CHAPTER 3. BASELINE VISITS AND PROCEDURES

3.1 Who Enters the Baseline Period?

Before entering the baseline period, participants will have been screened to ensure that they meet the inclusion criteria and that none of the exclusion criteria are present. The only exclusion criteria that should be in question at this point, is whether or not the SDUBPM is high enough for the patient to be eligible for the study.

If the patient meets all eligibility criteria except the 2-week averaged SDU Sys BP > 155 mmHg (which needs to be established during the baseline period) then proceed. If an exclusion is identified, do not bring the patient into the baseline period. Remember that, in some instances, depending on the nature of the exclusion criterion, the patient may be re-screened in the future for the study.

3.2 Length of the Baseline Period

Once a patient consents, baseline data collection should begin as soon as possible. The baseline period should be completed as efficiently as possible. It is hoped that for most patients, Baseline can be completed in four to six weeks. The time limit for randomization is 4 calendar months.

For the purposes of calculating length of time in baseline, the start date for baseline data collection is the date of the first Standardized Dialysis Unit Blood Pressure Measurement of the Baseline Period (Form 109, Q4). A patient must be randomized within 4 calendar months of the date on Form 109.

3.3 Purpose of the Baseline Period

The purpose of the baseline period is to:

1) Obtain 2-week averaged SDUBPM
2) Back titrate antihypertensive therapy (AHT), as needed, to achieve a 2-week averaged SDU Sys BP > 155 mmHg (required for enrollment)
3) Assess compliance with SDUBPM
4) Obtain all required baseline data including cardiac MRI

3.4 Deciding if Backtitration of AHT is Needed During the Baseline Period

SDUBPM will be measured before each dialysis treatment as described in Chapter 6. Enter the pre-dialysis SDUBPM readings for each dialysis treatment into the Standardized Dialysis Unit Blood Pressure Form 109. Once you have entered 2 weeks of Form 109s, a 2-week averaged SDUBPM will be automatically calculated and a BID Study Blood Pressure Summary Report will be generated (See Appendix B). Complete all of the information on Forms 110 and 111 (Form 110-Weekly Interventions and Symptoms and Form 111-Weekly Dialysis Details) and review it as well as the BID Study Blood Pressure Summary Report with the PI to determine whether the patient’s blood pressure is in range for randomization now, or whether antihypertensive therapy needs to be backtitrated.
If the average of the pre-dialysis SBPs over 2 weeks by SDU Sys BP is:

- **>155 mmHg**, and the patient is not experiencing intra-or post-dialysis hypotension, the participant is eligible for randomization. Schedule the MRI as soon as possible. If the patient is experiencing intra-or post-dialysis hypotension (as reviewed on Forms 110/111), the PI will decide whether or not the patient should be randomized. In general he/she should not be randomized if there is persistent hypotension during or after dialysis.

- **<155 mmHg** antihypertensive medications should be backtitrated (See Section 3.5).

### 3.5 Backtitrating Therapy During Baseline

Prior to any backtitration of medications, it is recommended that the Principal Investigator communicate with the participant’s personal physician that the participant may be randomized to either the 110-140 mmHg or 155-165 mmHg SYS BP goal.

In the vast majority of cases, backtitration of antihypertensive therapy will be the means to increase blood pressure to reach a 2 –week averaged SDU Sys BP of **> 155 mmHg**.

If the patient is taking more than one antihypertensive agent, the order in which AHT drugs are back titrated is per the discretion of the PI, with the exception of ACE inhibitors (ACEi) or Angiotensin Receptor Blockers (ARBs), which should be the last AHT medication to discontinue.

Inform the patient’s primary nephrologist and dialysis unit staff of any changes that the BID PI or other BID physician makes to the patient’s antihypertensive regimen. Review the change in medications with the patient and document the change in antihypertensive medications on Form 119, Oral Medications with Antihypertensive Properties.

Over the next 2 weeks, either the study coordinator or a member of the dialysis unit staff should obtain pre-dialysis SDUBPMs at each dialysis treatment to determine whether or not further backtitration of AHT is needed. When it has been 2 weeks since the change in AHT therapy, complete Form 111 and review the new 2-week averaged SDUBPM automatically generated in the BID Study Blood Pressure Summary Report.

Review Form 111 with the PI to decide if further backtitration of therapy is required. If further backtitration is required, the PI should identify the next AHT agent that should be reduced or discontinued. This process of backtitrating AHT, waiting 2 weeks to see its effects, and deciding whether further backtitration is needed, should continue until the 2 week averaged SDU Sys BP is **>155 mmHg**.

