CAPTION
Collaboration Among
Pharmacists and Physicians
To Improve Outcomes Now

The University of Iowa

The CAPTION Trial

MANUAL OF PROCEDURES

BLOOD PRESSURE USUAL CARE ARM

Version Date: 10/1/2011

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This study is funded by the National Heart, Lung and Blood Institute/ National Institutes of Health RO1 HL091841

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I. INTRODUCTION

Blood pressure (BP) control for hypertensive patients is low in the United States, with the lowest rates of control found among racial minorities and patients with lower socioeconomic status. The reasons for poor BP control include patient, physician, and structural factors, but sub-optimal treatment regimens and clinical inertia are also common contributors. The physician/pharmacist collaborative model (PPCM) has achieved high BP control rates in several studies. In this model, pharmacists work directly with patients' primary physicians to optimize treatment of hypertension. However, most trials using this model were small studies, did not use a standardized BP measurement technique, and did not include large numbers of patients from minority populations.

The goals of the present study are to determine:

1) If PPCM will be adopted and implemented broadly in diverse medical offices with high minority populations.
2) If BP control deteriorates after discontinuation of a 9-month PPCM intervention compared to continuing the intervention for 24 months.

We will conduct a 4.5 year, prospective, cluster-randomized multi-center clinical trial in 32 clinics across the United States. All clinics employ clinical pharmacists, and 47% of the clinic patients are under-represented minorities.

Clinics have been stratified based on the structure of pharmacy services and the percent of minority patients and randomized within strata to:

1) A 9-month PPCM intervention group
2) A 24-month PPCM intervention group
3) A control group

A Study Coordinator in each clinic will enroll 24 subjects with hypertension to the Active Observation control group. The Study Coordinator will monitor BPs for these subjects for 24 months following enrollment (total intervention and control sample=648). In addition, another 486 subjects (18 per clinic) with hypertension will be assigned to an observational cohort Passive Observation group.

A projected timetable for study activities is provided in APPENDIX I.

A. Protocol Synopsis

Primary Endpoint

The primary aim of the study is to determine if subjects who receive Physician-Pharmacist Collaborative Management (PPCM) of hypertension can achieve better blood pressure (BP) control at 9 months when compared with subjects who do not receive PPCM. The primary endpoint used to evaluate this aim will be a research-measured BP taken 9 months after each Active Observation subject is enrolled in the study.

Secondary Endpoints

Secondary aims and their associated endpoints are designed to:

1) Determine whether the PPCM intervention spreads to clinic subjects who are not consented into the study and who do not receive the PPCM intervention. The endpoint used to measure this question will be clinic BP measurements abstracted from the medical records of subjects assigned to the Passive Observation group.
2) Determine whether subjects in clinics randomized to the continuation of PPCM for 24 months achieve better long-term BP control when compared with subjects in clinics randomized to discontinuation of PPCM after 9 months and to subjects in the control clinics. The endpoint used to evaluate this question will be a research-measured BP taken at 12, 18 and 24 months after each Active Observation subject is enrolled in the study.
3) Determine whether adjustments to medication intensity vary across groups. The endpoint used to evaluate this question will be the change in medication intensity that occurs across the baseline, 9 month and 24 month time periods. Intensity measurement will be based upon patient interviews and medical records.
4) Evaluate barriers and enablers of the PPCM intervention. The endpoints used to evaluate this aim include: a) physician and pharmacist surveys that measure provider attitudes toward delivering PPCM, collected at baseline and at the end of the study; b) pharmacist billing data, collected for each pharmacist study visit with subjects.
5) Determine whether the PPCM is a cost-effective intervention. The endpoints used to evaluate this aim will be a calculated incremental cost as a function of differences in BP at baseline, 9 months, and 24 months.

B. Inclusion and Exclusion Criteria

Inclusion Criteria for Subjects in the Active Observation and Passive Observation Groups

1) English or Spanish speaking males or females
2) Over 18 years of age
3) Diagnosis of hypertension
4) Have an uncontrolled average BP at the baseline visit, defined as
   - ≥ 140 mm Hg SBP or ≥ 90 mm Hg DBP for patients with uncomplicated hypertension;

     OR
   - ≥ 130 mm Hg SBP or ≥ 80 mm Hg DBP for patients with diabetes or chronic kidney disease.

   The Study Coordinator will only invite patients to be screened who have demonstrated uncontrolled BP values on at least two past clinic visits.

   Qualification for the Active Observation group will be based on a seated research BP (average of the second and third reading) as measured in the office by the Study Coordinator using the study-approved instrument. Only one qualifying average BP will be required.

Qualification for the Passive Observation group will be a qualifying BP using usual office measurements that were taken during clinic visits approximately 2 years prior to patient identification for this group.

The Study Coordinator will determine if a patient has either diabetes or chronic kidney disease based on documentation in the problem list in the patient's medical record.

Exclusion Criteria for Subjects in the Active Observation and Passive Observation Groups

1) Current signs of hypertensive emergency (acute angina, stroke, or renal failure)
2) Severe HTN (average systolic BP >200 or average diastolic BP > 115 mm Hg at the baseline visit for active observation subjects)
3) History of MI, stroke, or unstable angina in the prior 6 months
4) Systolic dysfunction with a LV ejection fraction < 35% documented by echocardiography, nuclear medicine study, or ventriculography
5) Renal insufficiency, defined by a glomerular filtration rate less than 20 ml/min or previously documented proteinuria > 1 gram per day
6) Significant hepatic disease, including prior diagnoses of cirrhosis, Hepatitis B or C infection, or laboratory abnormalities (serum ALT or AST > 2 times control or total bilurubin > 1.5 mg/dl) in the prior 6 months
7) Pregnancy
8) Diagnoses of pulmonary hypertension or sleep apnea (unless either CPAP/ continuous positive airway pressure ventilation or BiPAP/bilevel positive airway pressure ventilation has been prescribed)
9) Poor prognosis with a life expectancy estimated less than 2 years
10) Residence in a nursing home or diagnosis of dementia
11) Inability to give informed consent (Active Observation Group only)
12) Impaired cognitive function (> 2 errors on the Short Portable Mental Status Questionnaire, Active Observation Group only)

C. Study Organization

Two teams of investigators at the University of Iowa are jointly conducting this study. Contact information is given for key members of each team.

The **Clinical Coordinating Center (CCC)** within the College of Pharmacy at the University of Iowa is responsible for the following key aspects of the trial:

1) Selection of participating sites
2) Assisting sites in obtaining approval for the study from their local Institutional Review Board
3) Negotiating with sites the work that is to be completed and the compensation that sites will receive
4) Training of site staff

Clinical Coordinating Center		
Barry L. Carter, Principal Investigator	barry-carter@uiowa.edu	319-335-8456
Gail Ardery, Clinical Site Director	gail-ardery@uiowa.edu	319-384-4128
Rosemary Tiwari, Project Manager	rosemary-tiwari@uiowa.edu	319-384-4651
CAPTION Fax Number		319-335-9511

The **Data Management Center (DMC)** within the Clinical Trials Statistical and Data Management Center in the College of Public Health at the University of Iowa is responsible for the following key aspects of the trial:

1) Creation of the trial's database
2) Creation of procedures for online submission of research data from sites.
3) Monitoring procedures at research sites.

Data Management Center		
Chris Coffey, Director, DMC	christopher-coffey@uiowa.edu	319-384-4197
Dixie Ecklund, Assoc. Director, DMC	dixie-ecklund@uiowa.edu	319-335-8446
Sushma Gampa, Protocol Coordinator/Monitor	sushma-gampa@uiowa.edu	319-384-4763
Jill Kuennen, Lead Data Manager	jill-kuennen@uiowa.edu	319-353-3041
Michele Costigan, Lead Protocol Coordinator	michele-costigan@uiowa.edu	319-384-4183
Kathy Gloer, Quality Assurance	katherine-gloer@uiowa.edu	319-353-4266
Elizabeth Cozzie, Data Manager	elizabeth-cozzie@uiowa.edu	319-384-2751
Ankita Singhal, Data Manager	ankita-singhal@uiowa.edu	319-384-2750

D. Regulatory Requirements and Clinical Study Document Collection

Each site will be required to complete the following study-related tasks and to store and transmit to the University of Iowa CCC the relevant documents listed for each task.

1) IRB Approval

   Each site must obtain approval for the study from its local Institutional Review Board, including approval of study procedures and approval of informed consent documents. Required documents include:

   - The Institutional Review Board's letter of approval for the study.
   - All stamped informed consent documents approved and dated by the local IRB.

2) Site Signature Log

   Each site must submit a Site Signature Log to the CCC. The website will include a template for the log which each site can download (see APPENDIX II). The Physician Leader, all pharmacists (for implementation of the asthma intervention only) and the Study Coordinator must print his/her name, indicate all of the responsibility codes that describe their role(s) on the study and sign the document.

3) Subaward Agreement with the University of Iowa

   Administrative personnel at each site must also negotiate and sign a Subaward document created by the University of Iowa Department of Sponsored Programs. The agreement describes the terms and conditions for reimbursing sites for study-related costs.

   Dr. Ardery at the CCC will serve as the lead contact for questions regarding the subaward process.

Each of these study documents should be stored in a central, secure location where they can be easily found by site personnel who are working on the project.

In addition, a copy of each document will also need to be sent to the University of Iowa CCC by one of the following methods:

Scan and email to the CCC at gail-ardery@uiowa.edu

Fax to 319-335-9511

II. SITE TRAINING AND MONITORING

A. Initial Training Sessions

Local training of clinic physicians and pharmacists

All physicians and pharmacists will receive the following written materials:

- The Express Report of the Joint National Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-7)
- Reference card from the JNC-7
- Card on "Improving Blood Pressure Treatment in the Community"
- Checklist for accurate BP measurement
- Published manuscript from The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

Follow-up contacts with University of Iowa Researchers

Following the initial local training sessions, Drs. Carter and Ardery will conduct a telephone conference with each physician-pharmacist pair to discuss any questions or issues that the providers were not able to answer regarding the study.

If there are organizational or financial barriers being encountered, Dr. Ardery will work with the clinic administrator to improve staffing, billing or other barriers. Drs. Carter and Ardery, in consultation with Dr. Vaughn, will continue to support these offices quarterly via telephone conference call during the first year and twice a year during year two.

Study Coordinator Training

The Study Coordinator will be required to obtain certification in human subjects protection education, either through a local educational institution or through a national certifying agency. This certification must meet criteria established by the site's governing Institutional Review Board.

Faculty and staff from the University of Iowa will hold a joint training session for Study Coordinators in Iowa City. Session content will include:

- Study design
- Ethical procedures for recruitment and informed consent
- Proper completion of case report forms
- Procedures for uploading data electronically to the DMC.
- Training (by Dr. Barry Carter) on proper blood pressure measurement technique using the Omron automated instrument and in accordance with the American Heart Association guidelines.

The CCC will email to all members of the site research team a weekly benchmark enrollment comparing study sites.

The Study Coordinator will be re-certified by study monitors on proper BP measurement at scheduled monitoring visits.

B. Site Activation

Before each site can be fully activated and begin enrolling subjects the following tasks must be completed:

1) The letter of approval from the site's local IRB must be emailed to the CCC.
2) The IRB-approved consent documents for each site must be reviewed and approved by the CCC.
3) Each site must generate a list of all patients who have a qualifying ICD9 code and inform the CCC of the total number of unique patients on the list. More detailed instructions are provided in Section III.A Patient Screening and Enrollment.
4) Each site must submit a Site Signature Log to the CCC. The website will include a template for the log which each site can download (see APPENDIX II). The study Physician Leader, Pharmacist Leader, clinic pharmacists (who will not be involved with BP control subjects) and Study Coordinator should each list their name and one or more responsibility code(s) to describe their role(s) on the study, and then sign their line. The site PI should sign and date at the bottom of the document after all personnel have completed their respective lines.

The completed Site Signature Log should either be faxed to the CCC at 319-335-9511 or scanned and sent via email to gail-ardery@uiowa.edu.

C. Interim Monitoring Visits

The purpose of the monitoring visit is to ensure that the protocol is being followed, that subject's rights and safety are being protected, and to confirm data integrity and quality.

All centers will be monitored as scheduled by monitors from the Data Management Center. The first monitoring visit will occur after the first five subjects have been enrolled at a center or approximately three months after the first subject is enrolled, whichever comes first. All centers will have a close-out visit.

Study monitors will have access to medical records but will have NO contact with patient subjects.

Pre-Monitoring Procedures

1) The monitor will email the Study Coordinator with possible dates for the monitoring visit approximately 4-6 weeks ahead of these dates. Plan on at least two days for the visit. The Study Coordinator and PI should be available to meet with the monitor during the visit.

2) The monitor will send a letter to the center approximately 2 weeks ahead of the scheduled monitoring visit date explaining objectives of the visit and necessary materials. The monitor will need a reserved space in which to work and access to a photocopy machine and electronic records, if applicable. The following items should be available for review:

    - Screening Logs
    - Patient Clinic/Medical records
    - Paper copy CRFs and any other study-related source documents and records
    - Regulatory Documents
        - Site Signature log
        - IRB approvals
        - Approved informed consent documents
        - Approved recruitment materials
        - IRB correspondence
        - Certifications

On-site Monitoring

1) An initial meeting (approximately 30 minutes) will occur between the Study Coordinator and the monitor to orient the monitor to clinic/medical records, answer study questions, and review protocol procedures. The Study Coordinator should be available periodically throughout the visit to answer questions or to make data corrections, if necessary.
2) In addition to review of the items listed above, the monitor will re-certify the Study Coordinator in BP measurement procedures.
3) At the end of the monitoring visit, the monitor will meet briefly with the Study Coordinator and PI to discuss findings and a plan of action.

Post-Monitoring

1) The monitor will send the Study Center a formal report containing feedback and a detailed listing of all findings within 4 weeks of concluding the monitoring visit.
2) The monitor will contact the Study Coordinator to discuss pending items until all items are resolved. The Study Coordinator will respond to pending items in a timely manner and inform the monitor of any issues delaying resolution of the item.

D. Protocol Review Calls

Following the local training sessions for physicians, Drs. Carter and Ardery will conduct a telephone conference with each Physician Leader-Pharmacist Leader pair to discuss any questions or issues that the site leaders were not able to answer.

Drs. Carter and Ardery will continue to support these offices through teleconferences to be held:

- Quarterly during the first year
- Twice during the second year

During these calls, Drs. Carter and Ardery will review the protocol and individual site performance.

E. Close-Out Visits

A study monitor from the University of Iowa will visit each site at the end of the study to close-out that site's participation in the study.

F. Organizing and Maintaining Study Files

1) Each patient should have a study file containing signed informed consent document, completed case report forms and other source documentation.
2) Arrange patient files in order of study visits.
3) Complete paper copy CRFs before entering data on the website.
4) If corrections to paper copies are needed, draw a single line through the incorrect response, write the correct response, and initial and date the correction. White-Out or other similar products that obscure the original response may not be used on source documents.
5) Keep all Regulatory documents together in a binder.
    - IRB documents tab: All approval letters, modification/amendment submissions, approved and stamped copies of documents such as recruitment materials and ICFs, any correspondence with the IRB.
    - IRB reports tab: Some IRBs have separate templates for sites to report serious adverse events and protocol deviations. If your IRB requires such reporting please include these reports under this tab.
    - CAPTION Study tab: monitoring pre-visit letters, monitoring post-visit letters, site signature logs and study related certifications such as protocol training, BP certification, data entry training for all staff members (past and present) who work on CAPTION should be filed here.

III. PROCEDURES FOR STUDY COORDINATORS

A. PATIENT SCREENING AND ENROLLMENT FOR ACTIVE OBSERVATION GROUP SUBJECTS

The Study Coordinator will consent up to 80 patients with uncontrolled BP. **Your enrollment target is 24 qualifying subjects** who meet all inclusion criteria, sign informed consent, and pass both mental status screening and BP measurement screening. The long term goal is that at least 20 of the 24 qualifying patients will complete the 24 month study. If you do not succeed in enrolling 24 qualifying patients before 80 patients have signed informed consent, you must submit an amendment/modification to your IRB before consenting ANY additional subjects. Since receiving approval to consent more than 80 subjects will take time, you should move forward with the IRB submission after you consent your 60th patient.

One focus of the study is management of hypertension in minority populations. Our goal across sites is for 40% of enrolled patients to represent a minority population. The enrollment numbers displayed in APPENDIX III serve as individual site targets for minority enrollment. Not all sites have a sufficiently large minority population to achieve this level of minority enrollment. Other sites are likely to achieve far greater minority enrollment. The randomization methodology described below should never be violated in order to increase minority enrollment. And minority patients should not be pressured to join the study. However, Study Coordinators can promote minority subject retention by working diligently to accommodate subjects' schedules and assisting with transportation costs when possible.

Enrollment of subjects involves the following steps:

1) Identifying Patients Who Might Qualify for the Study

   - Request from your Information Technology staff a list of all patients who were seen in the clinic during the past 24 months and who carry a diagnosis of hypertension (ICD9 code 401). Hypertension does not need to have been the primary reason for any visit. The list may be in any order, whether alphabetical, by medical record number, date or random. (See APPENDIX X for details on requesting the list.)
   - If the list is not numbered, insert a Patient Number next to each patient's name on the list you receive, assigning the first patient name on the list Patient Number 1, the second patient on the list Patient Number 2, etc. Continue numbering throughout the entire list.
   - Ask the lead pharmacist on the study to review the list for accuracy in numbering.
   - Communicate the total number of patients on your list to the CCC via email to gail-ardery@uiowa.edu.
   - NEVER send to the CCC a list that contains patient identifiers.
   - If you can de-identify the list (by deleting columns with names, birthdates or medical record numbers) and have anything except the numbering show, make a copy of the first 3 pages of your numbered list. Fax the first three pages of the resulting de-identified numbered list to 319-335-9511. The CCC will let you know of any concerns with the list or with the numbers assigned to the list.

- If you cannot de-identify the list, the CCC will review via telephone the critical indicators of an accurate list.
- Once the numbered list is finalized, you will receive Random Screening Numbers within 2 weeks. Do NOT begin screening until you receive Random Screening Numbers for patients on your list.

i. Determining the Order In Which Patient Records Are Screened

- You will receive from the CCC a Screening Log with multiple columns. A template for the log and a sample log are provided in APPENDIX IV.
- Use the screening log to track your screening and enrollment efforts. You may complete the log either on paper or electronically. Retain the ENTIRE log for the duration of the study. A sample screening log may be found in APPENDIX IV.
- Two columns of the Screening Log will be filled in:

  Column B: Random Screening Numbers, which indicate the order in which you should screen each patient

  Column C: Patient Numbers, which represent the numbers you assigned to your patient list from IT

ALWAYS SCREEN PATIENTS IN ORDER ACCORDING TO THE RANDOM SCREENING NUMBERS.

