documented in the participant's study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY PROCEDURES AND GUIDELINES:

8.1 Approach to blood pressure management

For participants in the usual care treatment group, blood pressure readings measured for clinical purposes at the dialysis unit will be tracked, recorded and in response we will modify the dry weight and anti-hypertensive medications per algorithm below (including the date in which any adjustments to dry weight and medication dose were implemented).

For participants in the home blood pressure treatment group, we will track and record the home blood pressure measures and modify the dry weight and anti-hypertensive mediations per algorithm below.

The following approach will be used to achieve SBP <140 mmHg and >100 in both treatment groups, which will be implemented every 2 weeks.

- Dry weight adjustment (with counseling on dietary sodium and fluid intake if appropriate)
- Adjustment of standard anti-hypertensive medications (e.g. angiotensin converting enzyme [ACE] inhibitors/angiotensin receptor blockers [ARB][collectively referred to as RAAS inhibitors]; β-blockers; calcium channel blockers). The protocol will be as follows

  1. If SBP<100 mmHg:
     - Increase dry weight by 0.2-0.5 kg until patient euvolemic
     - If SBP still <100 mmHg, will titrate down/off patient's existing medications in the following order: anti-adrenergic; vasodilators; alpha blockers; calcium channel blockers; β-blockers; RAAS inhibitors

  2. If SBP 100-140 mmHg:
     - No adjustment of dry weight or medications; recheck in two weeks

  3. If SBP>140 mmHg
     - Decrease dry weight by 0.2-0.5 kg until patient euvolemic
     - If SBP still >140 mmHg, will increase doses of patient's existing medications in the following order: RAAS inhibitors; β-blockers; calcium channel blockers; alpha blockers; vasodilators; anti-adrenergic
     - If patient is at maximum tolerated doses of current medications and SBP>140 mmHg, will add doses (and titrate up) of new medication

classes in the following order (not duplicating classes with patient's existing medications): RAAS inhibitors; β-blockers; calcium channel blockers; alpha blockers; vasodilators; anti-adrenergic. Choice of specific anti-hypertension medications within each class will prioritize those that have low dialyzability and are covered by the patient's existing insurance coverage. The dialyzability characteristics of specific medications is outlined in the table below (from Georgianos and Agarwal CJASN 2016[41]):[42-44]

Table 6. Pharmacokinetics of selected antihypertensive agents in patients on dialysis (5,33)

Drug Class and Drug	Usual Dosage	Route of Excretion	Removal with Dialysis, %	Supplement Dose for Dialysis, mg
Angiotensin–converting enzyme inhibitors				
Benazepril	5–40 mg every day	K (L)	20–50	5–10
Captopril	12.5–50 mg three times per day	K	50	12.5–25
Enalapril	2.5–10 mg every 12 h	K (L)	50	2.5–5
Fosinopril	10 mg every day	K (L)	None	None
Lisinopril	2.5–10 mg every day[a]	K	50	2.5–5
Perindopril	2–8 mg every day	K (L)	50	2
Ramipril	5–10 mg every day	K (L)	20	2.5
Trandolapril	0.5–4 mg every day	K (L)	30	0.5
Angiotensin receptor blockers				
Candesartan	8–32 mg/d	K (L)	None	None
Eprosartan	600–1200 mg/d	L	None	None
Irbesartan	75–300 mg/d	L	None	None
Losartan	50–100 mg every day	K (L)	None	None
Olmesartan	10–40 mg/d	K (L)	None	None
Telmisartan	40–80 mg/d	L	None	None
Valsartan	80–320 mg every day	K (L)	None	None
Mineralocorticoid receptor antagonists				
Spironolactone	25–50 mg every day	K (L)	None	None
Eplerenone	50–100 mg every day	K (L)	None	None
***β*-Blockers**				
Atenolol	25 mg every day[b]	K (L)	50	25–50
Bisoprostol	2.5–20 mg every day	L	None	None
Carvedilol	25 mg twice a day	L (K)	None	None
Labetalol	200–600 mg twice a day	K (L)	None	None
Metoprolol	50–100 mg twice a day	K (L)	None	None
Nadolol	80–100 mg twice a day	K	50	80
Propranolol	80–160 mg twice a day	K	None	None
Calcium-channel blockers				
Amlodipine	2.5–10 mg every day	L	None	None
Felodipine	5–10 mg every day	L	None	None
Nicardipine	20–40 mg three times a day	L	None	None
Nifedipine XL	30–90 mg every day	L	None	None
Lacidipine	2–6 mg/d	L (K)	None	None
Manidipine	10–20 mg/d	L	None	None
Diltiazem CD	180–360 mg	L (K)	None	None
Verapamil CD	180–360 mg every day	L (K)	None	None
***α*-Adrenergic blockers**				
Doxazosin	1–16 mg every day	L	None	None
Prazosin	1–15 mg twice a day	L	None	None
Terazosin	1–20 mg every day	L	None	None
Others				
Clonidine	0.1–0.3 mg twice a day/three times a day	K (L)	5	None
Hydralazine	25–50 mg three times a day/ twice a day	L	25–40	None

