Project Title:

Randomized Trial of Titrated Disease Management for Patients with Hypertension

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A. RESEARCH OBJECTIVES

Patients' with chronic disease benefit from having the doses and types of medication titrated based upon clinical parameters, for example, higher and lower blood pressure (BP). Similarly, patients may also require differing intensity of disease management based upon clinical outcomes. We propose to conduct a pragmatic clinical trial to evaluate the effectiveness of titrated disease management for patients with hypertension. A pragmatic trial is designed for "real world" practice and usually can be directly implemented. In this particular study intervention patients will have the intensity of their care titrated based upon their BP control.[1-3] By reserving the most intensive and expensive strategies to veterans with greatest need, this titrated strategy would lead to more efficient use of resources, which could result in an overall cost savings to the VA. Moreover, this approach, as opposed to a single disease management program that is delivered the same way to all veterans, is likely to be well-accepted and understood by clinicians. Our study of how to best and most efficiently allocate disease management resources will provide critical evidence about increasing access to enhanced primary care required under the VA patient-aligned care team (PACT) model. As such it is responsive to **two specific HSR&D funding priority areas – access and health informatics.**[4] Further, the trial addresses **multiple priority areas for comparative effectiveness identified by the Institute of Medicine,**[5] including comparing the effectiveness of strategies for enhancing patients' adherence to medication regimens, different disease management strategies for activating patients with chronic disease, and different delivery models (e.g., home blood pressure monitors, utilization of pharmacists to managed medicine) for controlling hypertension. Finally, the intervention we are testing not only can be directly implemented by VHA (if effective), but clinical leaders have indicated their willingness to do so (see attached letters).

We propose to conduct a **two-arm 18-month randomized clinical trial** for veteran patients with pharmaceutically treated hypertension with uncontrolled systolic blood pressure (SBP) defined as ≥ 140 mmHg for non-diabetic or ≥ 130 mmHg for diabetic patients. The intervention arm includes three levels of resource intensity targeted to improve patients' SBP.

- Medium/level 1 resource intensity: a **registered nurse (RN)** will provide monthly tailored behavioral support telephone calls + home BP monitoring.
- High/level 2 resource intensity: a **pharmacist** will provide monthly tailored behavioral support telephone calls + home BP monitoring + pharmacist-directed medication management.
- Booster (low) resource intensity: a **licensed practical nurse (LPN)** will provide non-tailored behavioral support telephone calls every two months to patients whose SBP comes under control

Control Arm: An LPN will provide behavioral support telephone calls that do not include goal setting and directed problem solving every two months (identical to booster (low) resource intensity component of the titrated intervention). This **control arm differs from usual care** in that it involves additional regular patient contact that has enhanced BP control in a clinical trial conducted by Durham investigators among veterans[6] and medication adherence in a quality improvement initiative in the North Carolina Medicaid program.[7] The control arm will utilize the same procedures as the booster level for intervention patients for whom SBP comes under control.

A.1. Specific Aims

A.1.a. Primary Research Question and Hypothesis – Change in SBP

Will the titrated disease management protocol result in reduced SBP over 18-months, compared to LPN-delivered behavioral support phone calls occurring every two months [control arm]?
Primary Hypothesis: (H1) Veterans randomized to the titrated disease management intervention arm will have greater improvement in mean SBP over the 18 months of follow-up than veterans in the control arm.

A.1.b. Secondary Research Question and Hypothesis-Hypertension Control

Will the titrated disease management protocol result in improved SBP control (i.e. dichotomized threshold as opposed to continuous measure [SBP ≥ 140 mmHG for non-diabetic patients, SBP ≥ 130 mmHG for diabetic

patients][8]) at 18-months, compared to LPN-delivered behavioral support phone calls occurring every two months [control arm]?
Secondary Hypothesis: (H2) Veterans randomized to the titrated disease management intervention arm will have a greater increase in the proportion of patients who have hypertension come into control over the 18 months of follow-up than veterans randomized to the control arm.

A.1.c. Secondary Research Question and Hypothesis-Cost Effectiveness.