2) Logging the Screening and Enrollment Process

- **RETAIN THE SCREENING LOG FOR THE DURATION OF THE STUDY.** You will be asked to fax or email a de-identified copy of the log to the CCC monthly.
- The Study Coordinator will review the medical records in the order supplied by the DMC to determine if each patient meets study inclusion criteria and does not meet any of the study's exclusion criteria.
- Begin screening with the patient who has been assigned Random Screening Number 1 in Column B of the log. Use the paired Patient Number given in Column C of the log to easily find the patient on your IT list. Write the patient's name into Column A of your log.
- Consider the following information from each patient's medical record:
  - Diagnoses: Patient has a diagnosis of hypertension
  - Clinic BPs: Review BPs measured over the previous 24 month period
  - Exclusion Criteria: Review Problem List and clinical notes to identify medical conditions that disqualify the patient.
  - Active in Clinic: Determine that patient remains in the practice.

- Complete columns D, E, F and G as follows:

  Column D: Enter Y if the patient's clinic BPs (documented in the medical record) did not qualify; otherwise, enter N. **Exclude (write in Y for) all patients who have had at least two controlled BPs during the previous 6 months.**

  Column E: Enter Y if the patient has other exclusion criteria that are disqualifying; otherwise, enter N.

  Column F: Enter Y if the patient has left the practice; otherwise, enter N.

  Column G: Enter Y if the patient seemed to meet screening criteria based on medical record review; otherwise, enter N.

YOU DO NOT NEED TO COMPLETE REMAINING COLUMNS FOR ANY PATIENTS FOR WHOM YOU WROTE "N" INTO COLUMN G.

If a patient appears to meet all of the inclusion criteria and none of the exclusion criteria, the Study Coordinator must inform the physician that the patient's BP is not controlled. However, notification may be delayed until a patient is brought in for the baseline visit and their qualification for the study is finalized.

Patients will be invited via mailed letter to participate in the active observation group of the study. If they agree to participate, they will be scheduled for a baseline visit, sign informed consent and be enrolled if they continue to meet the inclusion criteria.

3) Mailing out IRB-approved letters of invitation to potential active observation patients

Your IRB has approved (and possibly stamped) a letter of invitation about the study. This letter should be mailed to each patient who seems to meet all of the medical record screening criteria, that is, those for whom you entered Y into column G of the log. The mailing will include:

- An invitational letter that provides a brief description of the study. The letter will be written in Spanish if the patient only speaks Spanish. You should enroll Spanish-only speakers only if you have an IRB-approved Spanish invitation letter and consent form and your clinic has a staff member who can interpret during study visits.
- A response card and the date by which the card should be returned. The letter will include a statement that the patient will be called if the card is not returned by this date. The letter will include an explanation of how the patient can avoid the call by returning the card or calling the staff to decline participation.

Please mail out letters on your clinic letterhead according to the following procedures:

- Your first mailing can include the first 50 pre-screened patients designated by the random order list from the DMC.
- The size of subsequent mailings should be determined by the number of patients that you still need to enroll. Your target for total number of patients who sign consent AND pass all screening requirements = 24.

Some sample situations for how to handle subsequent mailings are described below. The goal is to not send out letters that will substantially exceed the number of patients

you need to enroll. Therefore, the size of each subsequent mailing should again be determined by the number of patients you still need to enroll.

- Once you enroll 5 patients and have exhausted most patients remaining in the initial mailing, you could mail out letters to the next 50 patients designated by the random order list.
- Once you have enrolled 15 patients and have exhausted all patients to whom you have mailed the letter of invitation, you could mail out letters to the next 20 patients designated by the random order list.
- Once you have enrolled 20 patients, you would only want to mail out letters to the next 4-5 patients on the list.

Although patients must be invited in the order specified on the random list, ***baseline visits may be scheduled per the patient's preference***. In other words, it is not necessary to have the 15th patient on the list be fully enrolled before you can schedule a visit with the 16th patient on the list.

If you have a patient contact you after you have categorized the patient as "Unable to Contact" (see column R below) and the patient is interested in participating, you may include that patient, even if your total number enrolled exceeds 24. However, due to limited funding and staff resources, please keep enrollments > 24 to a minimum.

4) Continue Logging the Screening and Enrollment Process

In columns H-K of the log, note the outcomes of your attempts to reach each patient by mail:

Column H: Enter the date on which the invitation letter was mailed.

Column I: Enter the date on which you received the return postcard. Enter N if the postcard is never returned.

Column J: Enter Y if the patient declined on the postcard and shred the postcard. Enter N if the postcard is never returned or if the patient expressed interest in hearing more about the study.

Column K: Enter Y if the patient expressed interest in hearing more about the study on the postcard. Enter N if the card is never returned or the patient declined on the card.

In columns L-V, log your attempts to reach the patient by phone. Review your IRB's determination regarding the timing and number of calls. If your IRB has approved a phone script, be sure to follow the script during these calls.

Columns L-Q: Write in each date on which you called the patient or the patient returned your call. Although the spreadsheet gives you room to log 6 calls, THE TIMING AND THE NUMBER OF CALLS THAT YOU MAKE SHOULD FOLLOW THE TIMING AND NUMBER OF CALLS APPROVED BY YOUR IRB AND SPECIFIED IN YOUR SITE'S LETTER OF INVITATION. Leave blank any columns M-Q that you do not use to log calls.

Column R: Enter Y if you were never able to reach the patient by phone. You do not need to attempt further contacts if you have exhausted the number of calls that your IRB has authorized. Enter N if you reached the patient by phone.

Column S: Enter Y if the patient declined over the phone to participate. Otherwise, enter N.

Column T: Enter Y if the patient reported a disqualifying health condition over the phone. Otherwise, enter N.

Column U: Enter Y if the patient indicated over the phone that s/he was interested in learning more about the study. Otherwise, enter N.

Column V: Enter Y if the patient was interested but you were not able to negotiate a date for the baseline study visit. Otherwise, enter N.

In columns W-AB, log the results of your efforts to schedule/complete the patient's baseline visit:

Column W: Enter Y if the patient declined to sign consent during the baseline visit. Otherwise, write in N.

Column X: Enter Y if the patient signed informed consent. Otherwise, enter N.

Column Y: Enter Y if the average screening BP that you obtained did not meet the inclusion criteria. Otherwise, enter N.

Column Z: Enter Y if the patient scored 3 or more incorrect responses on the Short Portable Mental Status Questionnaire. Otherwise, enter N.

Column AA: Enter Y if an exclusion criterion was discovered after the patient signed consent. Otherwise, enter N.

Column AB: Enter Y if the patient was fully enrolled in the study. Otherwise, enter N.

Exhausting the List of Patients

If the list of patients is exhausted before you enroll 24 patients who fully qualify for the study, a new patient list can be run. However, the CCC should be notified before a second list is run.

Newly Diagnosed Patients

Patients who develop hypertension after the initial patient list is generated cannot be included in the study. Once the original list is exhausted, let the CCC know that you need to generate a new list of patients. Patients with newly diagnosed hypertension can be added at that time.

Patient Referrals to the Study

Patients cannot refer themselves to the study. Physicians or other clinic personnel cannot refer patients to the study. The only way a patient can be considered for the study is if the Study Coordinator considers the patient in the randomized order specified by the DMC.

Procedures for an Incorrect Count on the Patient List

If you determine that you provided an incorrect total number of patients on your screening list, inform the CCC as quickly as possible.

Incorrect Patient Enrollment/Protocol Deviation

If you determine that you enrolled a patient who does not qualify for the study, you must complete CRF#24. Protocol Deviation form. For more information, see section VIII SERIOUS ADVERSE EVENTS AND PROTOCOL COMPLIANCE.

B. Standard Operating Procedures for Obtaining Informed Consent

Informed consent is obtained only from subjects enrolled in the Active Observation Group.

Only the Study Coordinator may obtain informed consent from patients. Other clinic staff may not refer patients to the study or review the consent document with patients. Staff members are welcome to take patient questions regarding the study and refer them to the Study Coordinator as needed.

The Study Coordinator MUST obtain signed consent from the patient on all consent documents before undertaking any other research procedures, including mental status screening and measurement of blood pressures.

1) Before meeting with the patient on the Baseline visit, make sure that your IRB-approved consent documents are still valid.
    - Each consent form is valid for a maximum of 12 months from the date of approval and often for less time if an amendment is filed.
    - If your IRB dates your approved consent documents, make sure that the date the patient is being enrolled falls within the dates specified on the consent. You should NEVER have a patient sign a consent that has expired.
2) When your IRB provides a new consent after each annual review, be sure to email all approved and dated/stamped documents and the IRB approval letter to gail-ardery@uiowa.edu.
3) The Study Coordinator will give the subject a consent document to read and review.
4) The Study Coordinator will specifically explain the following aspects of the study:
    - Purpose of the research study, duration of study participation, and the number of research visits or study contacts (e.g. telephone calls) required.
    - Which parts of the study are investigational (in this case the pharmacy intervention).
    - The study procedures/requirements.
    - The risks of the study.
    - The voluntary nature of the study – that the subject may stop the study at any time.
    - When a subject's participation in the study may be stopped (safety, compliance, sponsor stops the study).
    - HIPAA section – the clinic investigators must be allowed to have access to the participant's medical information and to create medical information in order for the subject to be in the study.
    - Contact information in case of a research-related Injury.
5) The Study Coordinator asks the subject what questions they have and provides answers.
6) For subjects whose capacity to consent, understand the study procedures, or read the consent form is in question, we recommend that the Study Coordinator provides some documentation of the patient's ability to sign consent. A template titled "Evaluation to Sign Informed Consent Document for Research" is provided in APPENDIX V. However, it is

imperative that sites follow pertinent procedures specified by the local IRB. The evaluation document should be stored in the subject's study file. It cannot be entered into the database. If you doubt that a patient is not able to sign informed consent, explain that you are choosing not to have the patient continue in the study.

7) If after reading the consent document and having their questions answered a patient agrees to participate in the study, the patient will sign and date the consent document.
8) The Study Coordinator then signs and dates the consent document.
9) The Study Coordinator will then make two COMPLETE copies of the consent document. One copy will be placed in the chart or medical record, unless the clinic does not permit this. The patient will be given a copy, and the original will be placed in the study case report binder. If clinic policy explicitly prohibits placing a copy of the signed consent in the patient's medical record AND the local IRB does not require placing a copy in the medical record, then clinic policy should be followed.
10) The signed consent forms will be reviewed by study monitors from the University of Iowa during interim monitoring visits to ensure compliance with the informed consent process.

1. Procedures for Spanish-Only Speakers

Either the University of Iowa Clinical Coordinating Center will translate your IRB-approved consent form into Spanish, or your clinic can arrange for translation.

Utilize bilingual Study Coordinators or interpreters within the office to explain the study and assist with obtaining informed consent.

When needed, have an interpreter present during clinic visits and telephone calls with the Study Coordinator.

The interpreter reads each question and obtains the responses from the patient.

The Study Coordinator remains present at these sessions to assist with any questions and to record data.

2. Procedures for Patients Who Cannot Read or Whose Ability to Give Informed Consent Is Not Clear

For subjects whose capacity to consent, understand the study procedures, or read the consent form is in question, we recommend that the Study Coordinator provides some documentation of the patient's ability to sign consent. A template titled "Evaluation to Sign Informed Consent Document for Research" is provided in APPENDIX V. However, it is imperative that sites follow pertinent procedures specified by the local IRB. The evaluation document should be stored in the subject's study file. It cannot be entered into the database. If you doubt that a patient is not able to sign informed consent, explain that you are choosing not to have the patient continue in the study.

If the Study Coordinator suspects that a patient has difficulty with reading comprehension, s/he may read the consent form to the patient, if the patient is willing and if this procedure is permitted by the local IRB.

C. Scheduled Visits for Active Observation Group Subjects

Administer the Short Portable Mental Status Exam

a. Adjust the subject's score for patient education level and race;

b. If the subject's adjusted score is 3 or higher, explain that s/he cannot remain in the study. Do not continue with other activities; document screen failure in the tracking log and on the website.

c. If the subject's adjusted score is 2 or lower, proceed with the remaining baseline activities.

d. Enter the subject's final adjusted score on CRF#1. Informed Consent.

2. Administer CRF#8. Research BP Measurement :

a. Measure the subject's blood pressure according to the blood pressure protocol. Measure the subject's blood pressure using the Omron HEM 907-XL device according to the blood pressure protocol (see Procedures for Monitoring Research Blood Pressures). Document the obtained blood pressures in the subject's medical record AND on CRF#8. Research Blood Pressure Measurement.

- **Subjects whose average blood pressure at the baseline visit is > 200 systolic OR > 115 diastolic may not continue in the study.**
- If the subject's blood pressure does **NOT** meet the inclusion criteria:

i. Inform the subject's physician

ii. Explain to the subject that s/he cannot participate in the study

iii. Do not continue with other activities; document screen failure in the tracking log.

iv. Electronically enter only eCRF#1 Informed Consent; you will not have access to other forms.

v. If the IRB has approved the study's re-screening procedures, subjects may be rescreened if they have an average baseline study visit systolic OR diastolic BP within 5 mm Hg of the inclusion criteria threshold value. Thus, subjects with uncomplicated hypertension should be rescreened if their baseline systolic BP was 135-139 mm Hg OR their diastolic BP was 85-89 mm Hg. Alternatively, a subject with diabetes or chronic kidney disease would be rescreened with a baseline systolic BP of 125-129 mm Hg OR a diastolic BP of 75-79 mm Hg. These subjects may be re-screened up to 3 times for meeting the blood pressure criteria within 7 months of the baseline visit. If their average BP at a re-screening visit meets eligibility criteria AND they meet all other eligibility criteria, then they may continue in the study.

- If the subject's blood pressure **DOES** meet the inclusion criterion, proceed with the next baseline activity.
- If the subject has EITHER an **average systolic BP reading > 200** OR an **average diastolic BP reading > 115**, initiate procedures according to the flowsheet Handling Hypertension Urgencies (page 27). The Study Coordinator should follow these procedures **at EVERY patient visit** where blood pressure elevations of this

magnitude are detected. **Subjects whose average blood pressure at the baseline visit indicates hypertensive urgency may not continue in the study.** However, subjects who exhibit hypertensive urgency at a follow-up visit may stay in the study.

3. Verify that the subject meets all inclusion criteria and does not meet any exclusion criteria. On the Source Document for Verification of Inclusion and Exclusion Criteria (APPENDIX VI) is a list of each inclusion and exclusion criterion. Circle Yes/No for each criterion to verify that the subject meets each inclusion criterion and does NOT meet any of the exclusion criteria. If the subject fails to meet any one of the inclusion criteria or if the subject meets one or more exclusion criteria, explain to the subject that s/he does not qualify and will not have further study visits. Do NOT collect additional data.

   When completed, file the Source Document for Verification of Inclusion and Exclusion Criteria in the subject's study file. The document is NOT entered into the study database.

4. Measure height, weight and pulse, and document on CRF#8. Research BP Measurement Form.

5. Administer surveys using the following forms:

   CRF#4. Blood Pressure Demographic

   CRF#9. Antihypertensive Medications – Only complete Part A at the baseline visit.

   CRF#5. Blood Pressure Medication Adherence

   CRF#7. Diagnosed Conditions

   CRF#10. Symptom Assessment Scale

6. Review the subject's medical record for the following information and supplement subject responses as needed on the following forms:

   a. CRF#4. Demographic Information: The duration of the patient's hypertension

   b. CRF#7. Diagnosed Conditions: The presence of other co-morbid conditions (e.g., diabetes, hyperlipidemia)

   c. CRF#9. Antihypertensive Medications: Only complete Part A at the baseline visit.

6 MONTH VISIT (scheduled 5-7 months after enrollment) – At this visit, the SC will:

1. Administer CRF#8. Research BP Measurement :
   a. Measure the subject's weight and pulse.
   b. Measure the subject's blood pressure according to the blood pressure protocol.
2. Administer CRF#9, Part A and Part B: Record current antihypertensive medications, doses and frequency of administration AND record medication changes documented in the medical record since the last study visit.
3. Administer CRF#2. Serious Adverse Event: Assess for a serious adverse event since the last Study Coordinator visit; only enter data electronically on events that qualify as SAEs.

9 MONTH VISIT (scheduled 8-10 months after enrollment) – At this visit, the SC will:

1. Administer CRF#8. Research BP Measurement :
    a. Measure the subject's weight and pulse.
    b. Measure the subject's blood pressure according to the blood pressure protocol.
2. Administer CRF#9, Part A and Part B: Record current antihypertensive medications, doses and frequency of administration AND record medication changes documented in the medical record since the last study visit.
3. Administer CRF#2. Serious Adverse Event: Assess for a serious adverse event since the last Study Coordinator visit; only enter data electronically on events that qualify as SAEs.
4. Re-administer patient surveys:
    a. CRF#5. Blood Pressure Medication Adherence
    b. CRF#7. Diagnosed Conditions
    c. CRF#10. Symptom Assessment Scale

12 MONTH VISIT (scheduled 11-13 months after enrollment) – At this visit, the SC will:

1. Administer CRF#8. Research BP Measurement :
    a. Measure the subject's weight and pulse.
    b. Measure the subject's blood pressure according to the blood pressure protocol.
2. Administer CRF#9, Part A and Part B: Record current antihypertensive medications, doses and frequency of administration AND record medication changes documented in the medical record since the last study visit.
3. Administer CRF#2. Serious Adverse Event: Assess for a serious adverse event since the last Study Coordinator visit; only enter data electronically on events that qualify as SAEs.

18 MONTH VISIT (scheduled 17-19 months after enrollment) – At this visit, the SC will:

1. Administer CRF#8. Research BP Measurement :
    a. Measure the subject's weight and pulse.
    b. Measure the subject's blood pressure according to the blood pressure protocol.
2. Administer CRF#9, Part A and Part B: Record current antihypertensive medications, doses and frequency of administration AND record medication changes documented in the medical record since the last study visit.
3. Administer CRF#2. Serious Adverse Event: Assess for a serious adverse event since the last Study Coordinator visit; only enter data electronically on events that qualify as SAEs.

24 MONTH VISIT (scheduled 23-25 months after enrollment) – At this visit, the SC will:

1. Administer CRF#8. Research BP Measurement :
    a. Measure the subject's weight and pulse.
    b. Measure the subject's blood pressure according to the blood pressure protocol.