K, kidney; L, liver.
[a]Preferred dosage for lisinopril is 10–40 mg three times weekly after dialysis. The maximum dose recommended in hemodialysis patients is 40 mg per day.
[b]Preferred dosage for atenolol is 25 mg–100 mg three times weekly after dialysis to maximize the antihypertensive effect and convenience of dosing.

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is diagrammed in Appendix 1.

8.2 Clinical Assessments

8.2.1 Demographics

Demographic information (date of birth, gender, race/ethnicity) will be recorded at the Screening visit.

8.2.2 Medical History and Concomitant Medications

Relevant medical history, including history of current disease and concomitant medication use (including dose, route and frequency of administration) will be recorded at screening visit and updated at all follow-up study visits.

8.2.3 Blood pressure: Assessment of episodes and symptoms of intra-dialytic hypotension

We will review the dialysis record approximately every 2 weeks for all study participants to determine frequency of intra-dialytic hypotension (IDH; defined as intra-dialytic SBP<90 mmHg[45]). This will be obtained from the dialysis unit medical record and quantified as % of sessions with IDH over the 4-month study duration. For symptoms assessment, we will contact participants (in both arms) once approximately every 2 weeks. Patients will be queried via interview (either phone or during dialysis) about adverse events noted during the past HD session(s) which will include symptoms of hypotension such as cramping (yes/no), dizziness/lightheadedness (yes/no) and fatigue (yes/no). We will also ask patients "how long did it take you to recover from your last dialysis treatment," a validated question that is an important patient-centered outcome.[46] Patient responses to this question will be reported in minutes.

8.2.4 Adverse Events

Information regarding occurrence of adverse events will be captured throughout the study. Outcomes in relation to study intervention will be recorded on the case report form (CRF).

8.3 Clinical Laboratory Measurements

Standard clinical laboratory measures will be documented for the study at all study visits. The University of Washington site will be collecting 10 ml of plasma and 10 ml of serum for planned biomarker measurements at the completion of the study. The University of Washington site will also collect 5 ml of serum for pregnancy test for women of childbearing potential at the screening visit.

9 EVALUATIONS BY VISIT

9.1 Visit 0: Screening visit

1. Review the study with the subject and obtain written informed consent and HIPAA authorization
2. Assign the subject a unique screening number.
3. Record demographics data.