In general you will not increase dry weight as a means to increase the BP, unless the PI believes the patient’s dry weight is too low. This is uncommon.
3.6 Collection of Required Baseline Data

Data may be collected at any point during baseline. The exception is the MRI, which we recommend to be done toward the end of baseline, when it appears a patient is likely to be randomized. However, since the MRI must be reviewed by the MRI Core, it is important that the MRI not be done too late in Baseline; allow enough time for the MRI to be sent to the core and the core to review it and key enter either the Form 252-Is the LV Mass Readable Form (required before randomization) or Form 253-MRI Central Results before the 16 weeks allowed for baseline expires.

The following forms must be completed and entered into the study database in order for a patient to be randomized:

100 Screening Form (This form establishes a patient’s alternative unique ID, the Alpha Code. It must be the first form key entered. Contact the DCC [bid_dcc@bio.ri.ccf.org] if additional patient identification numbers are needed)
101 Demographic Form
103 Baseline Physical Exam and Study Questionnaire Form
108 Baseline and Quarterly Form
109 Standardized Dialysis Unit Blood Pressure Form
110 Weekly Interventions and Symptoms Form
111 Weekly Dialysis Details Form
118 Discontinuation of Screening Oral Medications with Antihypertensive Properties Form
119 Oral Medications with Antihypertensive Properties Form
120 Concomitant Medications Form
123 EPO/Injectable Medications Form
204 Comorbidity and Medical History Form
205 Serum Pregnancy Test Results Form - completed for all women under 50 years of age who have not been surgically sterilized)
206 Residual Renal Function Form
215 Home Blood Pressure Form (See Chapter 7 for details on HBPM)
216 ABPM Initialization and Placement Form (for Albuquerque, Pitt, and Carolina only)
217 ABPM Downloading, Copy, Scan and Mailing Form
218 ABPM Results (for Albuquerque, Pitt, and Carolina only)
220 MOS 36-Item Short Form Survey (SF-36v2) and Special Questions Form(s)
250 Last Dialysis Session before the MRI Form
251 MRI Mailing Form (for Boston, Albuquerque, Pitt, and South Carolina)
252 Is the LV Mass Readable Form (required before randomization) or 253 MRI Central Results
272 Kt/V Results
275 Biochemistry Results

3.7 Laboratory Studies during the Baseline Period

The most recent set of serum chemistries will be reviewed. These lab tests must be dated within three months of randomization with the exception of serum ferritin, TSat and intact PTH measurements, the most recent of which must be dated within six months of randomization. In the unlikely event that any of these laboratory measurements is not available within this window, it will be drawn and processed as per usual care.
3.8 Comorbidity and Medical History Form

The electronic and paper medical record should be reviewed for at least the past 5 years to complete Form 204, the Comorbidity and Medical History Form. Key sources of information that should be used to complete this form include: discharge summaries, consultant’s clinic letters, the nephrologist’s history and physical exam at intake to the dialysis unit, the MIS Problem List (for DCI patients), and physician and nursing progress notes.

3.9 Pregnancy Testing

In women with childbearing potential, serum pregnancy tests are to be performed monthly during baseline and for the rest of the study. See details on sample handling and shipping in Chapter 2.

3.10 Residual Renal Function

For patients who produce urine, a 44-hour urine collection for urea nitrogen to estimate residual renal function will be obtained, starting at the end of a dialysis treatment and continuing until the start of the next dialysis treatment 44 hours later. Participants will be queried about the completeness of the 44-hour urine collection. If any one of the urine collections is missed or the collection is not stored in the refrigerator or on ice packs, then the urine is not valid and must be recollected. The urine collection will coincide with the day monthly labs are drawn for routine care. The pre- and post- serum BUN values coinciding with the 44-hour collection (from the monthly labs) will be used to calculate the urea nitrogen clearance.

3.11 RRF calculation

RRF will be measured as renal urea clearance. It will be calculated from the pre and post dialysis BUN drawn the day of the monthly blood draw that is used by the unit for routine urea kinetic modeling.

The patient will be instructed to empty their bladders at the end of that dialysis treatment and then collect urine, up until the start of the next dialysis treatment. The patient should be given a jug for collecting the 24 hour urine and if a female, a collection hat for collecting the urine. The urine collection should be kept in the refrigerator over the 44 hour collection period. The jug will be returned to the dialysis unit and processed by the dialysis unit staff, as per their routine procedure for processing a 44 hour urine collection for residual renal function measurement. The collection should be processed at the same laboratory that the dialysis unit usually uses for monthly labs, and that will be processing the pre/post BUN from the day the collection started.