2. Administer CRF#9, Part A and Part B: Record current antihypertensive medications, doses and frequency of administration AND record medication changes documented in the medical record since the last study visit.
3. Administer CRF#2. Serious Adverse Event: Assess for a serious adverse event since the last Study Coordinator visit; only enter data electronically on events that qualify as SAEs.
4. Re-administer baseline patient surveys:
    a. CRF#5. Blood Pressure Medication Adherence
    b. CRF#7. Diagnosed Conditions
    c. CRF#10. Symptom Assessment Scale

D. PROCEDURES FOR MEASURING RESEARCH BLOOD PRESSURES

NB: The manufacturer gives a method for checking accuracy (compared to a calibrated mercury manometer) on page 26 of the Instruction Manual and recommends doing this check if you get suspicious readings or if you drop the device. The manufacturer recommends re-calibration per the manufacturer every 5 years for light use (< 5 times daily), more often for heavy use.

Preparing the Subject

The subject ideally should refrain from smoking or ingesting caffeine for 20-30 minutes prior to the blood pressure measurement.

Have the subject remove all clothing that covers the location of cuff placement.

The subject should be comfortably seated in a chair, with:

- the back supported
- legs uncrossed and flat on the floor
- the arm supported, ideally at heart level on a desk
- the palm of the hand facing upward

Have the subject sit for at least 5 minutes. Instruct the patient to relax as much as possible.

Cuff Measurement

The ideal cuff should have a bladder length that is 80% of arm circumference and a width that is at least 40% of arm circumference. The **INDEX ↑** that is marked on the edge of the cuff should fall within the range bar on the cuff. Manufacturer-recommended cuff sizes are shown below:

If arm circumference is:	17-22 cm	22-32 cm	32-42	42-50 cm
Use this cuff:	Small adult	Adult	Large adult	Extra large adult

Subjects who require use of a thigh cuff cannot continue in the study.

Cuff Placement

Do not allow a sleeve to form a tourniquet on the arm.

Palpate the brachial artery in the antecubital fossa and place the **ART** ↓ marked on the midline of the bladder of the cuff so that it is over the arterial pulsation of the patient's bare upper arm.

The lower end of the cuff should be ½ to 1 inch above the inner side of the elbow joint.

The middle of the cuff should be at the level of the right atrium (the mid-point of the sternum).

Pull the cuff snugly around the bare upper arm so that you can insert only one finger between the cuff and the arm.

Blood Pressure Measurement

Have CRF#8. Research Blood Pressure Measurement and the Omron monitor on a desk.

Tell the subject that you will be taking at least 3 blood pressure readings.

Neither the subject nor the nurse should talk during the measurement.

Push the ON/OFF button on the monitor to turn on the power.

Take a single BP reading

- Set the MODE selector to "SINGLE."
- Set the P-Set knob to "AUTO."
- Push the START button.
- Record the displayed blood pressure on line 10 of CRF#8 Research Blood Pressure Measurement.

Take a double BP reading

- Set the MODE selector to AVG.
- Push the START button.
- The machine will show you TWO individual BP readings and the average of these two readings.
- Record the second reading on line 11 and the third reading on line 12 of CRF#8. Research Blood Pressure Measurement.
- If the second and third BP readings differ by $\leq$ 4mm, record the displayed average BP reading on CRF#8 Research Blood Pressure Measurement.

If the second and third BPs differ by > 4 mm

- Set the MODE selector to "SINGLE."
- Push the START button.
- Record the displayed fourth reading on line 13 of CRF#8 Research Blood Pressure Measurement.
- Manually average the **two closest systolic** measurements and the **two closest diastolic** from the 2nd, 3rd and 4th blood pressure readings, and enter those averages onto CRF#8 Research Blood Pressure Measurement. If all 3 systolic or diastolic readings are equidistant apart, select the two **HIGHEST** readings to average.

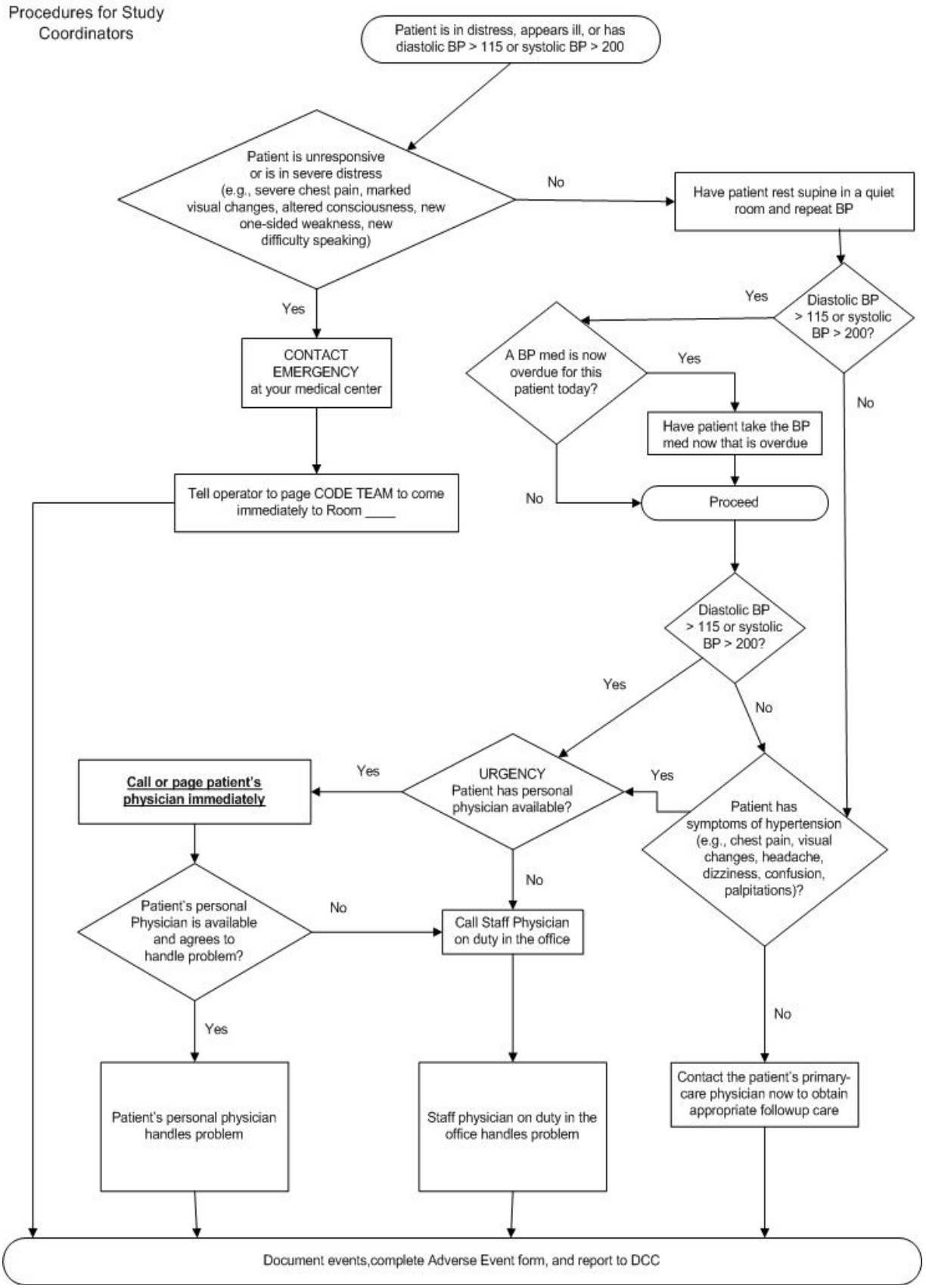
IF YOU GET AN ERROR MESSAGE AT ANY POINT, START THE SEQUENCE OVER.

IF YOU OBTAIN BLOOD PRESSURE READINGS DURING ANY VISIT THAT ARE > 115 DIASTOLIC OR > 200 SYSTOLIC OR IF THE PATIENT IS IN DISTRESS, FOLLOW THE DECISION TREE FOR HYPERTENSIVE URGENCIES.

SUBJECTS WHOSE AVERAGE BP *AT BASELINE* IS > 115 DIASTOLIC AND/OR > 200 SYSTOLIC CANNOT CONTINUE IN THE STUDY.

RE-SCREENING OF SELECT SUBJECTS WHOSE BP IS WITHIN 5 MM HG OF BEING UNCONTROLLED MAY BE RE-SCREENED UP TO 3 TIMES WITHIN 7 MONTHS *IF RE-SCREENING OF BLOOD PRESSURES HAS BEEN APPROVED BY THE LOCAL IRB*.

CAPTION Study: Handling Hypertension Urgencies



E. Screening and Assigning Patients to the Passive Observation Group

Study Coordinators will abstract medical record data for an additional 18 clinic patients who appear to be eligibility criteria based upon medical record review. These subjects are never brought in for a study visit, and they do **NOT** sign informed consent.

Screening of patients for the Passive Observation Group will not begin until two years after the first active observation subject is enrolled at a given site.

Human Subjects Issues

Sites who did not receive initial IRB approval for the passive observation group must amend their IRB application to include this component. Check to make sure this component has been approved by your IRB.

Most IRBs require that all medical record data to be abstracted for a given patient exist at the time that any portion of the patient's data is abstracted. Consequently, all medical record data to be abstracted for a given patient must exist at the time that any portion of the patient's data is abstracted.

Informed consent should **NOT** be obtained from patients assigned to the passive group.

Patient Selection

1. In order to begin assigning patients to the passive observation group, a site must meet BOTH of the following two conditions:
    a. The site is no longer enrolling subjects for the active observation group. That is, either:
        - the site has reached its target for enrolling active observation subjects OR
        - the site has received notice from the Clinical Coordinating Center that it can stop enrolling active observation subjects without reaching its target.
    b. At least 2 years have passed since the first eligible subject in the active observation group was enrolled.
2. As each active observation subject completes the 24 month study visit, the Study Coordinator may assign one patient to the passive observation group who meets all the eligibility criteria specified below. Thus, each active observation subject who completes the 24 month visit is 'paired' with a passive observation subject who has had clinic visits at the critical time points specified below.
3. The total number of passive observation subjects needed is 18 for original CAPTION sites and 9 for the new CAPTION sites added in 2011. Sites who have met their enrollment target for active observation patients (24 for original sites and 12 for new sites) should skip the pairing process for every 4th patient who completes the 24 month visit. Thus the first 3 active observation subjects who complete the study would be paired, the 4th would not be paired, the 5th-7th active observation subjects who complete the study would be paired, the 8th would not, etc. Sites that were not able to meet their enrollment target for active observation subjects should identify 3 passives for every 4 enrolled active subjects.
4. Sites should **NOT** pair a patient for active observation subjects who were terminated early and did not complete the 24 month study visit.
5. The first step is identification of patients who qualify based on the study's eligibility criteria. These patients should be identified using the following two steps:
    a. First, sites should include those patients who passed medical record screening criteria for the active observation group but that 1) were never consented into the active group and 2) never declined participation in the active observation group. Patients who

declined to participate in the active group should **NOT** be included in the passive observation group.

b. Second, sites may screen medical records for patients who were never screened for the active observation group. Sites that need to use this strategy should screen medical records for individuals on your screening log, beginning where you previously stopped on your screening log while recruiting patients for the active observation group.

6. Previously unscreened patients who are considered for inclusion in the passive observation group must:

   i. Have at least two uncontrolled clinic BPs documented during the two year period *prior* to the date your first active observation subject was enrolled. Do not include patients who had fewer than two uncontrolled BPs during that two year period. Adopt the same strategy for evaluating clinic BPs that was used when screening for active observation subjects.

   ii. Meet the study's other eligibility criteria (e.g., cannot be terminally ill, have Alzheimer's disease or severe liver or kidney disease, etc.).

   iii. Still be actively seen in the clinic.

7. Patients who qualify based on medical record screening may be assigned to the passive observation group if they meet **ALL THREE** of the following additional criteria:

   i. Have an UNCONTROLLED clinic BP that was documented during a clinic visit that occurred within the 6 month window that spans from 3 months prior to the enrollment date for the patient's 'paired' active observation subject to 3 months after the enrollment date for the 'paired' active observation subject.

   If the patient also has subsequent clinic visits that match the time frames specified in the following two bullets, this visit will become that patient's **'Index Clinic Visit'** and will mark the start of the two year time period for which you collect medical record data. **The clinic BP measurement documented for the Index Clinic Visit MUST BE UNCONTROLLED**.

   ii. Have a subsequent clinic visit where a clinic BP measurement is documented that occurs 6 months to 12 months following the Index Clinic Visit. If multiple visits occurred during this time period, select the one that is closest to 9 months following the Index Clinic Visit. This visit will represent the **9 month clinic visit** time point for medical record abstraction.

   iii. Have a subsequent clinic visit during the time frame that spans 21 months to 27 months following the Index Clinic Visit. If multiple visits occurred during this time period, select the one that is closest to 24 months following the Index Clinic Visit. This visit will represent the **24 month clinic visit** time point for medical record abstraction.

8. If more than one BP measurement was taken at a given clinic visit, use the lowest recorded pressure to determine eligibility (for the Index Clinic Visit). Also use the lowest documented pressure as the key outcome measurement for the 9 and 24 month time points.

IN SUMMARY, each patient assigned to the passive group must have documented visits that match the Index Clinic Visit time point, the 9 month clinic visit time point and 24 month clinic visit time point, as defined by the study visits dates for a 'paired' active observation subject.

A clinic BP must be documented for each of these three visits, and the clinic BP must be UNCONTROLLED at the Index Clinic Visit.

Logging Screening of Patients for the Passive Observation Group

Use the same screening log you used for active observation subjects to log your attempts to identify patients for the passive observation group:

1. For patients who were previously screened for the active observation group AND who have Y marked in Column G:
    a. If the patient has qualifying Index, 9 month **and** 24 month visits, write Y in Column AB (Patient Assigned to Passive Observation Arm).
    b. If the patient does not have qualifying Index, 9 month and 24 month visits, write N in Column AB.
2. For patients who were not screened for the active observation group:
    a. Begin screening using the next Random Screening Number in Column B of the log. Use the paired Patient Number given in Column C of the log to find the patient on your IT list. Write the patient's name into column A of your log.
    b. Complete columns D, E, F and G as follows:

        Column D: Write in Y if the patient's medical record documented at least two uncontrolled clinic BP measurements during the year prior to the start of screening for active observation subjects.

        Column E: Write in Y if the patient had other exclusion criteria that were disqualifying; otherwise, write in N.

        Column F: Write in Y if the patient has left the practice; otherwise, write in N.

        Column G: Write in Y if the patient seemed to meet all screening criteria based on medical record review; otherwise, write in N.

    c. Skip to Column AB:

        Patients with Y entered into Column G should be examined for the occurrence of qualifying Index, 9 month and 24 month visits:

        i. Patients who do not have clinic visits that match the time frames needed for the Index, 9 month and 24 month visits must be excluded from the passive observation group. Write N into the far right column (Patient Assigned to Passive Observation Arm).

        ii. Patients who DO have clinic visits that match the time frames needed for the Index, 9 month and 24 month visits qualify for further consideration for the passive observation group.

            Specifically, each patient's Index Clinic Visit must have occurred within $\pm$ 3 months of the baseline study visit for a 'paired' active observation subject.

            A patient whose clinic visits can be matched to the key study time points for an active subject should be included the passive observation group. Write Y into the far right column (Patient Assigned to Passive Observation Arm).

            A patient whose clinic visits cannot be matched to the key study time points for an active subject cannot be included in the passive observation group. Write N into the far right column.

            Only ONE passive observation patient can be paired with each active observation subject.

Electronic submission of Patient Data for the passive observation group

1. Patients assigned to the passive observation group are 'enrolled' into the study via completion and electronic submission of eCRF#1 Informed Consent. Electronic submission will result in creation of a subject ID for each patient in the passive observation group.
2. For each patient assigned to the passive observation group, the Study Coordinator will collect and document data from the patient's medical record on CRF#19 Passive Medical Record Abstraction, both hard copy and electronic versions. See page 41 for detailed instructions on completing eCRF#19.

IV. PROCEDURES FOR CLINIC PHYSICIANS

Physicians do not need to change their practice in any way because a patient is enrolled in the study. Physicians should care for their patients as usual.

V. INSTRUCTIONS FOR COMPLETING CASE REPORT FORMS

All case report forms (CRFs) excepting physician and pharmacist surveys will be stored on the website for downloading. Sample hard copy forms are provided in APPENDIX VIII.

All case report forms should be completed on paper. Paper forms are considered to be source documents and should be securely stored in the subject's research file in a locked file cabinet in a locked office.

Paper forms must carry each subject's study ID, not their name.

Study Coordinators should electronically enter data from the paper CRF to the electronic case report form (eCRF).

FORMS SCHEDULE: HYPERTENSION ACTIVE OBSERVATION GROUP

Scheduled visits should be completed during the 60 day period surrounding the due date, that is, 30 days before the due date –30 days after the due date.

Time Points (Study Visit)	Baseline	6 months	9 months	12 months	18 months	24 months	Event Driven
Visit Window	NA	+/- 1 mo	+/- 1 mo	+/- 1 mo	+/- 1 mo	+/- 1 mo	
CRF#1. Informed Consent	X						X
CRF#2. Serious Adverse Event		X	X	X	X	X	X
CRF#3. Study Termination							X
CRF#4. Blood Pressure Demographic	X						
CRF#5. Blood Pressure Medication Adherence	X		X			X	
CRF#7. Diagnosed Conditions	X		X			X	
CRF#8. Research Blood Pressure Measurement	X	X	X	X	X	X	
CRF#9. Antihypertensive Medications	X	X	X	X	X	X	
CRF#10. Symptom Assessment Scale	X		X			X	
CRF#24. Protocol Deviation Form							X
CRF#26. Blood Pressure Re-Screening							X

Some CRFs will require medications to be entered into a table. The medications are identified by a code on the list of Drug Codes for Antihypertensive Medications. The eCRF will not accept medications that are not on the list. If you need to enter such a medication, contact the CCC and provide the name of the medication. They will assign a code and inform the DMC that a new medication needs to be added to the list of medications. After this has occurred, the CCC will notify you that it is now possible to enter your data.

CRF#1.Informed Consent

This form must be completed for all subjects consented into the study. A subject ID will be generated when the form is submitted. Record this number on all paper CRFs completed for the subject.

Item 1: Select 'Hypertension active observation' as the type of consent.

Item 2: A version number and/or version date must be entered to identify the version of the informed consent document used.