4. Record medical history, including a history of ESRD, dialysis access, dialysis initiation date and history of prior kidney transplants through participant questionnaires and review of the medical record
5. Record concomitant medications through participant questionnaires and review of the medical record
6. Record and review previous pre-dialysis blood pressures from the prior 2 weeks
7. Record previous clinical laboratory values (with corresponding date) taken from the dialysis and other medical records
8. Administer questionnaire of symptoms of hypotension during the last hemodialysis session(s): cramping (yes/no), dizziness/lightheadedness (yes/no), and fatigue (yes/no).
9. Ask open-ended question: "How long did it take you to recover from your last dialysis session" (responses in minutes or hours)
10. Obtain blood (5 ml) for serum pregnancy test for women of childbearing potential.

9.2 Visit 1: Baseline Visit

1. Update information obtained at screening visit
2. Record the following information from the dialysis records from the prior two weeks: estimated dry weight, pre-dialysis blood pressures, episodes of intra-dialytic hypotension

3. Randomize participant to one of two study arms

4. If participant is randomized to home BP arm, train participant on use and transmission of home BP measures

5. Schedule subject for next study contact in approximately14 days, either during patient's regularly scheduled dialysis or a telephone call

6. Optional: Place 44-hour ambulatory blood pressure cuff and train patient on use (study team will also coordinate with patient return of 44-hour ambulatory blood pressure monitor.) Administer 44-Hour ABPM Experience Questionnaire.

7. Blood sample collected at beginning of dialysis treatment via dialysis access and usual dialysis procedures (at UW only)

9.3 Visits 2-8 (occurring approximately every 2 weeks)

1. Record any Adverse Experiences
2. Review any home BP measures (if applicable)
3. Concomitant medications review
4. Updated medical history/interim events/interim hospitalizations
5. BP medication review and assessment of adherence to BP medications

6. Review dialysis unit records: estimated dry weight, pre-dialysis blood pressures, episodes of intra-dialytic hypotension
7. Record any updated laboratory values (with corresponding date) taken from the dialysis records
8. Record vital signs, including weight and dialysis unit BP
9. Administer questionnaire of symptoms of hypotension during the last hemodialysis session: cramping (yes/no), dizziness/lightheadedness (yes/no), and fatigue (yes/no).
10. Ask open-ended question: "How long did it take you to recover from your last dialysis session" (responses in minutes or hours)
11. If subject is a woman of child-bearing age, she will also be asked about possible pregnancy (UW only).
12. Adjust estimated dry weight and medications as per study physician's recommendations

9.4 Visit 9 (final study visit)

1. Same procedures listed in for visits 2-8
2. Blood sample collected at beginning of dialysis treatment via dialysis access and usual dialysis procedures (at UW only)
3. Administer Home BP Device Experience Questionnaire.
4. Optional: Place 44-hour ambulatory blood pressure cuff and train patient on use (study team will also coordinate with patient return of 44-hour ambulatory blood pressure monitor). Administer 44-Hour ABPM Experience Questionnaire.

10 ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

10.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence during a clinical investigation and that does not necessarily have a causal relationship with the study intervention. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease that may or may not be associated with the administration of a study intervention.

The study team will probe, via discussion with the subject and review of the medical record, for the occurrence of AEs during each subject visit and record the information in the site's source documents. Adverse events will be recorded in the patient CRF. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study intervention, or if unrelated, the cause.

AE Severity

AE severity will be classified as:

Table 1. AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

AE Relationship to Study Intervention

The relationship of an AE to the study intervention should be assessed using the following the guidelines in Table 2.

Table 2. AE Relationship to Study Intervention

Relationship to Intervention	Comment
Definitely	Previously known effect of intervention; or an event that follows a reasonable temporal sequence from administration of the intervention; that follows a known or expected response pattern to the suspected intervention; and that is not explained by any other reasonable hypothesis.
Probably	An event that follows a reasonable temporal sequence from administration of the intervention; that follows a known or expected response pattern to the suspected intervention; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from administration of the intervention; that follows a known or expected response pattern to that suspected intervention; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study intervention.

10.2 Serious Adverse Experiences (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

10.2.1 Serious Adverse Experience Reporting

Study sites will document all SAEs that occur (whether or not related to study drug) per UCSF CHR and UW IRB Guidelines. The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed.