The BID Study coordinator should complete the RRF Form (Form 206) which asks about the volume of 44 hour urine collection and the completeness of the collection, per the patient's report. If there is < 200 ml of urine, the sample will not be processed and the patient will be considered to have no residual renal function. Review processing procedure in Section 3.12.

Calculation:
Renal Urea clearance will be calculated as UV/P where U is the urinary concentration to urea nitrogen in mg/dL, V is the volume of urine in the 44 hour period, and P is the plasma
concentration of BUN, which will be calculated as 0.5*pre-dialysis BUN + 0.5*post-dialysis BUN, on the day the 44 h urine collection starts. The estimate of the average BUN during the interdialytic period, is per Depner (Prescribing Hemodialysis: A Guide to Urea Modeling, Vol. 29 by T.A. Depner).

### 3.12 Instructions for Collecting and Processing a 44-hour Urine

A standardized procedure for collecting 44–hour urine samples has been established (see Participant Handouts Chapter). Instruct the participant to empty their bladder completely into the toilet after completing their dialysis treatment and prior to starting the urine collection. Then start to collect the urine immediately after the dialysis session coinciding with the monthly blood draws. All urine over a 44–hour period up to the next dialysis session is to be collected.

**Timing:** If the KM session is expected to be on Monday or Tuesday, have the patient start collecting the urine post final urination into the toilet at the end of dialysis session and continue collecting for 44 hours until the next dialysis session (which will be on Wednesday or Thursday). If KM session is expected to be on Wednesday or Thursday, have the patient start collecting the urine post final urination into the toilet at the end of the dialysis session that previous Monday or Tuesday and continue collecting for 44 hours until the next dialysis session (which will be on Wednesday or Thursday).

Participants collecting their urine at home must be instructed to keep the urine refrigerated or on ice during the collection (4–8 degrees C). The participant is to bring the urine collection jug with them to the visit, where the total collection volume will be recorded on Form 206 and the urine processed.

Instructions for the 44–hour urine collection for participants have been included below.

**Supplies:**
- Gallon jugs (no preservative) and label (participant name/ID#, start/stop, date/time)
- Collection "hat" or urinal
- Written instructions

**Preparation:**
1. One-gallon sample collection containers (containing no preservative) are to be used.
2. Patients are to be given necessary supplies, written instructions and verbal instructions.
3. The importance of complete collections should be emphasized.
4. The participant should drink the usual amount of liquid.
5. Sample collection should start right after dialysis post final emptying of bladder into toilet.

**Sample Collection:**
1. Collect every bit of urine for the next 44 hours post final emptying of bladder into toilet.
2. Collect urine in the "hat" or “urinal” provided; then carefully transfer all contents into the larger collection container.
3. If the participant is going to have a bowel movement, all urine should be collected first so none is lost. (Do not collect stool.)
4. After carefully transferring urine into the larger collection container, close the container securely and store upright.
5. Wash the "hat" or “urinal” and allow it to dry completely before next use.
6. Participants may wish to use various reminder techniques so they do not forget to collect their urine (note on the toilet seat, string around a finger, safety pin on clothing, etc.).

**Sample Storage:**
1. Store the sample in a refrigerator during the entire collection period and after.
2. If refrigeration is not available, store the sample in a cooler with ice packs.
3. Do not expose sample to extreme temperatures. Avoid freezing.
4. Always store the sample upright to avoid leakage.
5. Keep the sample refrigerated or on ice packs at all times during the collection and after.
6. Bring the sample to the clinical center (in a cooler with ice packs if possible).
7. At the Clinical Center, a study coordinator will complete the 44–hour Urine Checklist (Page 2 of the Instructions for the 44-Hour Urine Collection Handout to the participant) to confirm satisfactory collection.

**Clinical Center Specimen Processing and Shipping:**
1. Print a BID Study label for 44-hour urine urea concentration for this participant ID and affix to an 8 cc into red top vacutainer tube (without additives) or other 8-10 cc collection tube that does not contain additives. The label should have the study ID and alphacode and the test being ordered but not the patient’s name. Labels for 44-hour urine urea concentration will be available locally.
2. The coordinator will gently mix the jug containing the 44-hour urine collection.
3. Fill a 10 cc syringe with urine from the jug and inject 8 cc into a red top (no additive) vacutainer tube or other 8-10 cc collection tube that does not contain preservatives or additives.
4. Ship on cold packs using FEDEX OVERNIGHT to:
   DCI LABORATORY
   2917 Foster Creighton Drive
   Nashville, TN 37204

### 3.13 Home Blood Pressure Monitoring During Baseline

At least one week of home monitoring must be completed before the participant is able to be randomized.