> Item 2.a: Enter the version number available on the footer of the consent document. If no version number is available select the N/A check box. If the N/A check box is selected, any value entered in the version number field will be cleared.
>
> Item 2.b: Enter the version date or date of approval of the consent document or select the N/A check box. This information is typically available on page 1 of the informed consent document. If the N/A check box is selected, any value entered in the version date field will be cleared.

Item 3: Enter the date on which the subject signed the informed consent document referenced in Item 2.

Item 4: Enter the subject's final adjusted score on the Short Portable Mental Status Questionnaire used to screen subjects for mental deficiencies. If the score is >2, a subject ID will be generated but no additional eCRFs will become available for the subject.

Item 5: Indicate the subject's baseline blood pressure control by selecting one of the 4 options. If option 4 (Uncontrolled) is *not* selected for this item, a subject ID will be generated but no additional baseline eCRFs will become available for the subject.

> Item 5.a and 5.b: If option 4 (Uncontrolled) is NOT selected in Item 5 (i.e. the subject's baseline, research blood pressure is not eligible), enter the average research blood pressure in 5.a (Average Systolic) and 5.b (Average Diastolic).

Item 6: Indicate if the subject is ineligible for another reason not included in item 4 or 5. If yes is selected, enter an explanation in the text field (Item 6.a); a subject ID will be generated but no additional eCRFs will become available for the subject.

CRF#2. Serious Adverse Event

Complete Sections A and B on the hard copy form at the time of each Study Coordinator follow-up visit with subjects. These items will not be entered into the database. However, a copy of the completed paper form should be retained in the subject's file for monitoring.

Part A

> Visit Date: Enter the date of the study visit.
>
> Item A.1: Ask the subject the question as written on the CRF and select either the 'Yes' or 'No' option.
>
> Item A.2: Ask the subject the question as written on the CRF and select either the 'Yes' or 'No' option.

Part B

Item B.1: Review the medical record for the time period since the last study visit. Select 'Yes' for this item if an SAE is found documented in the medical record. Select 'No' otherwise.

Item B.2: If an SAE occurs during the study visit select 'Yes' for this item. Select 'No' otherwise.

If your answer to all of the items in Sections A and B is No, **STOP HERE** and **FILE the hard copy form** in the subject's folder. Do **NOT** complete Section C on the hard copy form. Do **NOT** submit the form electronically.

If your answer to one or more items in Sections A and B is Yes OR if you become aware of an SAE through another means, **skip to item C.9** and determine which of the listed outcome(s) occurred.

Part C, item C.9. Check/select any or all options a – g OR option h ('None of the above') to indicate the outcomes that are attributed to the event as documented in the subject's medical record (check all that apply):

☐ a. Death

Item C.9a.1: If death was an outcome of the SAE, enter the date of death in this field.

☐ b. Life-threatening

☐ c. Hospitalization – initial or prolonged

☐ d. Disability

☐ e. Congenital anomaly

☐ f. Required intervention to prevent permanent impairment/damage

Option 9.f should be used for an event that does not result in death, a life-threatening condition, hospitalization, disability or congenital deformity but that did jeopardize the subject and required a specific medical intervention to prevent one or more of outcomes C.9.a – C.9.e from occurring.

☐ g. Important medical event as determined by the site PI or designee

Option 9.g should only be chosen when the site judges the event to represent significant hazard or harm to the research subject.

☐ h. None of the above

If the outcome of the identified event is C.9.h. (None of the above), **STOP HERE** and **FILE the hard copy form** in the subject's folder. The event represents a non-serious adverse event. Do **NOT** complete items C.1-C.8 in Section C on the hard copy form. Do **NOT** submit the form electronically.

If the outcome of the identified event is one or more of the outcomes in C.9.a. – C.9.g., the event represents a SERIOUS adverse event. **Complete all items in Section C on the hard copy form, ENTER PART C ELECTRONICALLY**, and file the hard copy form in the subject's folder.

Item C.1: If the date of the SAE is documented in the medical record, enter that date here. If the date is not in the medical record, enter the event date reported by the patient.

Item C.2: Enter the date on which the **Study Coordinator** became aware of the SAE.

Item C.3: Select an option from the list of possible SAE descriptors in APPENDIX IX.

If none of the descriptors appear to match the SAE, click on the link below the drop down box on the electronic eCRF to view a more detailed explanation of each descriptor.

If you still cannot identify a descriptor from the list, contact the CCC for assistance before selecting 'Other'.

If you are instructed to select the 'Other' option, write in a descriptor in the space provided on the paper CRF. On the electronic CRF, select 'Other' from the drop down list. A text field will become available where you can enter the descriptor text recorded on the paper form.

Item C.4: Indicate if the SAE is an exacerbation of a condition existing prior to enrollment.

Item C.5: Indicate if the SAE was associated with one of the medications on the list of Drug Codes for Antihypertensive Medications. If 'Yes' is selected for this item, complete items C.5.a and C.5.b.

Item C.5.a: Write in/select the name and code of the medication.

Item C.5.b: Indicate if the medication was stopped because of the adverse event.

Item C.6, C.7, and C.8: Enter text describing the details of the SAE as requested.

CRF#3.Study Termination

This eCRF will be completed when a subject is terminated early from the study or when a subject has completed all follow-up study visits. If the subject was terminated due to an adverse event, also complete eCRF #2 Serious Adverse Event.

Item 1: Indicate if the subject has completed all research study visits or if the subject is being terminated early.

Item 1.a: If 'Yes' is selected for Item 1, enter the date of the subject's final study visit (i.e. 24 months).

Item 1.b: If 'No' is selected for Item 1, enter the date on which the subject was terminated.

Item 1.c: If 'No' is selected for Item 1, enter the date of the subject's last research study visit with the Study Coordinator.

Item 2: If 'No' is selected for Item 1, select the reason the subject was terminated early. Some options also require a text description if the option is selected. If the subject died due to an AE, selected 'Subject withdrew/terminated due to Adverse Event'; do *not* select 'Subject death'.

Item 3: Enter a comment (optional)

CRF#8.Research Blood Pressure Measurement

Visit: Check the study visit for which the form is being completed. This information will not be entered in the eCRF but should be recorded on the hard copy form.

Item 1: Enter the date of the study visit at which this information was collected.

Items 2 and 2.a: Enter the subject's height (2) and select the units (2.a). This information should only be collected at the baseline study visit.

Items 3 and 3.a: Enter the subject's weight (2) and select the units (2.a).

Item 4: Check/select an option indicating if the subject smokes.

> Item 4.a: If 'Yes' is checked/selected for Item 4, indicate if the time since the subject's last cigarette is ≤ or > 20 minutes. If the subject's last cigarette was ≤20 minutes ago, it is preferable but not required that you wait until over 20 minutes have elapsed before taking the subject's blood pressure.
>
> > Item 4.a.1: If '≤20 minutes ago' is checked/selected for Item 4.a, indicate if the subject waited at least 20 minutes before the research blood pressure was measured.

Item 5: Enter the time of day of the blood pressure recording in military time. If the measurement occurred in the morning, enter the hours and minutes as usual. If the measurement occurred in the afternoon, add 12 to the hours and enter the minutes as usual.

Item 6: Check/select the arm used for the blood pressure measurement. The right arm is preferred.

Item 7: Enter the midpoint circumference of the arm used for the blood pressure measurement. This information should only be collected at the baseline study visit.

Item 8: Check/select the cuff size used for the blood pressure measurement.

Item 9: Enter the subject's pulse in beats per minute at the time of the blood pressure measurement.

Item 10, 11, and 12: Record the first 3 blood pressure measurements.

Item 13: If the 2nd and 3rd systolic or the 2nd and 3rd diastolic measurements differ by more than 4 mm Hg, a 4th blood pressure measurement is required. Enter the 4th reading here.

Item 14: Calculate the average systolic blood pressure by adding Items 11.a and 12.a and dividing by 2. If Item 13.a is required, average the closest two measurements of Items 11.a, 12.a, and 13.a. If Items 11.a, 12.a, and 13.a are equidistant, average the highest two of these three measurements.

Item 15: Calculate the average diastolic blood pressure by adding Items 11.b and 12.b and dividing by 2. If Item 13.b is required, average the closest two measurements of Items 11.b, 12.b, and 13.b. If Items 11.b, 12.b, and 13.b are equidistant, average the highest two of these three measurements.

CRF#4.Blood Pressure Demographic

Item 1: Enter the date of the baseline study visit.

Item 2: Enter the subject's birth date.

Item 3: Select the subject's gender (male, female)

Item 4: Select any or all of options a – e or option f ('Declined to answer') according to the subject's response.

Item 5: Select the ethnicity the subject chose.

Item 6, 7, 8, 9, 10, and 12: For each item, indicate the options selected by the subject.

Item 11: Select the smoking status the subject chose. If the subject selected 'Currently smokes', complete items 11.a and 11.b. If the subject selected 'Former smoker', complete items 11.a, 11.b, and 11.c. If the subject selected 'Never smoked', do *not* complete item 11.a, 11.b, or 11.c.

Item 11.a: Enter the number of years the subject says s/he smoked.

Item 11.b: Enter the number of cigarettes the subject says s/he smoked each day.

Item 11.c: Select the time since quitting the subject chose.

Item 13: Select the option that best describes the duration of the subject's blood pressure diagnosis.

CRF#9.Antihypertensive Medications

Visit: Check the study visit for which the form is being completed. This information will not be entered in the eCRF but should be recorded on the hard copy form.

Item A.1: Enter the date of the study visit for which the information is being collected.

Table A.2: Write in/enter the subject's current antihypertensive medications at the time of the study visit into the table. Include all antihypertensive medications that are currently prescribed according to the medical record.

Item A.2.a: Write in the medication/enter the medication code in the text field.

Item A.2.b: Write in/select the strength of the medication from the list of options.

Item A.2.c: Write in/select the dose (i.e. number of tabs) from the list of options.

Item A.2.d: Write in/select the frequency from the list of options.

Item A.2.e: Check the box if the medication is prescribed on an “as needed” basis.

Item A.2.f: Check/select one option to indicate how the patient is taking each medication.

Part B: Do not complete this section at the Baseline Study Visit. At all subsequent study visits, complete Part B once for each clinic contact that occurred since the last scheduled study visit with the Study Coordinator, excepting phone calls to schedule appointments or to obtain medication refills.

Item B.1: Enter the date of the clinic visit documented in the medical record

Item B.2: Check/select the type of contact made with the subject.

Item B.3: Check/select any or all of the available healthcare professionals with whom the contact was made.

Item B.4: Check/select any or all of options a – g or option h (‘No lifestyle changes recommended’) to indicate the lifestyle changes that were recommended to the subject. If option g is checked/selected, specify the change in the space provided (Item 4g.1).

Item B.5: Indicate if increased blood pressure medication adherence was recommended to the subject during the clinic visit.

Table B.6: Complete this table if a change was made to any of the subject’s antihypertensive medications.

Item B.6.a: Write in the medication name/enter the medication code in the text field.

Item B.6.b: Check/enter the change type relative to the same medication as it is documented in the patient’s medical record. If a new drug is being added, check/select “Start New Drug” for that medication.

Item B.6.c: Write in the medication strength/select the strength of the medication from the list of options.

Item B.6.d: Write in the dose/select the dose (i.e. number of tabs) from the list of options.

Item B.6.e: Write in the frequency/select the frequency from the list of options.

Item B.6.f: Check the box to indicate if the medication is prescribed on an “as needed” basis.

CRF#5.Blood Pressure Medication Adherence

Visit: Indicate the study visit for which the form is being completed. This information will not be entered in the eCRF but should be recorded on the hard copy form.

Part A: Enter the date of the study visit at which the questionnaire was administered.

Part B

Item B.1: Check the subject's medical record to determine if there is at least one active prescription for a blood pressure medication. This should be done prior to the study visit if possible.

Items B.2, B.3, B.4, B.5, B.6, and B.7: If the subject has at least one active prescription (Item B.1 = 'Yes'), read each item to the subject and record his/her responses. Otherwise, do not complete Items B.2, B.3, B.4, B.5, B.6 or B.7.

CRF#10.Symptom Assessment Scale

Visit: Check the study visit for which the form is being completed. This information will not be entered in the eCRF but should be recorded on the hard copy form.

Part A: Enter the date of the study visit at which the questionnaire was administered.

Parts B – H: Circle/select the option that indicates the subject's response to the question.

CRF#7.Diagnosed Conditions

Visit: Check the study visit for which the form is being completed. This information will not be entered in the eCRF but should be recorded on the hard copy form.

Item 1: Enter the date of the study visit at which this information was collected.

Item 2: At the baseline study visit, check/select all conditions with which the subject has been diagnosed at the time of enrollment. At subsequent study visits, select only conditions with which the subject has been newly diagnosed since the last study visit.

Item 3: At the baseline study visit, enter the subject's two most recent serum creatinine tests occurring prior to or at enrollment; include the creatinine value obtained and the date the sample was drawn. At subsequent study visits, enter only tests that have occurred since the last study visit.

CRF#24.Protocol Deviation

Item 1: Enter the date of the deviation.

Item 2: Enter the date the Study Coordinator became aware of the deviation.

Item 3: Select any or all options 3.a – 3.h to indicate the type of deviation. If you select option 3.a, enter a description of the unmet inclusion criteria in the space provided. If you select option 3.b, enter a description of the exclusion criteria in the space provided. If you select option 3.g, enter the date of the SAE in Item 3.g.1 and provide a description in Item 3.g.2. If you select option 3.h, enter a description of the "Other" protocol deviation in the space provided.

Complete the Corrective Action Plan on hard copy. This is for your center's use only and will not be entered into the database.

CRF#26. Blood Pressure Re-screening

After a center has received IRB approval to re-screen blood pressure subjects and forwarded the necessary documentation to the CCC, the DMC will activate the Blood Pressure Re-screening eCRF for the center. The eCRF will then become available under the Baseline Visit for ineligible subjects who meet re-screening criteria.

Item 1: Enter the date on which the subject was re-screened.

Item 2: Indicate the subject's re-screening blood pressure control by selecting one of the 4 options.

> Item 2.a and 2.b: If option 4 (Uncontrolled) is not selected in Item 2 (i.e. the subject's research blood pressure remains ineligible), enter the average research blood pressure in 2.a (Average Systolic) and 2.b (Average Diastolic).

If the subject's blood pressure is uncontrolled, complete items 3 and 4.

> Item 3: Enter the subject's adjusted score on the Short Portable Mental Status Questionnaire used to screen subjects for mental deficiencies. You do not need to repeat the questionnaire unless you have reason to believe that the subject's mental status has declined since the original baseline visit.
>
> Item 4: Indicate if the subject is ineligible for another reason not included in item 3. If yes is selected, enter an explanation in the text field (Item 4.a)

Research blood pressure measurements that do not meet re-screening criteria (both systolic and diastolic below the specified ranges), item 3 > 2, or selecting yes for item 4 will disqualify the subject from future re-screening.

Hypertension Passive Observation Group

An Informed Consent eCRF must also be completed for subjects in the 'Hypertension passive observation' group; this allows the data management center to establish a subject ID number with which to track the subject's data. Select 'Hypertension passive observation' as the type of consent (Item 1). No other information is required. Submit the form to create a new subject ID.

FORMS SCHEDULE

The Passive Medical Record Abstraction eCRF will be completed **ONCE** for all patients assigned to the Hypertension Passive Observation group. This eCRF will not be available until 2 years following enrollment of the first subject into the Active Observation group.

Time Points*	Index Clinic Visit	9 months	24 months
Patient assigned to Passive Observation group			X
Window for Clinic Visits	Cannot occur before the first Active Observation subject was enrolled.	+/- 3 mo	+/- 3 mo
19. Passive Medical Record Abstraction form completed			X

* Subject makes NO research study visits. Time periods refer to regular clinic visits documented in the medical record

An Informed Consent eCRF must also be completed for subjects in the hypertension passive observation group; this allows the data coordinating center to establish a subject ID number with which to track the subject's data. Select 'Hypertension passive observation' as the type of consent (Item 1). No other information is required. Submit the form to create a new subject ID.

CRF#19.Passive Medical Record Abstraction

Item 1: Enter the date of the index clinic visit. This is the date of the initial clinic visit documented in the medical record that begins the 24 month observational study period.

Item 3: Enter the subject's birth date.

Item 4: Check/select the subject's gender (male, female)

Item 5: Indicate the subject's race by checking/electronically selecting any or all of options a – e OR option f ('Unknown/not reported').

Item 6: Check/select the subject's ethnicity.

Item 7 and 7.a: Enter the subject's height (7) and select the units (7.a). If the subject's height is not recorded in the medical record, select the "Height not documented" check box.

Item 8 and 8.a: Enter the subject's weight (8) and check/electronically select the units (8.a)

Item 9: Check/electronically select any or all of options a – f or option g ('Not documented') to indicate the type of health insurance the subject has.

Item 10: Check/select an option to indicate if the subject has insurance coverage for prescriptions.

Item 11: Check/select the option that best describes the subject's smoking history as documented in the medical record.

Item 12: Check/select to indicate the subject's current alcohol intake as documented in the medical record.

Item 13: Check/select any or all of options a – l or option m ('None of the above') to indicate any conditions with which the subject is diagnosed.

Item 14: List the subject's first and second most recent serum creatinine values and test dates in items 14.a and 14.b, respectively. Only enter values for tests that were done prior to the index clinic visit.

Item 15

Item 15.a: The system will pre-populate the date of the index clinic visit using the value entered in Item 1.

Item 15.b: Enter the subject's blood pressure as recorded in the medical record at the time of the index clinic visit.

Table 15.c: Enter each of the subject's prescribed antihypertensive medications at the time of the index clinic visit.

Item 16

Item 16.a: Enter the date of the clinic visit closest to the date 9 months after the index clinic visit. The date can be no earlier than 6 months and no later than 12 months after the index clinic visit. Subjects who did not have a clinic visit within this time period should NOT be assigned to the passive observation group.

Item 16.b: Enter the subject's blood pressure as recorded in the medical record at the time of the selected clinic visit.

Table 16.c: Enter each of the subject's prescribed antihypertensive medications at the time of the selected clinic visit.

Item 17

Item 17.a: Enter the date of the clinic visit closest to the date 24 months after the index clinic visit. The date can be no earlier than 21 months and no later than 27 months after the index clinic visit. Subjects who did not have a clinic visit within this time period should NOT be assigned to the passive observation group.

Item 17.b: Enter the subject's blood pressure as recorded in the medical record at the time of the selected clinic visit.

Table 17.c: Enter each of the subject's prescribed antihypertensive medications at the time of the selected clinic visit.