If the intervention results in greater reduction in SBP than the control group, is it cost effective?
Secondary Hypothesis: (H3) The titrated disease management protocol will be cost effective.

A.1.d. Secondary Research Question and Hypothesis-Medication Adherence.

Will a titrated disease management result in better medication adherence compared to the control arm?
Secondary Hypothesis: (H4) The improvement in medication adherence in the titrated disease management protocol will be greater than for those in the control arm.

A.2. Gaps in the Existing Evidence and Difference from Previous and Ongoing Work

Previous disease management trials, including those conducted at the Durham VAMC, have evaluated the effect of disease management strategies. Many of these studies demonstrate the efficacy of providing behavioral self-management support, especially in combination with other components such as home BP monitoring and pharmaceutical management, in reducing blood pressure.[6, 9-11] As with most trials, a common protocol was followed regardless of level of BP control. This common approach is inconsistent with clinical practice, where clinicians tailor the intensity of interventions to individual patients. Thus, we propose to conduct a pragmatic trial to rigorously evaluate a strategy in which the intensity of the disease management program is titrated based on clinically sensible criteria. In so doing, we are evaluating an innovative approach to disease management that mirrors the way providers practice, i.e., matching resource intensity to patients' clinically-dictated needs. If successful, this approach allows healthcare systems such as the VA to allocate limited resources to match patients' needs.

B. BACKGROUND, CONTEXT, AND PRELIMINARY STUDIES

B.1. Significance of Hypertension

Hypertension is the most widely recognized modifiable risk factor for stroke, myocardial infarction, peripheral vascular disease, heart failure, and end-stage renal disease.[8] In the Department of Veterans Affairs healthcare system, hypertension is the most prevalent chronic condition, affecting 37% of veterans.[12] An enormous body of evidence suggests that controlling hypertension improves cardiovascular and renal outcomes, and the mechanisms for achieving control (e.g., diet, exercise, medication) are well known and widely accepted. Unfortunately, despite its prevalence, impact, evidence-based guidelines, and > 100 anti-hypertensive medications, only a third of all U.S. hypertensive patients have their BP under control.[8] Notably, diabetes and hypertension commonly co-occur in patients, including veterans.[13] Data demonstrate that very tight BP control (130/80 mmHg) is critical to reducing cardiovascular disease (CVD) morbidity and mortality in hypertensive patients with diabetes,[14, 15] leading to several evidence-based guidelines recommending 130/80 mmHg as the target for patients with hypertension and diabetes.[8, 16]

B.2. Defining Titrated Disease Management

The majority of disease or self-management support trials have examined interventions in which patients enrolled into the trial receive the same level of services throughout the study. Although this is very appropriate for most efficacy trials, clinicians in practice tailor the intensity of treatment to an individual's health status. This is often in the form of stepped care, where patient's initial medication dose is low, and thereby minimizing risks of treatment (such as side effects). If patients are not responsive to initial treatments, their medication

regimen is intensified until clinical goals are met. Absent some change in the underlying pathophysiology of disease (e.g., weight loss) or side effects, patients do not have their treatment reduced once clinical goals are reached; it is assumed that any reduction in intensity would diminish level of control.[17-19] Stepped care of medications has been used for hypertension since at least the early 1980's.[20]

In mental health, stepped care has frequently been used as a synonym for collaborative care.[21-24] These models often involve increasing levels of psychotherapy, self-management support, and/or pharmaceutical therapy to treat conditions such as depression. Such stepped collaborative care interventions are consistent with the Chronic Care Model.[25] A meta-analysis of 37 randomized trials found significant improvement in depressive symptoms both short-term (6 months) and long-term (up to 5 years).[26] Similar interventions have also been shown to be effective for other conditions, including hypertension.[27, 28]