The patient’s arm circumference and the appropriate cuff size will have been figured out at the Screening Visit (Chapter 5 for devices and cuff sizes). During the baseline period, order an appropriately sized LifeSource 767 or 789 BP monitor from the following website:

3.14 MRI

The MRI should be scheduled toward the end of the baseline period, when it appears a participant is likely to be randomizable. The MRI should be done on a non-dialysis day that does not encompass a 3-day interdialytic period. I.e., for participants on the Mon/Wed/Fri schedule, cardiac MRI can occur on Tues or Thurs. For participants on a Tues/Thurs/Sat schedule, cardiac MRI can occur on Wed or Fri.

3.15 Quality of Life Questionnaires

Quality of life will be assessed using two self-administered standardized instruments, the SF-36 version 2 and FACIT fatigue score and in addition, a previously validated question regarding the time to recovery from dialysis. The SF-36 is available in English, Spanish and Chinese. See Chapter 10 for details on the Quality of Life Questionnaires.

3.16 Exclusions during the Baseline Period and Baseline Dropout Form 112

Participants will not be considered for randomization if any one of the following occurs during the baseline period: (1) suspected poor adherence to protocol and thus a poor candidate for randomization; (2) development of any exclusion criteria; or (3) participant no longer wants to participate. The Baseline Dropout Form 112 will record the reason for any patient who drops out during baseline, prior to randomization.

If a participant drops out of baseline for a reason not noted on Form 112, please contact the DCC by email to bid_dcc@bio.ri.ccf.org and the DCC staff will help you categorize the reason for drop out; a new code will be added to Form 112 if necessary.

If any of the following occurs during baseline, the patient should not be randomized. Report this on Form 320 Change in Dialysis Status form. You need not complete a Form 112 for these participants.

- Patient received a kidney transplant
- Patient switched to peritoneal dialysis
- Patient switched to home hemodialysis
- Patient recovered renal function
- Patient withdrew from dialysis
- Patient now routinely dialyzes fewer than 3 times per week (for example, now on a 2x/week regimen)
- Patient now routinely has one or more extra ultra-filtration session(s) every week in addition to 3 times per week dialysis
- Patient now routinely dialyzes more than 3 times per week

If a patient dies during baseline, complete the Form 305 Death Notification Form instead of Form 112. You will also need to complete Form 306, the Detailed Death Form, for any baseline deaths.

Every patient who is included in the database and shown as eligible on Screening Form 100 will either be randomized or will require a baseline drop out form, a change in dialysis status form, or a death form.
3.17 Ramifications of Excluding Patients during Baseline

It is anticipated that approximately 30% of patients who enroll in baseline will not be randomized. Baseline exclusions during baseline in the BID Pilot Study can show a problem with the external validity of the BID Protocol; that is, they may show that study requirements are causing BID to enroll too few patients, patients who are not representative of typical dialysis patients. These reasons will continually be summarized and if one of the enrollment criterion leads to the exclusion of too many patients, this criterion may be revised for the Full Scale study.

If a patient does not seem likely to be willing or able to cooperate with the BID protocol, it is better to exclude the patient prior to randomization, because once a patient is randomized, his data will be analyzed as part of the study primary analysis. Losses of patients after randomization harm the internal validity of the study, that is, whether the study was conducted in an unbiased and scientifically sound manner.

Most criteria that would have lead to a patient being excluded if they were found prior to randomization do not lead to the patient being excluded if they are found after randomization. Examples of these include 1) Patient now routinely dialyzes fewer than 3 times per week (for example, now on a 2x/week regimen), 2) Patient now routinely has one or more extra ultra-filtration session(s) every week in addition to 3 times per week dialysis, and 3) Patient now routinely dialyzes more than 3 times per week, 4) Patient cannot read a Kt/v of 1.2, or any of the criteria related to complete collection of data.

If a patient chooses not to contribute to some component of the study protocol or study data collection after randomization, he will not be removed from the study.

3.18 Re-Enrolling a Previously Enrolled Subject

Contact the DCC (bid_dcc@bio.ri.ccf.org) to let the staff know your center is intending to re-enroll a patient who: 1) has met the guidelines above and 2) the BID study team has determined the patient is willing to re-start the screening and baseline process again. Provide the DCC with the patient’s identification number and alphacode.

a. Patient’s previously assigned identification number and alphacode MUST be used. (Do not give the patient a new number.)
b. Patient must be reconsented.
c. Collect all new baseline data (but do not enter any forms in the database until you are notified by the DCC that it is okay to start entering). Exception: the cardiac MRI will not need to be repeated if it was performed less than 6 months prior to randomization.
d. Review and complete Form 400-Re-Enrollment of a Previously Enrolled Patient (click on Form 400 link on BID Study Forms Table of Contents). Fax the completed form to the DCC.
e. Await notification from the DCC that new forms can be entered into the database.