In accordance with the standard operating procedures and policies of the local Institutional Review Board (IRB), the site investigator will report SAEs to the IRB.

We will collect data on potential adverse events from several sources and incorporate them into the adverse event database. These sources include:

- Reports from participants of any occurrences of concern to them, to be obtained from calls to toll-free or local study numbers provided in the Consent Form and included in all post-enrollment Contact Forms
- Laboratory database and reports of new hospitalizations

Adverse events data from the study-site specific call lines will be reviewed weekly, as will AE reports from all sources, by the site PI and site study clinician(s), any Serious Adverse Events that are identified will be reported promptly to the DSMB and IRB(s).

10.2.2 Post-study Adverse Event

We will continue to collect information on Adverse Events for up to 4 weeks after the study follow up period ends for all participants unless they ask us to not collect follow-up data.

11 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

11.1 Early Discontinuation of Study Intervention

A subject may be discontinued from study intervention at any time if the subject or the investigator (Sponsor) feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Subject withdrawal of consent
- Subject is not adherent with study procedures
- Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue study treatment
- Protocol violation requiring discontinuation of study treatment

- Lost to follow-up

If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the investigator until the abnormal parameter or symptom has resolved or stabilized.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents. Subjects enrolled at least 1 month should be encouraged to come in for a final visit (and the procedures to be followed would include those for their next scheduled visit).

11.2 Replacement of Subjects

Subjects who withdraw from the study prior to 1 months will be replaced.

12 PROTOCOL VIOLATIONS

A protocol violation occurs when the subject or investigator (Sponsor) fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria
- Failure by the study team to schedule every other week participant contact

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The UCSF and UW IRBs will determine if a protocol violation will result in withdrawal of a subject.

When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by the investigator. A copy of the form will be filed in the site's regulatory binder and in the Sponsor's files.

13 DATA SAFETY MONITORING

The Data Safety Monitoring Board (DSMB) will review data relating to safety and efficacy, to conduct and review interim analyses, and to ensure the continued scientific validity and merit of the study, according to the Data Safety Monitoring Board Operations Manual and a DMC Charter to be established for this protocol. There will be one interim review conducted by the DMC for the purpose of monitoring study conduct and assessing patient safety. Further details regarding the timing and content of the interim reviews is included in the statistical section below.

14 STATISTICAL METHODS AND CONSIDERATIONS

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed. The SAP will contain any modifications to the analysis plan described below.

14.1 Data Sets Analyzed

All patients who are randomized into the study will be included in the analysis.

14.2 Demographic and Baseline Characteristics

The following demographic variables at screening will be summarized by study treatment group including (but not limited to): race/ethnicity, gender, age, dialysis vintage (number of years on maintenance dialysis), comorbidity.

14.3 Analysis of Primary Endpoint

We will quantify the screen: enroll ratio. We will quantify rates of retention and adherence in each arm of the study and report characteristics of those lost to follow-up.

We will quantify % of patients in the home BP arm who can successfully complete home BP training, % who can transmit every other weekhome BP readings in a timely manner to the study team via any method and % who successfully implement electronic transfer of data via Bluetooth/smartphone.

Adverse events will be tabulated by treatment group and will include the number of patients for whom the event occurred, the rate of occurrence, and the severity and relationship to study intervention.

We will determine frequency of excessively high or low blood pressures, frequency of intra-dialytic hypotension and symptoms related to these in all enrollees.

14.4 Analysis of Secondary Endpoints

In both groups, we will use descriptive statistics (such as mean and standard deviation) to quantify changes in pre-dialysis blood pressure and 44-hour ABMP results at the end of the study.

We will also describe patterns of dry weight target and blood pressure medication use (number and dosage).

14.5 Sample Size and Randomization

The target sample size is 50 participants (25 in each arm), which was chosen based on feasibility within the budget of these grants. This pilot study was designed to test study logistics and optimize study interventions, not to find statistically significant differences between the two arms

Randomization will be in done in random size blocks to minimize bias in randomization and to ensure balanced assignment within strata.