We are proposing a trial to examine **titrated, not stepped, disease management.** The primary difference is that in titrated disease management we are adjusting (titrating) **resource intensity** based upon the clinical status of individual patients. Resources are intensified until the level of treatment intensity required to achieve control is reached, but resource intensity can be reduced depending on a patient's clinical status. This difference in resource intensity involves: 1) who delivers the disease management; 2) the complexity of the treatment intensification (i.e., whether there is medication intensification); and 3) frequency of patient contacts. The assumption of this novel approach is that patients will be **titrated to different initial resource levels** and will be **evaluated during the intervention** to determine if they will: 1) remain at the same level of resource intensity; 2) be increased to a higher intensity level; **or** 3) be decreased to a lower resource intensity level. This addresses a criticism about stepped care: no plan to reduce level of drug or other resource use for patients with improving illness severity.[29] As suggested by a 2010 systematic review of clinical trials by the Cochran Collaborative,[30] a titrated strategy seeks to match system resources that can be combined with, and potentially enhance, stepped medication management.

B.3. Review of Prior CVD Risk Reduction Interventions

In a systematic review of 15 behavioral interventions for hypertension, results favored counseling over usual care with improvements in SBP (11 mmHg) and DBP (3.5 mmHg).[31] In another systematic review of 38 randomized controlled trials, patient education alone was largely unsuccessful at improving BP control.[32]

B.4. Benefits of Using the Telephone to Administer Interventions

Telephone interventions have been shown to be effective in changing multiple patient behaviors.[33-35] These increase reach to patients and may be viewed by patients as more acceptable and convenient than in-person interventions. Because virtually all (97%) US homes have phones,[36] telephone-based strategies can efficiently increase access to care. Thus, telephone-based strategies can facilitate individualized, personal interaction at minimal cost and without the time and transportation barriers that accompany in-person programs. This personal interaction allows the intervention to be adapted and tailored to participants' current concerns, health goals, and specific barriers to achieving these goals.

B.5. Benefits of Home BP Monitoring

Encouraging patients to home monitor their BP provides objective information to motivate patients to control their disease. Home monitoring also provides documentation of the effects of medications and allows for faster therapy adjustment which may improve patient adherence to prescribed treatments and subsequent disease control.[37, 38] Furthermore, as many as 1 in 8 patients will have normal BP readings in clinic, but have consistently elevated readings at home, a phenomenon known as masked hypertension.[39] Patient's home BP is a better predictor of clinical events than office measurement.[40] Finally, home monitoring may reduce the need for frequent office visits.[38] We will use the same training and assessment procedures used in previous studies such as TCYB and HINTS for the proposed study (Table 1).

B.6. Pharmacist Management of CVD Risk Factors

Four randomized trials have studied the effect of pharmacist BP management, one in community-based

pharmacies[41] and three in clinic-based settings.[42-44] In all these studies, a higher portion of patients achieved BP control in the intervention group compared to the control group. However, all of these protocols required extra visits to the treating facility by patients and were relatively expensive to perform, because they used substantial pharmacist time for relatively small numbers of patients.

B.7. Underlying Research – Previous Trials of CVD Disease Management Conducted by Study Team

For more than a decade, the Durham HSR&D COE has conducted a series of clinical trials aimed at reducing CVD risk through combinations of behavioral, self-monitoring, and pharmaceutical management. Table 1 summarizes 5 examples of such studies; detailed descriptions follow. All investigators on this grant, with the exception of Dr. Ho, have been involved in at least one of the summarized studies, demonstrating the experience of the study team. These studies have led us to the conclusion that a critical gap in the literature is how to titrate efficacious interventions to individual patients in real world clinical practices.