VI. PROVIDER AND CLINIC SURVEYS

Physician and Pharmacist Surveys (overseen by the University of Iowa IRB)

The following surveys will be mailed to sites as part of the ASTHMA intervention. Please see the asthma manual for more information.

- Physician Leader Implementation Survey
- Physician Mail Implementation Survey
- Pharmacist Mail Implementation Survey
- Barriers and Enablers of an PPCM Intervention

VII. PROTECTION OF HUMAN SUBJECTS

This project involves human subjects research that meets the definition of "clinical research" and also meets the NIH definition of a Phase III Clinical Trial.

A. OVERSIGHT BY LOCAL INSTITUTIONAL REVIEW BOARD

Each site must obtain approval for the study from its local Institutional Review Board. Study Coordinators and clinic investigators will need to obtain training and approval as specified by their local Institutional Review Board. Information pertinent to the IRB application is provided below.

Once IRB approval is obtained, each site should email their approval letter and a copy of each approved informed consent document to the CCC.

B. POTENTIAL RISKS AND PROTECTIONS AGAINST RISK

Active Observation Group

Risk to subjects is minimal since they will continue to receive at least their usual and customary medical care from their physician.

No patient will be coerced to participate or continue in the study. Patients will be informed that their decision about participation will have no effect on their relationship with their physician or their care and that they can withdraw from the study at any time if they choose. Each patient will also be informed that the investigators will obtain prescription, medical record, and billing data during the course of their participation in the study.

Each subject in the Active Observation group will sign informed consent. The subject will receive a copy of the signed consent document, and a copy will be placed in the patient's medical record per clinic and IRB protocol.

All subjects will be provided contact information for the Study Coordinator or clinic physician PI in the event the subject would like to discuss any study-related issue or adverse event that arises. All participating subjects will also be provided contact information for the local IRB and instructed to contact that office should questions about the rights of research subjects or research related injury arise.

There is the possibility that hypotension or adverse reactions could occur. Subjects will be encouraged to contact their providers immediately if adverse events do occur. In addition, the study's Data and Safety Monitoring Board will evaluate the differences between groups and any adverse events at least twice a year or more frequently if adverse outcomes occur.

All data concerning blood pressure, adverse reactions and adverse outcomes will be reviewed by the Data Safety Monitoring Board at least twice a year. Serious events will be evaluated immediately via email and/or conference call. Any serious adverse effects will be reported to the local IRB. If any adverse outcomes might influence the continued participation of patient subjects, all active observation patients will be informed.

Passive Observation Group

Patients with hypertension who are assigned to the passive observation group will not undergo any research visits, surveys or have research-related contact with study personnel. All of their data will simply be abstracted retrospectively from the medical record and de-identified prior to

transmission to the University of Iowa. Therefore, sites should seek IRB approval to waive informed consent for assigning of patients to the passive observation group. Waiving consent is critical for obtaining an unbiased cross section of the clinic's practice so that the study is less likely to be subject to the Hawthorne effect.

Provider Subjects

Surveys will be mailed to site providers and clinic personnel as part of the ASTHMA intervention. This portion of the study will be overseen by the University of Iowa IRB. Risk to these subjects is minimal, and provider subjects can decline participation. Please see the asthma manual for more information.

C. LINKAGES TO SUBJECTS AND ACCESS TO PATIENT IDENTITIES

Original data information that contains patient subject identifiers will be stored in locked cabinets and offices at participating sites and will only be accessible to the members of the site research team and, under their supervision, the University of Iowa study monitor. To help protect subject confidentiality, we will use identification code numbers rather than names on study forms. Data will be maintained in locked offices and storage areas, and sites will use password-protected computer files. The list linking the subjects' study identification codes and their names will be stored in a separate location that is accessible only to the Study Coordinator and, under site supervision, to University of Iowa study monitors.

The only personnel who will have direct contact with patient subjects will be the Study Coordinator and physicians employed at the clinic. The study monitors from the Data Management Center will only have access to the subjects' medical records in the course of the monitoring visits. Monitors will have no contact with clinic patients. The Study Coordinator will record data on worksheets that serve as case report forms. The only identifiers that will be collected are the subject's birth date and the dates of clinic visits. The only persons with access to link the code number to the subject will be the Study Coordinator and, under site supervision, the University of Iowa study monitors.

Subjects assigned to the passive observation group will only have data collected by retrospective review of the medical record. The Study Coordinator will compile medical record data onto standardized forms with the subject identified only by a study ID. Only the Study Coordinator will know the identity of subjects in the passive observation group. Neither monitors nor investigators from the University of Iowa investigators will be able to identify subjects.

Patient subject data will be electronically uploaded by the site Study Coordinator to a database located on a secure server at the University of Iowa Clinical Trials Statistical & Data Management Center. Access to the database is strictly password-protected.

Survey and interview data provided by the clinic pharmacists, physicians, Study Coordinator and Office Administrator as part of the asthma intervention trial will be completed by telephone or mailed survey. Providers will be assigned unique study codes, and only these codes will be placed onto data collection instruments. Links between provider codes and provider names will be stored electronically on secure, password-protected files at the University of Iowa. University of Iowa researchers will enter provider data into password-protected databases located on secure servers within the Clinical Trials Statistical & Data Management Center and the Clinical Coordinating Center. Hard copy data collection forms will be filed in locked cabinets in locked offices in the University of Iowa Clinical Coordinating Center. Provider data will be analyzed without links to provider names.

D. THE FEDERAL HEALTH INSURANCE PORTABILITY AND ACCOUNTABILITY ACT (HIPAA)

We will keep subjects' participation in this research study confidential to the extent permitted by law. They will be informed that it is possible that certain individuals may become aware of their participation in this study including the study monitor, federal government regulatory agencies, auditing departments and the local Institutional Review Board.

The Federal Health Insurance Portability and Accountability Act (HIPAA) requires that the patient's health care system obtains permission from all subjects in the active observation group so that the research team may access or create "protected health information." Sites should request IRB permission to waive consent on passive observation patients in which only chart review is performed by the Study Coordinator employed in the patient's clinic so long as the abstracted information is completely de-identified.

All data will be transmitted electronically via a secured website in an encrypted format and saved to the database at the University of Iowa Clinical Trials Statistical & Data Management Center. All data are backed up daily on an independent server and also backed up weekly and stored offsite. The servers are located in secured offices at the Clinical Trials & Statistical Data Management Coordinating Center. There are multiple security measures in place to ensure data protection. Subjects will be informed that we may share their health information related to this study with other parties including federal government regulatory agencies, the Department of Health and Human Services, the patient's health system Institutional Review Board and the University of Iowa Institutional Review Boards and study monitors. They will be informed that they cannot participate in this study unless they permit us to use their protected health information. If they choose not to allow us to use their protected health information, we will discuss non-research alternatives available to them. The subjects will be informed that their decision will not affect their right to medical care that is not research-related. They will also be informed that their signature on the Consent Document authorizes their health care facility to give us permission to use or create health information about them.

Subjects will be informed that they may not be allowed to see study information until after this study is over, but that they may be given access to their health care records by contacting their health care provider. They will also be informed that permission for us to access or create protected health information about them for purposes of this study has no expiration date. They will also be informed that if we have sent their health information to a third party, such as the study sponsor, or we have removed their identifying information, it may not be possible to prevent its future use.

E. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO SUBJECTS OR OTHERS

Potential benefits to physicians include an increase in knowledge about their patient's drug therapy and improved blood pressure management for their patients. We expect that patients in the intervention group will have improved blood pressure control and fewer adverse reactions or drug interactions. If the intervention is effective, it might be used on a broader scale for a wide variety of health systems.

F. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

In general, BP for hypertensive subjects is poorly controlled even for patients who frequently visit their physician. This leads to large numbers of preventable cardiovascular events. Research including our preliminary results suggests that blood pressure control can be markedly improved by using physician/pharmacist collaborative teams. Our preliminary studies suggest that the intervention may effectively overcome racial and socioeconomic barriers to poor blood pressure control. More than 37 million Americans have uncontrolled hypertension and it is our conviction that this model will have a substantial impact to improve control rates. We are confident that this intervention model can become one strategy to help achieve the blood pressure goals for Healthy People 2010.

G. INCLUSION OF WOMEN AND MINORITIES

This application will include both men and women. There may be more women and elderly because we anticipate the population to be over-represented by older female patients with isolated systolic hypertension. We expect 60% of patients will be women.

Patients from minority groups will be eligible for this study, and no patient will be excluded based on race or ethnic group. The goal of the study nationally will be to recruit at least 40% of patients from under-represented minority groups.

H. DATA AND SAFETY MONITORING

The Clinical Trials & Statistical Data Management Center's DMC will be responsible for receiving and processing submitted reports of Serious Adverse Events (SAEs) and Unanticipated Problems (UPs) and for forwarding such reports to one of two Medical Monitors. The Medical Monitors perform the following functions: 1) ongoing, real-time reviews of all individual SAE reports to determine if events are unanticipated, related and serious, and suggestive of greater risk; 2) monthly reviews of cumulative SAE data to judge whether there are concerning trends in the occurrence of events, and the possible relationship of those trends to the trial; 3) review any reports of UPs identified by the DMC or CCC that meet the NHLBI criteria for reporting. When needed, a Medical Monitor may ask the CCC to communicate with a site in order to obtain additional chart information pertinent to a submitted report.

The study's Data and Safety Monitoring Board (DSMB) is responsible for safeguarding the interests of study participants by assessing the safety and efficacy of study procedures, and by periodic monitoring of safety data and the overall conduct of the study. The DSMB will develop an operational plan during the first six months of the study. The operational plan will be consistent with NHLBI's Policy on Human Subjects Research: Data and Safety Monitoring Plans dated May 2005. The plan will include conflict of interest disclosure statements for each member, frequency and location of meetings, policies and procedures and dissemination of meeting materials, notification of NHLBI staff, data to be reviewed and procedures for evaluating data and reporting findings.

The DMC will provide the Data and Safety Monitoring Board data on numbers of patients recruited into the study, patient outcomes, and serious adverse events. The DSMB reviews the following types of safety data provided by the DMC: 1) quarterly reports; 2) bi-annual reports for DSMB meetings; and 3) individual concerns identified by the Medical Monitors. After reviewing pertinent reports, the DSMB determines whether any trend that may be identified is related to the trial, whether the study's informed consent form and process needs to be modified, whether the study's procedures need to be modified and whether the study should be discontinued due

to serious adverse drug events or adverse outcomes in either the control group or those related to the intervention. The DMC application describes methods for interim analyses and how data will be supplied to the DSMB.

The DSMB consists of the following members:

- Barry Davis, MD, PhD, The University of Texas School of Public Health – Chair and statistician
- Keith Ferdinand, MD, The Morehouse School of Medicine
- Michael D. (Mick) Murray, PharmD, MPH, The University of North Carolina School of Pharmacy
- Katherine Gloer, PhD, The University of Iowa – Executive Secretary

VIII. SERIOUS ADVERSE EVENTS AND PROTOCOL COMPLIANCE

Serious Adverse Event Assessment and Reporting

Study Coordinators should assess subjects for the occurrence of a serious adverse event. ***A serious adverse event does NOT need to be related to the study in order to be reported.***

As specified by NHLBI policy, serious adverse events (SAEs) are considered to be those events that result in at least one of the following outcomes:

a. Death

a.1 Date: __ __/__ __/__ __ __ __ (mm/dd/yyyy)

b. Life-threatening

c. Inpatient hospitalization or prolongation of an existing hospitalization

d. Persistent or significant disability/incapacity

e. A congenital anomaly/birth defect

f. Other events that might jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

Option 9.f should be used for an event that does not result in death, a life-threatening condition, hospitalization, disability or congenital deformity but that did jeopardize the subject and required a specific medical intervention to prevent one of these outcomes from occurring.

g. Important medical event as determined by the site PI or designee

Option 9.g should only be chosen when a site judges the event to represent significant hazard or harm to research subjects.

If there is any question about whether an event should be classified as an SAE, please contact the CCC for further direction.

ALL SERIOUS ADVERSE EVENTS SHOULD BE REPORTED WITHIN 24 HOURS OF THE TIME THAT A RESEARCH TEAM MEMBER BECOMES AWARE OF THE EVENT. If the Study Coordinator is not available to submit eCRF #2 within the 24 hour timeframe, a member of the study team may complete the hard copy version of the SAE form and either FAX the hard copy form to the DMC Protocol Coordinator or scan the form into an electronic file and email the file to the DMC Coordinator. The DMC will then enter the information into the electronic data system.

Study Coordinators collect serious adverse event data on CRF#2. Serious Adverse Event at all visits AFTER the baseline visit:

Part A. Administer screening questions (1) and (2) at every visit AFTER the baseline visit.

Question 1: Have you had any changes in your health since the last study visit?

Question 2: Have you been hospitalized or received care in an Emergency Room since your last study visit

Part A. Complete questions (1) and (2) for events that are documented in the medical record but that are not reported by the subject

COMPLETE PARTS A and B ON HARD COPY ONLY, NOT IN THE DATABASE.

Part C. Complete item C.9 if 1) Yes is selected for any question in Part A or Part B or a serious adverse event is identified in the medical record or through any other means AND 2) one or more of the items in 9.a – 9.g is/are checked. Part C should NOT be completed if item 9.h is checked.

If the outcome of the event is identified to be C.9.h (None of the above) **STOP** and **FILE** the hard copy in the subject's folder. The event represents a non-serious adverse event. Do **NOT** complete items C.1-C.8 in Section C on the hard copy form. Do **NOT** submit the form electronically.

If the outcome of the identified event is one or more of the outcomes in C.9.a. – C.9.g., the event represents a SERIOUS adverse event. **Complete all items in Section C on the hard copy form, ENTER PART C ELECTRONICALLY**, and file the hard copy form in the subject's folder.

See Section V. INSTRUCTIONS FOR COMPLETING CASE REPORT FORMS for more details on completion of CRF#2. Serious Adverse Event.

A list of serious adverse event descriptors is provided in APPENDIX IX. Please use these descriptors to complete Item 3 in Part C of the form.

Protocol Compliance

All providers participating in the study should make all efforts to comply with the study protocol. Deviations from the specified protocol should be submitted on paper and electronic CRF #24. Protocol Deviation.

Critical areas of compliance for Study Coordinators include:

1. Ensuring that all enrolled subjects meet the study's inclusion and exclusion criteria.
2. Ensuring that all subjects enrolled into the active observation group of the study sign informed consent.
3. Having subjects complete their 9 month and 24 month visits.
4. Screening for and promptly reporting adverse events.

APPENDIX I: PROJECTED STUDY TIMETABLE

Activity	Months							Responsible Staff
	0- 9	*10- 12*	*13- 16*	*17- 21*	*22- 33*	*34-45*	*46-52*	
Train nurses in enrollment, data collection, BP								Ecklund (DMC), Ardery, Carter
Physician Surveys								Study Coordinators, clinic physicians, Ardery
Recruit Active Observation patients with hypertension		**10 enrolled**	**10 enrolled**	**4 enrolled**				Study Coordinators, DMC
Monitor each BP subject's BP X 24 months								Study Coordinators, DMC
Identify passive observation patients and abstract records						**18 identified/ abstracted**		Study Coordinators, DMC
Organizational support and evaluation								Vaughn, Carter, Ardery
Safety and BP monitoring evaluations by DSMB								DMC, DSMB
Final BP Data analysis								DMC, Coffey
Cost effectiveness analysis								Brooks, Polgreen
Study close out								Study Coordinators, DMC

APPENDIX II: SITE SIGNATURE LOG TEMPLATE

Investigator Name		***Site Name and Location***		***Page Number***	___ ***of*** ___

Name and Title of Site Staff Use Block Capitals	**Signature**	**Initials**	**Responsibilities*** (See below)							**Involved From** DD-MMM-YY	**Involved To** DD-MMM-YY

****DELEGATION OF RESPONSIBILITIES CODES***	***NOTES FOR COMPLETING THIS FORM***
A. Study Coordinator *B. Study Pharmacist* *C. Study Lead Physician* *D. Study PI*	• *Please PRINT CLEARLY when completing this form* • *Please enter all dates in the MM-DD-YYYY format (e.g., 01-21-2005)* • *Use 'Involved From' and 'Involved To' to record staff changes during the study* • *Enter a new line and applicable dates when responsibilities change*

Principal Investigator Signature:_____ Date Initially Completed:_____

Principal Investigator Signature:_____ Date Updated:_____

Principal Investigator Signature:_____ Date Updated:_____

FAX COMPLETED FORM TO GAIL ARDERY AT 319-335-9511

APPENDIX II: SITE SIGNATURE LOG TEMPLATE

Investigator Name		***Site Location***		***Page Number***	***___ of ___***

Principal Investigator Signature:______________________________ Date Updated:______________________________

Principal Investigator Signature:______________________________ Date Updated:______________________________

Principal Investigator Signature:______________________________ Date Updated:______________________________

Principal Investigator Signature:______________________________ Date Updated:______________________________

Principal Investigator Signature:______________________________ Date Updated:______________________________

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Principal Investigator Signature:______________________________ Date Updated:______________________________

Principal Investigator Signature:______________________________ Date Updated:______________________________

APPENDIX III: INDIVIDUAL SITE ENROLLMENT TARGETS FOR HYPERTENSION SUBJECTS

TARGETED/PLANNED ENROLLMENT:			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	3	2	5
Not Hispanic or Latino	19	18	37
Ethnic Category: Total of All Subjects *	**22**	**20**	**42**
Racial Categories			
American Indian/Alaska Native	1	0	1
Asian	0	1	1
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	4	4	8
White	16	15	31
Racial Categories: Total of All Subjects *	**22**	**20**	**42**

The numbers above include subjects enrolled into both the active observation group (N=24/site) and the passive observation group (N=18/site).