15 DATA COLLECTION, RETENTION AND MONITORING

15.1 Data Collection Instruments

The investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug.

Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF) OR paper CRF when the information corresponding to that visit is available. *For eCRFs:* If a correction is required for an eCRF, the time and date stamps track the person entering or updating eCRF data and creates an electronic audit trail. *For paper CRFs:* If a correction is made on a CRF, the study staff member will line through the incorrect data, write in the correct data and initial and date the change.

The investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the investigator. A copy of the CRF will remain at the investigator's site at the completion of the study.

15.2 Data Management Procedures

The data will be entered into a validated database. The research team will be responsible for data processing. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

15.3 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

15.4 Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of final reports), data for analysis is locked and cleaned per established procedures.

15.5 Availability and Retention of Investigational Records

The investigator must make study data accessible to the DSMB, IRB, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained

that includes the signed Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that subject. The investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents (patient files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of two years following completion of the study.

15.6 Monitoring

Informal site visits will be conducted to assess completeness of record-keeping (e.g., consents), compliance with Good Clinical Practice (GCP) criteria, and assure that the protocol is being implemented consistently at the study site.

15.7 Subject Confidentiality

In order to maintain subject confidentiality, only a site number, subject number and subject initials will identify all study subjects on CRFs.

16 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject. The investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

16.1 Protocol Amendments

Any amendment to the protocol will be written by the investigators. Protocol amendments cannot be implemented without prior written IRB approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days.

16.2 Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the IRB of each participating center prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB in accordance with the standard operating procedures and policies of the IRB, and the investigator will keep the IRB informed as to the progress of the study. The investigator will obtain assurance of IRB compliance with regulations.

Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB. The IRB's written unconditional approval of the study protocol and the informed consent form will be in the possession of the investigator before the study is initiated. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

16.3 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a, b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The investigator will prepare the informed consent form, assent and HIPAA authorization and provide the documents to the Sponsor or designee for approval prior to submission to the IRB. The consent form generated by the investigator must be approved by the IRB. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonization and will also comply with local regulations. The investigator will send an IRB-approved copy of the Informed Consent Form to the Sponsor (or designee) for the study file.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects (or their legal representatives) must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB, assent from the subject will also be obtained. If a subject is unable to sign the informed consent form (ICF) and the HIPAA authorization, a legal representative may sign for the subject. A copy of the signed consent form (and assent) will be given to the subject or legal representative of the subject and the original will be maintained with the subject's records.

16.4 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by participating investigators. The publication or presentation of any study results shall comply with all applicable privacy

laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

16.5 Investigator Responsibilities

By signing the Protocol Agreement, the investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the IRB, except when to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the study.
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Report to the Sponsor or IRB any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
5. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the IRB.
7. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
8. Promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to subjects or others.
9. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
10. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

APPENDIX 1.

	VISIT 0 SCREENING VISIT	VISIT 1 Baseline Visit	VISITS 2-8 (in person during regularly scheduled dialysis or phone call) 14 (+/-7) days apart	VISIT 9
Informed Consent	X			
Medical History	X	X	X	X
Recording of vital signs, including blood pressure and weight	X	X	X	X
Review of medical and dialysis records	X	X	X	X
Medication review	X	X	X	X
Record laboratory values	X	X	X	X
Questionnaires on episodes and symptoms of high or low blood pressure	X	X	X	X
Randomization		X		
Teaching of home BP monitor		X		
Reviewing BP medications and pre- and post-dialysis weights			X	X
Review home BP readings (if applicable)			X	X
Concomitant Medication Review			X	X
Adjust EDW or BP medications			X	X
Adverse Experiences			X	X
44-hour ambulatory blood pressure monitor		X		X
Blood draw		X		X

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