Table 1: Recent Randomized Trials of CVD Disease Management

Study Name (sample size)	**Veterans Study to Improve Control of Hypertension – V-STITCH[6, 45] (n = 588)**	**Take Control of Your Blood Pressure Study – TCYB[9, 46-48] (n=593)**	**Hypertension Intervention Nurse Telemedicine Study – HINTS[49] (n=593)**	**Diabetes Group Visits Trial (n = 239)[11, 50]**	**Tailored Case Management for Diabetes and Hypertension – TEACH-DM (n = 400)**
Current Status	Completed	Completed	Completed	Completed	Recruitment Ongoing
Study Sample	• Hypertensive veterans • Enrolled from primary care	• Hypertensive community patients • Enrolled from university and community clinic	• Hypertensive veterans with inadequate BP control • Enrolled from primary care	• Hypertensive and diabetic veterans with inadequate BP and glycemic control • Enrolled from primary care at two VAMCs	• Diabetic patient with poor glycemic control • Enrolled from community primary care practices
Intervention Components	• 9 tailored behavior, education modules • Provider decision support (VA-developed ATHENA)	• 11 tailored behavioral, education modules • Home BP tele-monitoring	• 11 tailored behavioral, education modules • Medication management via decision support system • Home BP tele-monitoring	• Group medical appointment: 7-8 patients • Nurse-led education • Pharmacist and physician team medication management	• Tailored nurse-delivered telephone behavioral educational modules
Intervention Frequency	Every 2 months for 24 months	Every 2 months for 24 months	Every 2 months when BP is out of control for 18 months	Every 2 months (7 visits over 12 months)	Every 2 months for 24 months
Results/Outcome	Behavior interv – BP control improved by 21% (13% relative usual care); cost = $112/patient/year	Combined interv – BP control improved by 13% (17% relative to usual care). SBP improved 4 mmHg over usual care over 24 months; cost = $416/patient/year	SBP declined 3.6 mmHg in the combined arm over usual care at 18 months	SBP declined 7.2 mmHg over usual care over 12 months. Cost was approx. $460 per patient per year.	Change in glycemic and BP control

B.7.a. Veteran – Study To Improve The Control of Hypertension (V-STITCH) [Bosworth, PI].

V-STITCH was a randomized controlled trial that tested whether a patient intervention, a provider intervention, or combination of both is more effective in improving BP control. In V-STITCH, providers were randomized to receive or not receive a hypertension decision support intervention. A sub-sample of the providers' patients was randomized to receive the patient intervention or not. The V-STITCH sample included patients with hypertension who had filled a prescription for hypertensive medication in the previous year. Patient enrollment was independent of prior BP control. Of 816 eligible patients approached, 588 (76%) were enrolled and randomized. The behavioral intervention involved a nurse contacting patients by telephone every 2 months for 24 months. At each call, the nurse delivered both standard and tailored information to patients in 9 educational and behavioral modules. Of the 294 patients randomized to the nurse intervention, 84% of the sample received all 12 intervention telephone calls. The average length of time to administer the intervention call was 3.7 minutes (SD=2.5 minutes). After 24 months of follow-up, BP control increased from 44% to 65% in the nurse intervention group compared to the control group from 44% to 53% (p=.03; an absolute difference of 12.6%). The mean annual cost of implementing the intervention was estimated to be $112 per patient (range $61-$259).[51] The intervention did not lead to significant increases in overall observed inpatient or outpatient costs. There was no difference in the number of primary care visits over the 2 years.[6, 52]

B.7.b. Take Control of Your Blood Pressure Study (TCYB) [Bosworth, PI].

TCYB was a randomized clinical control trial of hypertensive patients in two Duke University-affiliated clinics. The focus was behavior modification through self-management based on home BP monitoring.[9, 46, 47] Patients were randomized to one of four groups: usual care; a nurse-administered behavioral intervention alone; home BP monitors alone; or, both the behavioral intervention and home BP monitors. We enrolled 636 hypertensive adults in 12 months, 91% of whom were retained for the 24-month study. Patients given a brief explanation of how to use the home BP monitor were able to use the devices effectively and accurately when assessed at a follow-up visit. On average, 11 of the 12 planned interventions were completed for the 318 in the nurse arm. Patients randomized to the combined behavioral/home BP monitor group showed the greatest BP control improvement (70.4% at baseline to 83.2% at 24 months). The largest sustained improvement in SBP was observed in the combined intervention group (SBP improved from 126 mmHg at baseline to 120 mmHg at 24 months).[9] The average phone call was 15 minutes per encounter (180 minutes over 24 months) and the cost of the combined intervention was $416 over 24 months.[48] TCYB demonstrated that patients could successfully measure their home BP over 24 months. Further, it provides evidence for using a combination of behavioral phone calls and home BP monitoring for patients with hypertension.