			Medical Record Screening Process				Attempted contacts by mail			
Column A Patient Name	Column B Random Screening Number	Column C Patient Number	Column D Clinic BPs Disqualified	Column E Disqualified by Other Exclusion Criteria	Column F Patient Left Practice	Column G Meets Med Record Screening Criteria	Column H Date Letter Mailed	Column I Date Postcard Received	Column J Declined on Postcard	Column K Expressed Interest on Postcard in Hearing More About the Study

		Attempted contacts by phone										
Column B Random Screening Number	Column C Patient Number	Column L Date Phone Call 1	Column M Date Phone Call 2	Column N Date Phone Call 3	Column O Date Phone Call 4	Column P Date Phone Call 5	Column Q Date Phone Call 6	Column R Unable to contact	Column S Declined on Phone	Column T Exclusion Criterion Identified on Phone	Column U Indicated Interest on Phone in Hearing More About the Study	Column V Unable to Schedule Baseline Visit

		Baseline Visit Outcomes						Passive Arm
Column B Random Screening Number	Column C Patient Number	Column W Declined Consent at Baseline Visit	Column X Signed Informed Consent	Column Y Screening BP Did Not Meet Criteria	Column Z SPMSQ Scored Did Not Meet Criteria	Column AA Exclusion Criterion Discovered After Consent Signed	Column AB Fully Enrolled into Study	Patient Assigned to the Passive Observation Arm

Column A Patient Name	Column B Random Screening Number	Column C Patient Number	Medical Record Screening Process				Attempted contacts by mail			
			Column D Clinic BPs Disqualified	Column E Disqualified by Other Exclusion Criteria	Column F Patient Left Practice	Column G Meets Med Record Screening Criteria	Column H Date Letter Mailed	Column I Date Postcard Received	Column J Declined on Postcard	Column K Expressed Interest on Postcard in Hearing More About the Study
Andrea Adams	1	783	Y	N	N	N				
Bob Barker	2	1891	N	N	N	Y	1/13/2010	2/6/2010	Y	N
Carol Carter	3	38	Y	N	N	N				
David Dirksen	4	149	N	N	N	Y	1/13/2010			
Eric Evans	5	1057	N	Y	N	N				
Fred Flowers	6	588	Y	N	N	N				
Gail Gerber	7	1380	Y	N	N	N				
Henry Hill	8	875	Y	N	N	N				
Ingrid Iverson	9	68	N	N	N	Y	1/13/2010	1/18/2010	N	Y
Jenny Jackson	10	4	N	N	N	Y	1/13/2010	2/2/2010	Y	
Karl Karsen	11	1577	N	N	N	Y	1/13/2010	2/2/2010	Y	
Linda Levson	12	411	Y	N	N	N				
Mary Matson	13	349	Y	N	N	N				
Nancy Noyes	14	12	N	N	N	Y	1/13/2010			
Oliver Olson	15	1133	Y	N	N	N				
Peter Pan	16	624	N	N	N	Y	1/13/2010			
Quo Q'hai	17	217	N	N	N	Y	1/13/2010	1/22/2010	N	Y
Richard Robertson	18	99	N	N	N	Y	1/13/2010			
Steven Sampson	19	1492	Y	N	N	N				
Tim Taylor	20	255	N	N	N	Y	1/13/2010	1/12/2010	N	Y
Una Uberhaus	21	1776	Y	N	N	N				
Victoria Velasquez	22	401	Y	N	N	N				
Walter Winchel	23	1666	Y	N	N	N				
Xavier Xupha	24	52	N	N	N	Y	1/13/2010			
Yvonne Yogerst	25	596	N	N	Y	N				
Zia Zobert	26	44	Y	N	N	N				

Attempted contacts by phone										
Column L Date Phone Call 1	Column M Date Phone Call 2	Column N Date Phone Call 3	Column O Date Phone Call 4	Column P Date Phone Call 5	Column Q Date Phone Call 6	Column R Unable to contact	Column S Declined on Phone	Column T Exclusion Criterion Identified on Phone	Column U Indicated Interest on Phone in Hearing More About the Study	Column V Unable to Schedule Baseline Visit
1/30/2010	2/7/2010					N	N	N	Y	N
1/30/2010	2/7/2010	2/14/2010	2/21/2010	2/28/2010	3/3/2010	Y				
1/30/2010							Y			
1/30/2010	2/7/2010					N	N	N	Y	N
1/30/2010	2/7/2010					N	N	N	Y	N

Baseline Visit Outcomes						Passive Arm
Column W Declined Consent at Baseline Visit	Column X Signed Informed Consent	Column Y Screening BP Met Criteria	Column Z SPMSQ Score Qualified	Column AA Exclusion Criterion Discovered After Consent Signed	Column AB Fully Enrolled into Study	Patient Assigned to the Passive Observation Arm
N	Y	Y	Y	N	Y	
N	Y	Y	Y	N	Y	
N	Y	Y	Y	N	Y	

APPENDIX V: EVALUATION TO SIGN INFORMED CONSENT DOCUMENT FOR RESEARCH

(Complete for each patient whose capacity to read or sign informed consent is in question and file in the patients study folder)

Check the following indicators of the patient's mental status:

	Yes	No
Subject is alert		
Subject is able to communicate without difficulty		

If you check "No" to EITHER statement above, explain to the patient that s/he cannot participate and check "No" in the Certification of Ability to Sign Informed Consent section below.

If you check "Yes" to BOTH statements above, ask the patient to undertake each task listed below and check to denote whether each response is appropriate.

	Patient Responds Appropriately	
	Yes	No
Please name at least two potential risks of participating in the study		
Please name at least two things that you will be expected to do during the study.		
Please explain what you would do if you did not wish to continue participating in the study.		
Please explain what you would do if you experienced distress or discomfort during the study.		

If the patient does NOT respond appropriately to all four questions, explain to the patient that s/he cannot participate and check "No" in the certification section below

If the patient DOES respond appropriately to all four questions, check "Yes" in the certification section below.

CERTIFICATION OF ABILITY TO SIGN INFORMED CONSENT

	Yes	No
Patient meets the above criteria required to sign informed consent.		

_____ _____

Study Coordinator Signature Date

APPENDIX VI: SOURCE DOCUMENT FOR VERIFICATION OF INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria	Has Inclusion Criterion*	
English or Spanish speaking males or females	Yes	No
Over 18 years of age	Yes	No
Has a diagnosis of hypertension	Yes	No
Has uncontrolled BP defined as: ▪ ≥ 140 mm Hg SBP or ≥ 90 mm Hg DBP for patients with uncomplicated hypertension OR ▪ ≥ 130 mm Hg SBP or ≥ 80 mm Hg DBP for patients with diabetes or chronic kidney disease. The Study Coordinator will only invite patients to be screened who have demonstrated uncontrolled BP values on at least two past clinic visits. Qualification *in the* Active Observation group will be based on a seated research BP (average of the second and third reading) as measured in the office by the Study Coordinator. Only one qualifying average BP will be required. Qualification in the Passive Observation group will be a qualifying BP using usual office measurements that were taken during clinic visits approximately 2 years prior to patient identification for this group. The Study Coordinator will determine if a patient has either diabetes or chronic kidney disease based on documentation in the problem list in the patient's medical record.	Yes	No
Exclusion Criteria	**Has Exclusion Criterion***	
Current signs of hypertensive emergency (acute angina, stroke, or renal failure)	Yes	No
Severe HTN (average systolic BP >200 or diastolic BP >115 mm Hg at baseline visit)	Yes	No
History of MI, stroke, or unstable angina in the prior 6 months	Yes	No
Systolic dysfunction with a LV ejection fraction < 35% documented by echocardiography, nuclear medicine study, or ventriculography	Yes	No
Renal insufficiency, defined by a glomerular filtration rate less than 20 ml/min or previously documented proteinuria > 1 gram per day	Yes	No
Significant hepatic disease, including prior diagnoses of cirrhosis, Hepatitis B or C infection, or laboratory abnormalities (serum ALT or AST > 2 times control or total bilurubin > 1.5 mg/dl) in the prior 6 months	Yes	No
Pregnancy	Yes	No
Diagnoses of pulmonary hypertension or sleep apnea (unless treated by either CPAP or BiPAP)	Yes	No
Poor prognosis with a life expectancy estimated less than 2 years	Yes	No
Residence in a nursing home or diagnosis of dementia	Yes	No
Inability to give informed consent (*Active Observation Group only*)	Yes	No
Impaired cognitive function (> 2 errors on the Short Portable Mental Status Questionnaire (*Active Observation Group only*)	Yes	No

***SUBJECT MUST MEET ALL OF THE INCLUSION CRITERIA AND NONE OF THE EXCLUSION CRITERIA TO REMAIN IN THE STUDY.**

Checklist is NOT available for electronic submission to the study database. Complete only on hard copy.

APPENDIX VII: LIST OF HYPERTENSION DRUG CODES

***Diuretics* – Class Code = 100**

Code	Generic Name	Brand Names	Strengths Available
101	amiloride	Midamor	5 mg
102	amiloride/hydrochlorothiazide	Moduretic	5/50 mg
103	bumetanide	Bumex	0.5 mg, 1 mg, 2 mg
104	chlorothiazide	Diuril	250 mg, 500 mg
105	chlorthalidone	Hygroton and others	25 mg, 50 mg, 100 mg
106	furosemide	Lasix	20 mg, 40 mg, 80 mg
107	hydrochlorothiazide	Hydrodiuril & others	12.5 mg, 25 mg, 50 mg
108	triamterene/hydrochlorothiazide	Dyazide, Maxide	37.5/25 mg, 50/25 mg, 75/50 mg
109	indapamide	Lozol	1.25 mg, 2.5 mg
110	metolazone	Mykrox, Zaroxolyn	2.5 mg, 5 mg, 10 mg
111	polythiazide	Renese	1 mg, 2 mg, 5 mg
112	spironolactone/hydrochlorthiazide	Aldactazide	25/25 mg, 50/50 mg
113	torsemide	Demadex	5 mg, 10 mg, 20 mg, 100 mg
114	triamterene	Dyrenium	50 mg, 100 mg
115	Ethacrynic acid	Edecrin	25 g

***Beta Blockers* – Class Code = 200**

Code	Generic Name	Brand Names	Strengths Available
201	acebutolol	Sectral	200 mg, 400 mg
202	atenolol	Tenormin	25 mg, 50 mg, 100 mg
203	betaxolol	Kerlone	10 mg, 20 mg
204	bisoprolol	Zebeta	5 mg, 10 mg
205	metoprolol tartrate	Lopressor	25 mg, 50 mg, 100 mg
206	metoprolol succinate (extended release)	Toprol XL	25 mg, 50 mg, 100 mg, 200 mg
207	nadolol	Corgard	20 mg, 40 mg, 80 mg, 120 mg, 160 mg
208	penbutolol	Levatol	20 mg
209	pindolol	Visken	5 mg, 10 mg
210	propranolol	Inderal	10 mg, 20 mg, 40 mg, 60 mg, 80 mg
211	propranolol long-acting	Inderal LA	60 mg, 80 mg, 120 mg, 160 mg

***Beta Blockers* – Class Code = 200 (cont)**

Code	Generic Name	Brand Names	Strengths Available
212	timolol	Blocadren	5 mg, 10 mg, 20 mg
213	atenolol-chlorthalidone	Tenoretic	50/25 mg, 100/25 mg
214	bisoprolol-hydrochlorothiazide	Ziac	2.5/6.25 mg, 5/6.25 mg, 10/6.25 mg
215	metoprolol-hydrochlorothiazide	Lopressor HCT	50/25 mg, 100/25 mg, 100/50 mg
216	nadolol-bendroflumethiazide*	Corzide	40/5 mg, 80/5 mg
217	propranolol LA-hydrochlorothiazide	Inderide LA	40/25 mg, 80/25 mg
218	timolol-hydrochlorothiazide*	Timolide	10/25 mg
219	Nebivolol	Bystolic	2.5 mg, 5 mg, 10 mg, 20 mg

***Alpha/Beta Blockers* - Class Code = 200**

Code	Generic Name	Brand Names	Strengths Available
220	carvedilol	Coreg	3.125 mg, 6.25 mg, 12.5 mg, 25 mg
221	labetalol	Normodyne, Trandate	100 mg, 200 mg, 300 mg
222	carvedilol extended release	Coreg CR	10 mg, 20 mg, 40 mg, 80 mg

***ACE Inhibitors* – Class Code = 300**

Code	Generic Name	Brand Names	Strengths Available
301	benazepril	Lotensin	5 mg, 10 mg, 20 mg, 40 mg
302	captopril	Capoten	12.5 mg, 25 mg, 50 mg, 100 mg
303	enalapril	Vasotec	2.5 mg, 5 mg, 10 mg, 20 mg
304	fosinopril	Monopril	10 mg, 20 mg, 40 mg
305	lisinopril	Zestril, Prinivil	2.5 mg, 5 mg, 10 mg, 20 mg, 30 mg, 40 mg
306	moexipril	Univasc	7.5 mg, 15 mg
307	perindopril	Aceon	2 mg, 4 mg, 8 mg
308	quinapril	Accupril	5 mg, 10 mg, 20 mg, 40 mg
309	ramipril	Altace	1.25 mg, 2.5 mg, 5 mg, 10 mg
310	trandolapril	Mavik	1 mg, 2 mg, 4 mg
311	benazepril-hydrochlorothiazide	Lotensin HCT	5/6.25 mg, 10/12.5 mg, 20/12.5 mg, 20/25 mg

***ACE Inhibitors* – Class Code = 300 (cont)**

Code	Generic Name	Brand Names	Strengths Available
312	captopril-hydrochlorothiazide	Capozide	25/15 mg, 25/25 mg, 50/15 mg, 50/25 mg
313	enalapril-hydrochlorothiazide	Vaseretic	5/12.5 mg, 10/25 mg
314	fosinopril-hydrochlorothiazide	Monopril-HCT	10/12.5 mg, 20/12.5 mg
315	lisinopril-hydrochlorothiazide	Prinzide, Zestoretic	10/12.5 mg, 20/12.5 mg, 20/25 mg
316	moexipril-hydrochlorothiazide	Uniretic	7.5/12.5 mg, 15/12.5 mg, 15/25 mg
317	quinapril-hydrochlorothiazide	Accuretic	10/12.5 mg, 20/12.5 mg, 20/25 mg

***Calcium Channel Blockers* – Class Code = 400**

Code	Generic Name	Brand Names	Available Strengths
401	amlodipine	Norvasc	2.5 mg, 5 mg, 10 mg
402	diltiazem	Cardizem, Dilacor, Tiazac	60 mg, 90 mg, 120 mg, 180 mg, 240 mg, 300 mg, 360 mg, 420 mg
403	felodipine	Plendil	2.5 mg, 5 mg, 10 mg
404	isradipine	DynaCirc	2.5 mg, 5 mg, 10 mg
405	nicardipine	Cardene	20 mg, 30 mg, 45 mg, 60 mg
406	nifedipine	Adalat, Procardia	10 mg, 20 mg, 30 mg, 60 mg, 90 mg
407	nisoldipine	Sular	8.5 mg, 10 mg, 17 mg, 20 mg, 25.5 mg, 30 mg, 34 mg, 40 mg
408	verapamil	Calan, Isoptin, Verelan, Coer, Covera HS	40 mg, 80 mg, 100 mg 120 mg, 180 mg, 200 mg, 240 mg, 300 mg, 360 mg

***Calcium Channel Blocker/ACE Inhibitor Combinations* – Class Code = 300, 400**

Code	Generic Name	Brand Names	Available Strengths
410	amlodipine/benazepril	Lotrel	2.5/10 mg, 5/10 mg, 5/20 mg, 5/40 mg, 10/20 mg, 10/40 mg
411	enalapril/felodipine	Lexxel	5/2.5 mg, 5/5 mg
412	trandolapril/verapamil	Tarka	1/240 mg, 2/180 mg, 2/240 mg, 4/240 mg

Calcium Channel Blocker/Angiotensin II Receptor Blocker Combination
Class Code = 400, 600

Code	Generic Name	Brand Names	Available Strengths
420	amlodipine/valsartan	Exforge	5/160 mg, 10/160 mg, 5/320 mg, 10/320 mg
421	amlodipine/valsartan/hydrochlorothiazide	Exforge HCT	5/160/12.5 mg, 10/160/12.5 mg, 5/160/25 mg, 10/160/25 mg, 10/320/25 mg
422	amlodipine/olmesartan	AZOR	5/20 mg, 5/40 mg, 10/20 mg, 10/40 mg

Calcium Channel Blocker/Angiotensin II Receptor Blocker/Diuretic Combination
Class Codes = 100, 400, 600

Code	Generic Name	Brand Names	Available Strengths
450	amlodipine/olmesartan/HCTZ	Tribenzor	5/20/12.5 mg, 5/40/12.5 mg, 5/40/25 mg, 10/40/12.5 mg, 10/40/25 mg

***Alpha blockers* – Class Code = 500**

Code	Generic Name	Brand Names	Available Strengths
501	doxazosin	Cardura	1 mg, 2 mg, 4 mg, 8 mg
502	prazosin	Minipress	1 mg, 2 mg, 5 mg
503	terazosin	Hytrin	1 mg, 2 mg, 5 mg, 10 mg
504	prazosin/polythiazide	Minizide	1/0.5 mg, 2/0.5 mg, 5/0.5 mg

***Angiotensin II receptor antagonists (ARB)* – Class Code = 600**

Code	Generic Name	Brand Names	Available Strengths
601	candesartan	Atacand	4 mg, 8 mg, 16 mg, 32 mg
602	eprosartan	Teveten	400 mg, 600 mg
603	irbesartan	Avapro	75 mg, 150 mg, 300 mg
604	losartan	Cozaar	25 mg, 50 mg, 100 mg
605	olmesartan	Benicar	5 mg, 20 mg, 40 mg
606	telmisartan	Micardis	20 mg, 40 mg, 80 mg
607	valsartan	Diovan	40 mg, 80 mg, 160 mg, 320 mg
608	candesartan-hydrochlorothiazide	Atacand HCT	16/12.5 mg, 32/12.5 mg, 32/25 mg
609	eprosartan-hydrochlorothiazide	Teveten-HCT	600/12.5 mg, 600/25 mg
610	irbesartan-hydrochlorothiazide	Avalide	150/12.5 mg, 300/12.5 mg, 300/25 mg
611	losartan-hydrochlorothiazide	Hyzaar	50/12.5 mg, 100/12.5 mg, 100/25 mg
612	olmesartan medoxomil-hydrochlorothiazide	Benicar HCT	20/12.5 mg, 40/12.5 mg, 40/25 mg
613	telmisartan-hydrochlorothiazide	Micardis-HCT	40/12.5 mg, 80/12.5 mg, 80/25 mg
614	valsartan-hydrochlorothiazide	Diovan-HCT	80/12.5 mg, 160/12.5 mg, 160/25 mg, 320/12.5 mg, 320/25 mg
615	Azilsartan Medoxomil	Edarbi	40 mg, 80 mg

Centrally Acting Alpha 2 blockers – Class Code = 700

Code	Generic Name	Brand Names	Strengths Available
701	clonidine	Catapres	0.1 mg, 0.2 mg, 0.3 mg
702	clonidine topical patch	Catapres TTS	0.1 mg, 0.2 mg, 0.3 mg
703	guanabenz	Wytensin	4 mg, 8 mg
704	guanfacine	Tenex	1 mg, 2 mg
705	methyldopa	Aldomet	250 mg, 500 mg
706	methyldopa-hydrochlorothiazide	Aldoril	250/15 mg, 250/25 mg
707	clonidine-chlorthalidone	Clorpres	0.1/15 mg, 0.2/15 mg, 0.3/15 mg