Appendix A. Ready to Randomize Report – Sample – see next page
Is this patient eligible to be randomized to the BID Pilot Study? NO
1 Does this patient meet all of the eligibility criteria and can be randomized now? NO

Assessment of 2 week Running Means (at least one of these 2-week running means must be in range)

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<th>Visit Date</th>
<th>Average Systolic Mean Systolic</th>
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<tr>
<td>08/17/2013</td>
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<tr>
<td>08/13/2013</td>
<td>107.5</td>
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</table>

Is there a 2-week running mean in range? NO

Form 100: Screening Form entered into database and supports eligibility? YES
1 100% of items have valid answers? YES
2 Has the patient been dialyzing for more than 90 days? YES
3 Patient is eligible based on the data on this form? YES

Form 101: Demographic Form entered into database? YES
1 100% of items have valid answers (refused is a valid answer for Race/Ethnicity)? YES

Form 103: Baseline Physical Exam and Study Questionnaire Form Entered? NO
1 010: Pt is receiving 3x/week in-center dialysis? NO
2 Is pt female and if 011=YES, are 011b and 11c = Yes? NO
3 100% of items have valid answers? NO

Form 108: Baseline and Quarterly Form Entered? YES
1 06: Midpoint arm circumference measurement >13cm and <60cm? YES
2 100% of items have valid answers? YES

Form 109: Standardized Blood Pressure Forms Entered? NO
1 Are there at least 2 weeks of Form 109 data entered? YES
2 Are there at least 4 readings? YES
3 Has the 2-week running mean ever had systolic > 155 mmHg? NO
4 Date of most recent valid 2-week running mean ****

Form 110: Weekly Interventions and Symptoms Forms Entered? NO
1 Are there at least 2 Form 110’s entered? NO

Form 111: Weekly Dialysis Details Form Entered? NO
1 Are there at least 2 Form 111’s entered? NO

Form 118: Discontinuation of Screening Oral Medications with Antihypertensive Properties Form Entered? NO
1 100% of items have valid answers? NO

Form 119: Oral Medications with Antihypertensive Properties Form Entered? NO
1 Is the Date of Visit for this form within 2 weeks of today? NO
2 100% of items have valid answers? NO

Form 120: Concomitant Medications Form Data Available? NO
1 100% of items have valid answers? NO
<table>
<thead>
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<th>Description</th>
<th>Yes/No</th>
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<td>123</td>
<td>EPO/Injectable Medications Form</td>
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<tr>
<td>204</td>
<td>Comorbidity and Medical History Form Entered?</td>
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<td>205</td>
<td>Serum Pregnancy Test Results Form Entered?</td>
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</tr>
<tr>
<td>206</td>
<td>Residual Renal Function Form Entered?</td>
<td>NO</td>
</tr>
<tr>
<td>215</td>
<td>Home Blood Pressure Form Entered?</td>
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<td>MOS 36-Item Short Form Survey (SF-36) and Special Questions Form completed by patient and entered by study staff?</td>
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<td></td>
<td><strong>ABPM: For Pts with Arm Circumference&lt; 50cm at UNM, MUSC and Pitt</strong></td>
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<td>216</td>
<td>ABPM Initialization and Placement Form Entered?</td>
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<td>217</td>
<td>ABPM Downloading, Copy, Scan and Mailing Form?</td>
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<tr>
<td>218</td>
<td>ABPM Results?</td>
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<td><strong>MRI: For Centers Performing MRI at Boston, UNM, MUSC and Pitt</strong></td>
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<td>Last Dialysis Session before the MRI Form Entered?</td>
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<td>MRI Mailing Form (administered and transmitted to core) Entered?</td>
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<td>MRI Central Results Form entered?</td>
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<td>KM Results Entered?</td>
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<td>275</td>
<td>Biochemistry Results Entered?</td>
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<td></td>
<td>Within 4 calendar months of screening/baseline visit date?</td>
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</tr>
<tr>
<td></td>
<td>DCC has copy of patient's de-identified Consent Form signature page on file?</td>
<td>YES</td>
</tr>
</tbody>
</table>

**Notes:**
- "YES" indicates that the criteria has been met.
- "NO" indicates that the criteria has not been met.
- "0" indicates that the criterion is not applicable.
- "NA" indicates that the criterion is not available.