B.7.c. Hypertension Intervention Nurse Telemedicine Study (HINTS) [Bosworth PI].

Recently completed, the VA-funded HINTS study enrolled 593 hypertensive patients from 3 VA primary care clinics.[49] Participants were randomly allocated to one of four arms (usual care, tailored nurse- administered behavioral adherence intervention, medication management, and a combined behavioral adherence and medication management intervention). For each patient, the nurse-administered intervention was activated only when home BP monitoring indicated inadequate BP control (patients without diabetes $\geq$135/85; patients with diabetes $\geq$135/80 based on VA guidelines). Patients assigned to the behavioral intervention received a nurse-administered tailored self-management intervention to promote adherence with medication. Patients randomized to the medication management arm had their hypertension regimen changed by a nurse and study physician using a validated hypertension decision support system. Preliminary results indicate a combination of tailored behavioral support, home BP monitoring, and algorithmic medication management led to approximately a 5mmHg reduction in systolic BP as compared to a 1 mmHg reduction for patients in usual care. This study indicates that medication management changes made by a research team are acceptable to patients' primary care providers (PCP) as < 5% of medication changes were overridden by PCPs.

B.7.d. Diabetes Group Visits Trial [Edelman, PI].

The HSR&D funded Diabetes Group Visits Trial tested the effect of providing group medical appointments

on the hypertension and blood pressure control of patients with diabetes and hypertension. We enrolled 239 patients with poorly controlled diabetes and blood pressure (BP) who received primary care at the Durham or Richmond VAMCs. Patients were randomized within VAMC to receive either group medical clinics or usual care. Each group was composed of 7-8 patients, and a care team consisting of a primary care general internist, a pharmacist, and a nurse or other certified diabetes educator. The same patients met in groups every 2 months for seven visits with the same care team. However, separate groups had different care teams. Each session included group education and structured group interactions moderated by a registered nurse or other certified diabetes educator. Additionally, individual medication adjustments were made by the pharmacist and physician to manage HbA1c and BP. HbA1c and systolic BP were measured at baseline, intervention midpoint (median 6.8 months) and intervention completion (median follow-up 12.8 months) at separate scientific visits.[11, 50] Subjects attended 78% of all scheduled group visit sessions. After adjusting for baseline and clustering, the 12-month difference between arms in systolic BP was 7.2 mmHg (p=0.01). After adjustment, the difference between arms in HbA1c at 12 months was 0.3% (p=0.4).[11]

B.7.e. Tailored Case Management for Diabetes and Hypertension (TEACH-DM) [Edelman, PI].

TEACH-DM is an ongoing, 5-year randomized, controlled trial conducted in community-based primary care private practices. The trial is designed and powered to systematically evaluate the effectiveness of a telephone administered, tailored patient health education and behavioral intervention among patients diagnosed with both diabetes and hypertension, and with poor control of their diabetes. Primary outcomes are systolic blood pressure and Hemoglobin A1c. The trial will also measure the effect of the intervention on self-efficacy, weight loss, physical activity, and medication adherence. Finally, the costs of the study will be measured, as will the effect of the intervention on health services utilization.

B.8. Conceptual Model for Behavioral Telephone Calls

The revised Health Decision Model (HDM)[53] is the theoretical framework for identifying factors to target for intervention in the proposed intervention. It is based on the Health Belief Model (HBM)[54] and combines decision analysis, behavioral decision theory, and health beliefs to yield a unified model of health decisions and resultant behavior. The HDM focuses more specifically on health decisions and combines the influences of health beliefs and modifying factors with contributions from the patient preference literature. The revised HDM expands on the previous model by including patient characteristics such as memory and experience of side effects associated with medication.[55, 56]

In addition to using the revised HDM to identify potential factors that may explain poor CVD control, we use the Transtheoretical Model to understand factors that hinder or promote health behaviors.[57] The crux of the model is that behavioral change occurs in a series of temporally ordered discrete stages. Movement between stages is influenced by the ratio of pros and cons of the problem behavior, self-efficacy, temptations to revert to the problem behavior, and coping mechanisms used to change the problem behavior.[57] The proposed intervention will focus heavily on both the initiation (e.g., contemplation and preparation) and the maintenance phase.