Peripheral Adrenergic Blocking Agents – Class Code = 800

Code	Generic Name	Brand Names	Strengths Available
801	reserpine	Serpalan, Serpasil	0.1 mg, 0.25 mg
802	reserpine-chlorthalidone	Demi-Regroton	0.125/25 mg
803	reserpine-chlorothiazide	Diupres	0.125/250 mg, 0.125/500 mg
804	reserpine-hydrochlorothiazide	Hydropres	0.125/25 mg, 0.125/50 mg
805	reserpine-hydralazine-hydrochlorothiazide	Ser-Ap-Es	0.1/25/15 mg

Vasodilators – Class Code = 900

Code	Generic Name	Brand Names	Strengths Available
901	hydralazine	Apresoline	10 mg, 25 mg, 50 mg, 100 mg
902	isosorbide dinitrate	Isordil	2.5 mg, 5 mg, 10 mg, 20 mg, 30 mg, 40 mg
903	isosorbide mononitrate	Imdur	10 mg, 20 mg, 30 mg, 60 mg, 120 mg
904	minoxidil	Loniten	2.5 mg, 10 mg
905	hydralazine-hydrochlorothiazide		25/25 mg, 50/50 mg, 100/50 mg
906	isosorbide dinitrate-hydralazine	BiDil	20/37.5 mg

Aldosterone Receptor Blockers – Class Code = 1000

Code	Generic Name	Brand Names	Strengths Available
1001	eplerenone	Inspra	25 mg, 50 mg
1002	spironolactone	Aldactone	25 mg, 50 mg, 100 mg

Direct Renin Inhibitor – Class Code = 2000

Code	Generic Name	Brand Names	Strengths Available
2001	aliskiren	Tekturna	150 mg, 300 mg
2002	aliskiren-hydrochlorothiazide	Tekturna HCT	150/12.5 mg, 150/25 mg, 300/12.5 mg, 300/25 mg
2003	aliskiren-valsartan	Valturna	150/160 mg, 300/320 mg

APPENDIX VIII: HARD COPY CASE REPORT FORMS

Date Administered: _ _/_ _/_ _ _ _ (mm/dd/yyyy)

QUESTIONNAIRE

"I will now ask you some questions that require use of your memory. Please rely only on your memory." *(Do not allow the patient to look at a calendar, newspaper, or other memory aid.)*

	Subject Response	Instructions	Scoring Correct (0)	Scoring Incorrect (1)
1. What is the date today?	_____	Scored correctly only when the exact month, date, and year are given correctly (need all 3 parts).		_____
2. What day of the week is it?	_____			_____
3. What is the name of the place you are currently located?	_____	Scored correctly if any correct description of the location is given – my home or correct name of town of residence.		_____
4. What is your telephone number?	_____	Verify with number in Contact Information. Area code not necessary.		_____
5. How old are you?	_____	Scored correctly when stated age corresponds to date of birth.		_____
6. When were you born?	_____	Scored correctly only when the month, exact date, and year are all given (need all 3 parts).		_____
7. Who is the President of the U.S. now?	_____	Requires only the last name of the President.		_____
8. Who was President just before him?	_____	Requires only the last name of the President.		_____
9. What was your mother's maiden name?	_____	Does not need to be verified. Scored correct if a female 1st name plus a last name other than the subject's last name is given.		_____
10. Subtract 3 from 20 and keep subtracting 3 from each new number, all the way down. [20-17-14-11-8-5-2]	_____	Requires that the entire series must be performed correctly to be scored as correct. Any error in the series or unwillingness to attempt is scored as incorrect.		_____
		Total Number of Errors:		_____

ADJUSTED SCORING

a) Decrease total number of errors by 1 if the subject:
   - Only has a grade school education
     OR
   - Is African-American

b) Decrease total number of errors by 2 if the subject:
   - Only has a grade school education
     AND
   - Is African-American

c) Increase the total number of errors by 1 if the subject:
   - Has had education beyond high school

Adjusted Score: _____

If adjusted score is: 0-2 Errors – Keep in study
3-10 Errors – Exclude from study

1. Type of consent
   - ○ Hypertension active observation
   - ○ Alternative asthma intervention
   - ○ Hypertension passive observation

If 'Hypertension passive observation' is selected above, stop. Submit the form without answering any remaining questions.

2. Version of consent document

   The version number or version date should appear in either the header or footer of the informed consent document or on a stamp applied to that document. *Note: The informed consent form approved by your IRB may contain either a version number or a version date, but not necessarily both. If one of the items does not appear on the form, check the N/A box for that item.*

   a. Version number: _____ ☐ N/A
   b. Version date: __ __/__ __/__ __ __ __ (mm/dd/yyyy) ☐ N/A

3. Date informed consent signed: __ __/__ __/__ __ __ __ (mm/dd/yyyy)

SCREENING ELIGIBILITY

4. Short Portable Mental Status Questionnaire (SPMSQ) score: ____

   If the SPMSQ score is >2, the subject is NOT eligible.

5. Baseline blood pressure control (Complete only if 'Hypertension active observation' is selected for Item 1.)

   ○ Average systolic <130 mm Hg AND average diastolic <80 mm Hg AND subject IS currently diagnosed with diabetes OR chronic kidney disease

   Blood pressure is controlled; subject is NOT eligible.

   ○ Average systolic <140 mm Hg AND average diastolic <90 mm Hg AND subject IS NOT currently diagnosed with diabetes OR chronic kidney disease

   Blood pressure is controlled; subject is NOT eligible.

   ○ Average systolic blood pressure >200 mm Hg OR average diastolic blood pressure >115 mm Hg

   Refer to the Manual of Operations for instructions on handling hypertensive urgencies; subject is NOT eligible.

   ○ Uncontrolled

   If one of the following options is selected for Item 5, enter the subject's average research blood pressure in items 5.a and 5.b:

   Option 1 – 'Average systolic <130 mm Hg AND average diastolic <80 mm Hg AND subject IS currently diagnosed with diabetes OR chronic kidney disease'

   Option 2 – 'Average systolic <140 mm Hg AND average diastolic <90 mm Hg AND subject IS NOT currently diagnosed with diabetes OR chronic kidney disease'

   Option 3 – 'Average systolic blood pressure >200 mm Hg OR average diastolic blood pressure >115 mm Hg'

   a. Average Systolic: __ __ __
   b. Average Diastolic: __ __ __

(Continue to 'Item 6' on page 2.)

6. Is the subject ineligible for another reason not listed above?
   - ○ Yes
   - ○ No

      a. If yes, specify: _____

SUBJECT MUST MEET ALL OF THE INCLUSION CRITERIA AND NONE OF THE EXCLUSION CRITERIA TO REMAIN IN THE STUDY

(Do not enter into database)

Inclusion Criteria	Has Inclusion Criterion	
English or Spanish speaking males or females	Yes	No
Over 18 years of age	Yes	No
Has a diagnosis of hypertension	Yes	No
Has uncontrolled BP defined as: ▪ ≥ 140 mm Hg SBP or ≥ 90 mm Hg DBP for patients with uncomplicated hypertension OR ▪ ≥ 130 mm Hg SBP or ≥ 80 mm Hg DBP for patients with diabetes or chronic kidney disease. The Study Coordinator will only invite patients to be screened who have demonstrated uncontrolled BP values on at least two past clinic visits. Qualification *in the* Active Observation group will be based on a seated research BP (average of the second and third reading) as measured in the office by the Study Coordinator. Only one qualifying average BP will be required. Qualification in the Passive Observation group will be a qualifying BP using usual office measurements that was taken during clinic visits approximately 2 years prior to patient identification for this group. The Study Coordinator will determine if a patient has either diabetes or chronic kidney disease based on documentation in the problem list in the patient's medical record.	Yes	No
Exclusion Criteria	**Has Exclusion Criterion**	
Current signs of hypertensive emergency (acute angina, stroke, or renal failure)	Yes	No
Severe HTN (systolic BP >200 or diastolic BP >115 mm Hg)	Yes	No
History of MI, stroke, or unstable angina in the prior 6 months	Yes	No
Systolic dysfunction with a LV ejection fraction < 35% documented by echocardiography, nuclear medicine study, or ventriculography	Yes	No
Renal insufficiency, defined by a glomerular filtration rate less than 20 ml/min or previously documented proteinuria > 1 gram per day	Yes	No
Significant hepatic disease, including prior diagnoses of cirrhosis, Hepatitis B or C infection, or laboratory abnormalities (serum ALT or AST > 2 times control or total bilurubin > 1.5 mg/dl) in the prior 6 months	Yes	No
Pregnancy	Yes	No
Diagnoses of pulmonary hypertension or sleep apnea (unless treated by continuous positive pressure ventilation)	Yes	No
Poor prognosis with a life expectancy estimated less than 2 years	Yes	No
Residence in a nursing home or diagnosis of dementia	Yes	No
Inability to give informed consent (*Active Observation Group only*)	Yes	No
Impaired cognitive function (> 2 errors on the Short Portable Mental Status Questionnaire (*Active Observation Group only*)	Yes	No

Complete Part A and Part B of the paper form at <u>EVERY study visit</u> (per protocol) after the baseline visit. These items (part A and B) <u>will not</u> be entered into the database. Retain a copy (of the completed paper form) in the subject's study file for monitoring.

A. Visit Date: __ __/__ __/__ __ __ __ (mm/dd/yyyy)

Screening Questions (to be read to the subject)

1. **"Have you had any changes in your health since your last study visit?"**
   ○ Yes ○ No

2. **"Have you been hospitalized or received care in the emergency department since your last study visit?"**
   ○ Yes ○ No

B. Serious adverse event not reported by the subject

1. Serious adverse event (SAE) found documented in medical record (Study Coordinator to review medical record for time period since last study visit):
   ○ Yes ○ No

2. SAE occurred at the time of the study visit:
   ○ Yes ○ No

If your answer to one or more items in Sections A and B is Yes, skip to Section C, item 9 to verify that the event is an SAE. If the outcome of the identified event matches one or more of items C.9.a. – C.9.g., the event represents a SERIOUS adverse event (SAE). ***Complete all items in Section C*** *on the hard copy form,* ***ENTER THE FORM ELECTRONICALLY****, and file the hard copy form in the subject's folder.*

Also complete Section C and enter the form electronically ***ANY*** *time an event is identified that matches one or more of the outcomes listed in C.9.a. – C.9.g (e.g., another clinic staff member or the study pharmacist becomes aware of a serious adverse event outside of a scheduled study visit).*

If the outcome of the identified event is C.9.h. (None of the above), select C.9.h and ***STOP HERE.*** *FILE the hard copy form in the subject's folder. The event represents a non-serious adverse event. Do NOT complete items C.1 – C.8 on the hard copy form. Do NOT submit the form electronically.*

Serious Adverse Event (SAE)

1. Date of SAE: __ __/__ __/__ __ __ __ (mm/dd/yyyy)

2. Date site became aware of SAE: __ __/__ __/__ __ __ __ (mm/dd/yyyy)

3. SAE descriptor: _____

4. Was the SAE an exacerbation of a pre-existing condition (i.e. existing prior to enrollment)?

   ○ Yes ○ No

5. Was the SAE related or might it have been related to a medication on CAPTION study list of drug codes?

   ○ Yes ○ No

a. Medication	b. Stopped because of Adverse Event?
_____ Code: __ __ __ __	○ Yes ○ No
_____ Code: __ __ __ __	○ Yes ○ No
_____ Code: __ __ __ __	○ Yes ○ No
_____ Code: __ __ __ __	○ Yes ○ No

6. Describe any details about the SAE that might help us determine whether it is drug-related.

_____

_____

_____

_____

_____

_____

7. Describe relevant scans/tests/laboratory data, including dates.

_____

_____

_____

_____

_____

_____

_____

_____

8. Describe other relevant history, including pre-existing medical conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction).

_____

_____

_____

_____

_____

_____

_____

9. Outcomes that are attributed to the SAE in the medical record or reported by the subject at the study visit (check all that apply) :

☐ a. Death

a.1 Date: __ __/__ __/__ __ __ __ (mm/dd/yyyy)

☐ b. Life-threatening

☐ c. Hospitalization – initial or prolonged

☐ d. Disability

☐ e. Congenital anomaly

☐ f. Required intervention to prevent permanent impairment/damage

Option 9.f should be used for an event that does not result in death, a life-threatening condition, hospitalization, disability or congenital deformity but that did jeopardize the subject and required a specific medical intervention to prevent one or more of outcomes C.9.a – C.9.e from occurring.

☐ g. Important medical event as determined by the site PI or designee

Option 9.g should only be chosen when a site judges the event to represent significant hazard or harm to a research subject.

☐ h. None of the above

*If there is **any** question about whether an event should be classified as an SAE, please **contact the CCC by phone or email for a recommendation on this decision**.*

1. Did the subject complete all study visits with the Study Coordinator?
   - ○ Yes
     a. Date of final visit: __ __ / __ __ / __ __ __ __ (mm/dd/yyyy)
   - ○ No
     b. Date of early termination: __ __ / __ __ / __ __ __ __ (mm/dd/yyyy)
     c. Date of last study visit with Study Coordinator or Pharmacist: __ __ / __ __ / __ __ __ __ (mm/dd/yyyy)

2. If the subject terminated the study early, please indicate the reason.
   - ○ Subject eligibility status changed
     a. Reason: _____
   - ○ Subject chose to withdraw
     b. Reason: _____
   - ○ Subject lost to follow-up (Unable/unwilling to travel/moved from area/unable to locate)
   - ○ Research team chose to discontinue subject
     c. Reason: _____
   - ○ Subject withdrew/terminated due to Adverse Event
     d. Specify: _____
   - ○ Subject death (enter death date for question 1.b)
   - ○ Other
     e. Specify: _____

3. Comments:

_____

_____

_____

_____

_____

_____

_____

_____

_____

1. Visit Date: _ _/_ _/_ _ _ _ (mm/dd/yyyy)

   INSTRUCTIONS (to be read to the subject):

   "The first questions ask for some basic information about you."

   (Research nurse is to check the box corresponding to the subject's answers.)

2. Birth Date: _ _/_ _/_ _ _ _ (mm/dd/yyyy)

3. Gender
   - ○ Male
   - ○ Female

4. Race (check all that apply)
   - ☐ a. American Indian or Alaska Native
   - ☐ b. Asian
   - ☐ c. Native Hawaiian or other Pacific Islander
   - ☐ d. Black or African-American
   - ☐ e. White
   - ☐ f. Declined to answer

5. Ethnicity
   - ○ Hispanic or Latino
   - ○ Non-Hispanic or Non-Latino Origin
   - ○ Declined to answer

6. Education (Select the highest grade completed or degree/certificate received.)
   - ○ 1 – 5 years
   - ○ 6 – 8 years
   - ○ 9 – 12 years
   - ○ Post-high school technical /associate degree or certificate
   - ○ 4-year BA or BS degree
   - ○ Master's degree
   - ○ Doctoral degree

7. Insurance Status (Select only the primary insurer.)
   - ○ Private insurance
   - ○ Medicare
   - ○ Medicaid
   - ○ Other insurer
   - ○ None/Self-pay
   - ○ Free care

8. Insurance Coverage for Prescriptions
   - ○ Yes
   - ○ No

9. Annual Household Income
   - ○ <$10,000
   - ○ $10, 000-$24, 999
   - ○ $25,000- $39,999
   - ○ $40,000-$54,999
   - ○ $55,000-$79,999
   - ○ $80,000-$99,999
   - ○ >$100,000
   - ○ Refused to answer

10. Marital Status
   - ○ Never married
   - ○ Married
   - ○ Living as married
   - ○ Divorced or separated
   - ○ Widowed

11. Smoking Status
   - ○ Currently smokes (If 'Currently smokes' is selected, skip question 11.c)
   - ○ Former smoker
   - ○ Never smoked (If 'Never smoked' is selected, skip questions 11.a – 11.c)

   a. Number of years smoked: __ __
   b. Number of cigarettes smoked per day: __ __
   c. Elapsed time since quitting
      - ○ < 5 years
      - ○ 5-14 years
      - ○ ≥ 15 years

12. Current Alcohol Intake
   - ○ None
   - ○ < 1 drink per day
   - ○ 1-2 drinks per day
   - ○ 3-4 drinks per day
   - ○ > 4 drinks per day

13. Duration of High Blood Pressure
   - ○ New diagnosis
   - ○ < 6 months
   - ○ 6 months - 1 year
   - ○ >1 - 3 years
   - ○ >3 - 5 years
   - ○ >5 - 10 years
   - ○ >10 years

Visit: ○ Baseline
○ 9 months
○ 24 months

A. Visit Date: _ _/_ _/_ _ _ _ (mm/dd/yyyy)

B. Medication Adherence

1. Check medical record prior to visit: Patient has at least one active prescription for a blood pressure medication. (If not, do NOT ask remaining questions.) ○ Yes ○ No

2. Some people have difficulty in taking blood pressure medication as prescribed. Do you have difficulty with this? ○ Yes ○ No

3. How many days in the past week did you forget to take your blood pressure medication?
_____ days

4. How many days in the past week did you <u>not</u> take your medication on purpose?
_____ days

5. How many days in the past week did you add an extra pill?
_____ days

6. In the last 6 months, did you ever take less medicine because you felt you needed less? ○ Yes ○ No

7. In the last 6 months, if you felt worse when you took the medicine, did you ever stop taking it? ○ Yes ○ No

Visit: ○ Baseline
○ 9 months
○ 24 months

1. Visit Date: _ _/_ _/_ _ _ _ (mm/dd/yyyy)

2. Diagnosed conditions (check all that apply)

For the baseline study visit, select all conditions with which the subject has been diagnosed at the time of enrollment. For each subsequent study visit, select only conditions with which the patient has been newly diagnosed since the last study visit.