An important feature of the proposed targeted intervention is that it incorporates tailored information and feedback. Tailored feedback has been demonstrated to be effective in multiple health behaviors. While a generic healthcare administered intervention may improve adherence, a tailored intervention can address issues that are specifically relevant to a particular patient.[58] These issues include addressing inadequate knowledge and understanding of treatment and counseling on specific behavioral/lifestyle changes. We have shown effectiveness using an early version of this tailored intervention (see section B7, Underlying Research). Thus, drawing on stages of change,[56, 59] and the revised health decision model[56] the intervention addresses how to 1) set healthful goals and gain self-efficacy, 2) implement healthful behaviors and monitor performance, and 3) maintain the behaviors and associated CVD control over time.

To help patients set healthful goals, the intervention will provide training in identification of realistic goals that reflect patient preference and readiness; self-management that teaches self-efficacy, especially skills needed to carry out medical regimens and guide behavior changes; and social and emotional support to promote self-efficacy.[60-63] To help set goals, the intervention will promote antecedent and cue management, self-reward, rehearsal, and cognitive reframing.

To help patients implement healthful behaviors and monitor their process, the health behaviors are

described to make them easy to implement. The intervention is designed to develop action plans that enable progress toward goals. As part of motivational intervention, the case manager will discuss how to remove resistance and barriers to performance. Financial barriers will be addressed by emphasizing low-cost diet and methods of exercising. Patients will be taught to identify the life experiences that impede self-control and will rehearse strategies to use when willpower is low.

To help patients maintain healthful behaviors, adults will be encouraged to establish routines for critical health behaviors. For example, patients having difficulty with medication adherence will be encouraged to take their medications in standardized ways (e.g., place medication in the bathroom so it can be taken immediately after brushing teeth). Patients having difficulty with exercise will be encouraged to insert exercise into existing routines (e.g., take stairs instead of elevator). Patients having difficulty with eating will be encouraged to reduce portion size in routine ways (e.g., use smaller dishes; second servings only on vegetables). In so doing, healthful behaviors can become routinized, habitual, and embedded in daily life events and locations.

The intervention will also incorporate methodology acquired from the Collaborative care model[62] and includes: 1) patient self-management training that teaches skills needed to carry out medical regimens and guide behavior changes; 2) provision of social and emotional support to promote self-efficacy; and 3) sustained follow-up. Similar to our prior studies, participants will be asked to develop personal goals related to CVD-related behaviors (e.g., smoking reduction, weight reduction), and these goals will be discussed during telephone sessions. Perceived facilitators and barriers to health behavior changes will be addressed as part of the goal-setting process. Participants will develop specific action plans that will enable them to progress toward their goals, and we will ask participants to identify facilitators and barriers that may impact their ability to complete these plans.

B.9. Benefits to the VA

As a result of Secretary Shinseki's leadership, VHA is prepared to implement the patient aligned care team (PACT)/patient-centered medical home (PCMH) model to coordinate the multiple biopsychosocial needs of patients with chronic illness. There is some evidence that when implemented well, PACT/PCMH can improve quality of care and patient and provider satisfaction.[64-66] There is a more significant body of literature that indicates interventions and primary care programs designed around models underlying the PACT/PCMH (e.g., Chronic Care Model) are associated with improved patient care processes and outcomes.[28, 67-69] Further evidence is available that self-management support is likely a necessary, if not in and of itself sufficient, component of PACT/PCMH.[67] The proposed research would examine whether programs aimed at matching resources to patient disease control lead to superior outcomes than simply having booster phone calls in addition to usual care. Answering this question will provide important evidence concerning the overall goal of sustained long-term implementation of the disease management programs as part of PACT/PCMH in the VA and other healthcare systems.[70]

C. METHODS

C.1. Overview of Study Design

We propose to conduct a two-arm 18-month randomized clinical trial for veteran patients with pharmaceutically treated hypertension with uncontrolled systolic BP (≥ 140 mmHg for non-diabetic or ≥ 130 mmHg for diabetic patients). The primary outcome is degree of improvement is systolic blood pressure. **We seek to enroll until we are able to randomize 400 patients.**

Intervention Arm (n = 200 patients): Patients' hypertension control, assessed at baseline, 6, and 12 months, will be used to decide the resource intensity of strategies:

- Medium/level 1 resource intensity: a **registered nurse (RN)** will provide monthly tailored behavioral support telephone calls + home BP monitoring.
- High/level 2 resource intensity: a **pharmacist** will provide monthly tailored behavioral support telephone calls + home BP monitoring + pharmacist-directed medication management.
- Booster (low) resource intensity: a **licensed practical nurse (LPN)** will provide non-tailored behavioral support telephone calls every two months to patients whose systolic blood pressure comes under control

Control Arm (n = 200 patients): An LPN will provide non-tailored behavioral support telephone calls every two months (identical to booster (low) resource intensity component of the titrated intervention). The control

arm will utilize the same procedures as the booster (low) intensity level in the intervention arm.

Table 2: Summary of Study Intervention and Timeline

TITRATED DISEASE MANAGEMENT SUPPORT (expected patients = 200, program duration of 18 months)
Individuals randomized to the titrated disease management arm will receive medium/level 1 resource intensity [RN delivered] or high/level 2 [pharmacist delivered] disease management support depending on their level of blood pressure control. Initial assignment will be based on clinic blood pressure results over the past year. At the 6-month and 12-month study visit, disease management program intensity will be reiterated to medium/level 1 or high/level 2 resource intensity levels based on a combination of home, clinic, and study BP levels. Patients who's systolic blood pressure becomes in-control will be place at a booster resource level [LPN delivered]. There will also be a trigger to increase resource intensity. Resource levels consist of: **Medium/Level 1 resource intensity** – RN-delivered monthly tailored telephone behavioral self-management support calls + Home BP monitoring with feedback to RN nurse educator. Based on preliminary analysis Durham VAMC patients, we expect ~130 of 200 intervention patients in this category at baseline. **High/Level 2 resource intensity** – Pharmacist delivered telephone behavioral self-management support + Home BP monitoring with feedback to pharmacist + Algorithmic medication changes directed by pharmacist (with physician backup). Based on preliminary analysis Durham VAMC patients, we expect ~70 of 200 intervention patients in this category at baseline. **NOTE:** Patients who are considered to be in control at months 6 and/or 12 (systolic BP <140 for non-diabetic and < 130 for diabetic patients)[6] will be moved to **booster resource level** [LPN-delivered telephone behavioral self-management support calls delivered approximately every 2 months].
BOOSTER RESOURCE LEVEL CONTROL **(expected patients = 200, program duration of 18 months)**
Booster Level [LPN delivered] – LPN-delivered telephone behavioral self-management support calls delivered approximately every 2 months for 18 months.

Table 3: Summary of Differences in Intervention Resource Levels

Attributes	Resource Level		
	Medium/Level 1	**High/Level 2**	**Low/Booster**
Delivered by	RN	Pharmacist (highest paid)	LPN (lowest paid)
Key clinician attributes	• Can use clinical judgment to answer clinical questions and provide related assistance to patients • Can do clinical nursing assessments	• Can prescribe medication • Trained in medication management • Can provide clinical assessments of patients	• Able to follow directions of higher level clinicians per protocol • May not do clinical assessments
Behavioral call frequency	Monthly	Monthly	Every two months
Modules activated by telephone calls will be tailored to patient	Yes	Yes	No
Clinician trained in motivational interviewing	Yes	Yes	No
Home BP monitoring	Yes	Yes	Not part of intervention
Pharmaceutical management	No	Yes	No

Please note that references to specific roles or individuals who will conduct study procedures are indented to represent roles on the study team, not specific individuals. Roles may be performed by study team members with appropriate license and/or scope of practice. With appropriate changes made to the staff listing, specific individuals in study roles may change during the course of the study.