☐ a. Diabetes
☐ b. Chronic Kidney Disease
☐ c. Coronary Artery Disease
☐ d. Congestive Heart Failure
☐ e. Hyperlipidemia
☐ f. Stroke or TIA
☐ g. Peripheral Artery Disease
☐ h. Asthma or COPD
☐ i. Depression or anxiety
☐ j. Arthritis/DJD/Chronic Pain
☐ k. Seizures/Other Neurological Disorder
☐ l. Liver Disease

3. Serum creatinine tests

Enter only serum creatinine tests performed since the last study visit. For the baseline study visit, enter the subject's two most recent tests occurring prior to or at enrollment.

a. First most recent serum creatinine test
    1. Value: __ __
    2. Date drawn: __ __/__ __/__ __ __ __ (mm/dd/yyyy)

b. Second most recent serum creatinine test
    1. Value: __ __
    2. Date drawn: __ __/__ __/__ __ __ __ (mm/dd/yyyy)

Visit: ○ Baseline ○ 6 months ○ 9 months
○ 12 months ○ 18 months ○ 24 months

1. Visit Date: _ _/_ _/_ _ _ _ (mm/dd/yyyy)

2. Height: __ __ __ . __ a. O centimeters O inches (Complete at baseline study visit only.)

3. Weight: __ __ __ . __ a. O kilograms O pounds

4. Does the patient smoke?
   ○ Yes ○ No

   a. If yes, patient's last cigarette was smoked:
      ○ > 20 minutes ago
      ○ ≤ 20 minutes ago

      a.1 If ≤ 20 minutes ago, did the patient wait > 20 minutes since his/her last cigarette before the research blood pressure was measured?
      ○ Yes ○ No

5. Time of day of BP recording: __ __ __ __ (use military time, e.g. 1645)

6. Arm used for BP measurement (right is preferred):
   ○ Right ○ Left

7. Midpoint circumference of arm being used (cm): __ __ (Complete at baseline study visit only.)

8. Size of cuff used:
   ○ Small (17-22 cm) ○ Large (32-42 cm)
   ○ Medium (22-32 cm) ○ Extra Large (42-50 cm)

9. Seated pulse (beats per minute): __ __ __

	a. Systolic BP (mm Hg)	b. Diastolic BP (mm Hg)
10. First sitting BP measurement	___ ___ ___	___ ___ ___
11. Second sitting BP measurement	___ ___ ___	___ ___ ___
12. Third sitting BP measurement	___ ___ ___	___ ___ ___
13. Fourth sitting BP measurement (take ONLY if 2nd & 3rd BPs for systolic or diastolic differ by > 4 mm Hg)	__ ___ ___	___ ___ ___

14. Average Systolic Pressure (add the 2 closest measurements from 11a, 12a and 13a and divide by 2): ___ ___ ___

15. Average Diastolic Pressure (add the 2 closest measurements from 11a, 12a and 13a and divide by 2): ___ ___ ___

Rule for average pressures (items 14 and 15): If a 4th measurement is taken, and the 3 values (either systolic or diastolic) are equidistant apart, choose the HIGHER two values. For example, if systolic pressures = 148, 136, and 142, the average would be (142 + 148) ÷ 2 = 145.

Study Visit: ○ Baseline ○ 6 months ○ 9 months
○ 12 months ○ 18 months ○ 24 months

A. <u>Antihypertensive</u> Medications Currently Prescribed at the Time of the Study Visit (to be completed at each study visit)

<u>INSTRUCTIONS (to be read to the subject)</u>: "I have a list of the blood pressure medications that we think you are taking. Please tell me how much of each medication you are taking or if you are not taking the medication."

1. Date of Study Visit: _ _/_ _/_ _ _ _ (mm/dd/yyyy)

2. Medications:

a. Medication	b. Unit Strength	c. Dose	d. Frequency	e. PRN	f. Patient Report on Adherence
________________ Code: __ __ __ __				☐	O Patient taking as prescribed O Patient taking but at a different dose or frequency O Patient not taking now
________________ Code: __ __ __ __				☐	O Patient taking as prescribed O Patient taking but at a different dose or frequency O Patient not taking now
________________ Code: __ __ __ __				☐	O Patient taking as prescribed O Patient taking but at a different dose or frequency O Patient not taking now
________________ Code: __ __ __ __				☐	O Patient taking as prescribed O Patient taking but at a different dose or frequency O Patient not taking now
________________ Code: __ __ __ __				☐	O Patient taking as prescribed O Patient taking but at a different dose or frequency O Patient not taking now

B. Contacts and Antihypertensive Medication Changes Documented in the Medical Record since the Last Study Visit with the Study Coordinator

Do not complete this section at the Baseline Study Visit. At all subsequent study visits, please record each contact that occurred since the last scheduled study visit with the study coordinator (including contacts unrelated to hypertension). Items B.1 –B.5 are always completed for every contact. ***Table B.6 is only completed if there is a change*** *to an antihypertensive medication at the contact (as compared to Item A.2 (table) at the last study visit). If there are* ***no changes*** *to the antihypertensive medications at the contact, only complete Items B.1 - B.5.*

1. Date of Contact: _ _/_ _/_ _ _ _ (mm/dd/yyyy)

2. Contact Type
   - ○ Hypertension visit
   - ○ Other visit
   - ○ Phone call

3. Contact with (check all that apply)
   - ☐ a. Nurse/CMA
   - ☐ b. Physician
   - ☐ c. Pharmacist

4. Recommended lifestyle change options (check all that apply):

☐ a. ↓ weight ☐ b. DASH plan ☐ c. ↓ sodium ☐ d. Other diet recommendation ☐ e. ↑ activity

☐ f. ↓ smoking ☐ g. Other

g.1 Specify: _____

☐ h. No lifestyle changes recommended

5. ↑ BP medication compliance recommended
   - ○ Yes
   - ○ No

6. Medication Changes:

a. Medication	b. Change Type	c. Unit Strength	d. Dose	e. Frequency	f. PRN
_____ Code: __ __ __ __	O Start New Drug O Decrease Dose O Discontinue Drug O Regimen Change (same dose) O Increase Dose				☐
_____ Code: __ __ __ __	O Start New Drug O Decrease Dose O Discontinue Drug O Regimen Change (same dose) O Increase Dose				☐
_____ Code: __ __ __ __	O Start New Drug O Decrease Dose O Discontinue Drug O Regimen Change (same dose) O Increase Dose				☐
_____ Code: __ __ __ __	O Start New Drug O Decrease Dose O Discontinue Drug O Regimen Change (same dose) O Increase Dose				☐

Visit: ○ Baseline
○ 9 months
○ 24 months

A. Visit Date: _ _/_ _/_ _ _ _ (mm/dd/yyyy)

INSTRUCTIONS (to be read to the subject):

The following questions ask about symptoms you might be experiencing. Each question begins, "In the past 4 weeks, how much have you been bothered by _____" and is followed by a symptom. Please select a number from 0 to 4 that reflects **how much the symptom has bothered you,** where 0 indicates that the symptom has not bothered you at all, 1 indicates that it has bothered you a little bit, 2 indicates it has bothered you somewhat, 3 indicates it has bothered you quite a bit and 4 indicates it has bothered you very much.

B. In the past 4 weeks how much have you been bothered by….	Not at All [0]	A Little Bit [1]	Some-what [2]	Quite A Bit [3]	Very Much [4]
1. Feeling fatigued or tired	0	1	2	3	4
2. Feeling confused or disoriented	0	1	2	3	4
3. Feeling irritable or easily annoyed	0	1	2	3	4
4. Feeling fidgety or restless	0	1	2	3	4
5. Feeling anxious or nervous	0	1	2	3	4
6. Forgetfulness or memory problems	0	1	2	3	4
7. Seeing things or hearing things not really there (hallucinations)	0	1	2	3	4
8. Feeling sad or down in the dumps	0	1	2	3	4
9. Problems concentrating	0	1	2	3	4
10. Feeling drowsy or sleepy	0	1	2	3	4
11. Trouble getting to sleep or staying asleep	0	1	2	3	4
12. Feeling dizzy or woozy	0	1	2	3	4

C. In the past 4 weeks how much have you been bothered by….	Not at All [0]	A Little Bit [1]	Some-what [2]	Quite A Bit [3]	Very Much [4]
1. Tremor or shakiness in your hands	0	1	2	3	4
2. Feeling that your muscles are weak	0	1	2	3	4
3. Decreased coordination or feeling clumsy	0	1	2	3	4
4. Pain, aches, or stiffness in your joints	0	1	2	3	4
5. Muscle aches, pain, or soreness	0	1	2	3	4
6. Back Pain	0	1	2	3	4
7. Falls	0	1	2	3	4

D. In the past 4 weeks how much have you been bothered by….	Not at All [0]	A Little Bit [1]	Some-what [2]	Quite A Bit [3]	Very Much [4]
1. Difficulty breathing when resting	0	1	2	3	4
2. Difficulty breathing with usual activities	0	1	2	3	4
3. A cough	0	1	2	3	4
4. The feeling that your heart is beating strongly or quickly (palpitations)	0	1	2	3	4
5. Feeling dizzy or lightheaded when sitting up or standing up	0	1	2	3	4
6. Chest pain or tightness in your chest	0	1	2	3	4

E. In the past 4 weeks how much have you been bothered by….	Not at All [0]	A Little Bit [1]	Some-what [2]	Quite A Bit [3]	Very Much [4]
1. Dry mouth	0	1	2	3	4
2. Feeling like there is sand in your eyes, irritated eyes or dry eyes	0	1	2	3	4
3. Blurry vision	0	1	2	3	4
4. Ringing in your ears	0	1	2	3	4
5. Changes in how foods taste or an unusual taste sensation (for example a metallic taste)	0	1	2	3	4
6. Difficulty swallowing	0	1	2	3	4
7. A stuffy or congested nose	0	1	2	3	4
8. Headaches	0	1	2	3	4

F. In the past 4 weeks how much have you been bothered by….	Not at All [0]	A Little Bit [1]	Some-what [2]	Quite A Bit [3]	Very Much [4]
1. Constipation or hard stools	0	1	2	3	4
2. Diarrhea or loose stools	0	1	2	3	4
3. An upset stomach or nausea	0	1	2	3	4
4. Heartburn, sour taste in your mouth, or reflux	0	1	2	3	4
5. A decrease in appetite or not feeling like eating	0	1	2	3	4

G. In the past 4 weeks how much have you been bothered by….	Not at All [0]	A Little Bit [1]	Some-what [2]	Quite A Bit [3]	Very Much [4]	
1. Leaking of urine or incontinence	0	1	2	3	4	
2. Difficulty urinating or starting to urinate	0	1	2	3	4	
3. Frequent urination during the day or at night	0	1	2	3	4	
4. Problems with having or enjoying sexual intercourse	0	1	2	3	4	Does Not Apply

H. In the past 4 weeks how much have you been bothered by….	Not at All [0]	A Little Bit [1]	Some-what [2]	Quite A Bit [3]	Very Much [4]
1. Swelling in your feet, legs, or hands	0	1	2	3	4
2. Numbness or loss of feeling in your feet, legs, or hands	0	1	2	3	4
3. Tingling or pins and needles sensation in your feet, legs, or hands	0	1	2	3	4
4. A skin rash	0	1	2	3	4
5. Increased or unusual bruising of your skin	0	1	2	3	4

SUBMIT THIS FORM ELECTRONICALLY WITHIN 24 HOURS OF BECOMING AWARE OF A PROTOCOL DEVIATION

1. Date of Deviation: __ __ / __ __ / __ __ __ __ (mm/dd/yyyy)

2. Date Site became Aware of Deviation: __ __ / __ __ / __ __ __ __ (mm/dd/yyyy)

3. Type of Deviation (check all that apply)

☐ a. Subject did not meet all inclusion criteria
a.1 Describe unmet criterion or criteria: _____

☐ b. Subject met one or more exclusion criteria
b.1 Describe criterion or criteria: _____

☐ c. Subject did not sign informed consent or consent information was not provided to the subject according to IRB-approved procedure

☐ d. A fourth blood pressure measurement was not taken when the second and third measurements differed by greater than 4 mm Hg.

☐ e. Subject missed window for 9 month study visit

☐ f. Subject missed window for final visit (18 month Asthma or 24 month BP)

☐ g. Serious adverse event was not reported within 24 hours
g.1 Event Date: __ __ / __ __ / __ __ __ __ (mm/dd/yyyy)
g.2 Describe Event: _____
_____
_____
_____

☐ h. Other
h.1 Specify: _____
_____
_____
_____

Corrective Action Plan (For site use only; do not enter into database.):
_____
_____
_____
_____
_____
_____
_____
_____

1. Date of re-screening: __ __/__ __/__ __ __ __ (mm/dd/yyyy)

2. Blood pressure control

   ○ Average systolic <130 mm Hg AND average diastolic <80 mm Hg AND subject IS currently diagnosed with diabetes OR chronic kidney disease

   Blood pressure is controlled; subject is NOT eligible.

   ○ Average systolic <140 mm Hg AND average diastolic <90 mm Hg AND subject IS NOT currently diagnosed with diabetes OR chronic kidney disease

   Blood pressure is controlled; subject is NOT eligible.

   ○ Any systolic blood pressure >200 mm Hg OR any diastolic blood pressure >115 mm Hg

   Refer to the Manual of Operations for instructions on handling hypertensive urgencies; subject is NOT eligible.

   ○ Uncontrolled

   If one of the following options is selected for Item 2, enter the subject's average research blood pressure in items 2.a and 2.b:

   Option 1 – 'Average systolic <130 mm Hg AND average diastolic <80 mm Hg AND subject IS currently diagnosed with diabetes OR chronic kidney disease'

   Option 2 – 'Average systolic <140 mm Hg AND average diastolic <90 mm Hg AND subject IS NOT currently diagnosed with diabetes OR chronic kidney disease'

   Option 3 – 'Any systolic blood pressure >200 mm Hg OR any diastolic blood pressure >115 mm Hg'

   a. Average Systolic: __ __ __
   b. Average Diastolic: __ __ __

If Item 2 = 'Uncontrolled', complete items 3 and 4 below. If subject's blood pressure continues to be controlled, stop here; do not complete any of the remaining items.

3. Most recent Short Portable Mental Status Questionnaire (SPMSQ) score: ____

   If the SPMSQ score is >2, the subject is NOT eligible.

4. Is the subject ineligible for another reason not listed above? (***Review inclusion and exclusion criteria listed in the CAPTION MOP***)

   ○ No
   ○ Yes

   a. If yes, specify: _____

APPENDIX IX: SERIOUS ADVERSE EVENT DESCRIPTORS

Following is a list of Serious Adverse Event descriptors that will be used to populate a drop-down box for Item C.3. on CRF # 2 Serious Adverse Event.

If you wish to report a specific symptom that is not on the list below, please check with the CCC before using the 'Other' descriptor.

Descriptor Name	Instructions for Use
Fever	Do not report if fever is related to a cold or viral infection.
Rash/itching	Covers rash, itching, hives, flushing or similar change in skin. Do not report if symptoms are related to contact with an allergen such as poison ivy or oak.
Angioedema	Covers swelling of the lips, face or tongue.
Rhythm disorder	Covers any new rhythm disorder such as tachycardia or a racing heartbeat that is not typical for the subject.
Chest pain	Covers any new development or worsening of chest pain that does not reflect stable angina.
Headache	Do not report if subject has a history of frequent headaches.
Other pain	Other pain that is not related to an injury or chronic condition.
Shortness of breath	Covers shortness of breath, wheezes, stridor, and gasping for breath that is not typical for the subject.
Cough	Use only for a new cough that is not related to a cold, other infection or seasonal allergy and that follows initiation of a new medication.
Weight gain	Use for new and unintended weight gain with sudden onset, e.g., related to CHF.
Lower extremity edema	Swollen legs or lower extremity edema that is new in onset or substantially worse than usual for the subject.
Kidney problem	Covers a new or worsening kidney problem such as acute renal failure or a 20% increase in creatinine level; do not report a kidney infection.
Liver problem	Covers a new or worsening liver problem such as an increase in one or more liver function tests to > 2 times normal.
Nausea or vomiting	Do not report instances related to influenza, other infection or food poisoning.
Other GI problem	Use only for a new GI problem such as diarrhea, constipation, cramping or abdominal pain that is not related to influenza, other infection or food poisoning; do not use to report nausea or vomiting
Neurological change	Use only for a new or worsening neurological change, e.g. tingling in hands or feet
Trouble walking or falls	Trouble walking or falls
Lightheadedness or passing out	Lightheadedness, dizziness, passing out, or loss of consciousness
Orthostatic hypotension	Orthostatic hypotension (that is not chronic)
Urinary problem	Urinary problem such as urgency or frequency that is not related to infection

Descriptor Name	Instructions for Use
Blood disorder	Bleeding that is not related to a blood dyscrasia such as leucopenia or thrombocytopenia
Change in lab values	Change in lab values related to a drug side effect such as a marked drop in potassium or sodium or a marked increase in serum creatinine.
Mood change	A marked change in mood, such as new or recurrent depression, anxiety or agitation; not intended to cover chronic conditions
Problem with sexual activity	Development of a new problem with sexual activity
Weakness	Covers new onset or worsening of weakness, fatigue, lethargy or other marked decrease in strength
Hypertensive urgency	As indicated by the average blood pressure found at a study visit or a single BP found during a clinic visit that occurred since the last study visit
Other	CHECK WITH CCC BEFORE USING THE ‘Other’ DESCRIPTOR

APPENDIX X: PROCEDURES FOR GENERATING PATIENT LISTS

1) Ask your IT staff to run a list of all patients who have been seen in the clinic within the last 24 months and who have an ICD9 code of 401 (indicating a diagnosis of hypertension).

2) IT should eliminate duplicates from the list if at all possible. Ideally, you would receive the list in Excel so that you could sort to double-check for duplicates.

3) If possible, have your IT staff number each unique patient on each list sequentially starting with "1." Otherwise, manually write in sequential numbers until every unique patient has been assigned a number. You may simply write in the numbers adjacent to the names.

4) Once you have the list numbered, discuss with the CCC whether or not de-identifying the first 2-3 pages would leave remaining any indication of visits. If we determine that it would, make a copy of the first 3 pages of the list. Write in your clinic name at the top of this list. Take a black magic marker and cross out the patient names on these copied pages. Then fax those 3 pages to 319-335-9511.

5) If de-identifying the list leaves only the numbering visible, the CCC will review via telephone the critical indicators of an accurate list.

6) Please make sure that the clinic name is at the top of the first page and that your numbering shows.

7) Also let the CCC know via email the total number of patients on the complete list that you received from IT.

8) We will review the list and let you know if the number of patients on the list seems reasonable and if your numbering appears accurate.

9) If your de-identified list of patients only shows the list of numbers, the CCC will review with you the checks we want you to perform on the list.

10) We will then reach consensus on the total number of patients that we should randomize for the study.

11) The CCC will send the total number of unique patients to the DMC and they will randomize patients.

12) The CCC will return to you a log that has your patients randomized. You should use the log for tracking patients who are screened for the study.