C.2. Site

The study will be conducted among patients receiving primary care at the Durham VAMC, including VA Community Based Outpatient Clinics (CBOC) as appropriate. These venues are staffed by 77 (35.68 FTEE) PCPs who deliver care to over 21,000 unique ambulatory care patients with a diagnosis of hypertension (~10,100 in Durham). The clinics serve a diverse patient population, with approximately 34% African-American

patients. Decisions related to targeting specific Durham VAMC affiliated clinics as part of the enrollment process may be made by the PI.

C.3. Patient Identification

To be enrolled, patients must meet **all inclusion** criteria and have **none of the exclusion** criteria:

C.3.a. Inclusion Criteria Determined by Initial Review of the VA Electronic Health Record (CPRS).

- Age ≥ 18 years
- Assigned PCP in one of the clinics of the Durham VAMC (including CBOCs).
- Had at least 1 primary care visit at the Durham VA or affiliated CBOC in the last year.
- Diagnosis of hypertension requiring medication, as determined by:
  - ICD 401.0, 401.1, or 401.9 for ≥ 2 outpatient encounters during the prior year **and**
  - Received a prescription for at least 1 of the following classes of hypertensive medication in the previous year: 1) ACE inhibitors; 2) alpha blockers; 3) angiogenesis II inhibitors; 4) beta blockers; 5) calcium channel blockers; 6) diuretics; 7) antihypertensive combination; and/or 8) antihypertensives, other
- Out of control systolic blood pressure: Durham VAMC (including CBOCs or other affiliated clinics captured in the Durham VAMC electronic health record) outpatient BP measurements ≥ 150 mmHg for non-diabetic or ≥ 140 mmHg for diabetic patients over the last year. If additional patients need to be approached to be offered the opportunity for further screening, non-diabetic patients with mean outpatient systolic BP of ≥ 140 mmHg or diabetic patients with mean outpatient systolic BP of ≥ 130 mmHg over the past year may be approached. Systolic BP cutoffs are based on the Seventh Report of the Joint National Commission on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7).[8] **Initial screening BP levels have been inflated because of evidence that patients frequently have lower study baseline BPs than would be expected based on the mean of clinic BP results over the last year.**[71]

C.3.b. Inclusion Criteria Determined During Initial Screening Phone Call with Potential Subjects.

Patients must indicate that they both:

- Have a VA or affiliated clinic provider that they consider to be their main PCP.
- Receive the majority of healthcare at the Durham VAMC (or affiliated clinic).

These inclusion criteria are used to ensure that patients in the trial consider themselves to be VA primary care patients who are receiving hypertension care in the VA. We conceive of this pragmatic trial as informing interventions that would be suggested by the PACT/PCMH model. Key to this model is the integration of patient-responsive services within a care team. Clinicians in this study will have the ability to communicate with the patients care team. This link to primary care differentiates the proposed program and eventual implementation from stand-alone disease management programs that may be provided by outside groups. Our approach is supported, by the PACT/PCMH and the Chronic Care Model.[72] In a 2006 mailed survey of Durham VAMC patients with diabetes that we conducted,[73] 17% respondents reported that they do not have a PCP at the Durham VAMC who provides the majority of their diabetes care. If a patient switches to another VA facility during our study we will no longer conduct monthly or bimonthly encounter calls but we will continue to schedule study follow up visits.

C.3.c. Exclusion Criteria Determined by Initial Review of the VA Electronic Health Record (CPRS).

- Active diagnosis of psychosis.
- Diagnosis of metastatic cancer.
- Type 1 diabetes
- Class IV congestive heart failure (CHF).
- Currently receiving kidney dialysis or if estimated glomerular filtration rate (eGFR) levels are ≤ 15.
- Former, current or pending solid organ or bone marrow transplant patient.
- Chronic obstructive pulmonary disease (COPD) requiring oxygen.
- Resident in nursing home or receiving home healthcare.
- Patient is pregnant.

- At the time of potential enrollment, participating in another ongoing hypertension, diabetes, cholesterol, or cardiovascular disease clinical trial or patient-level hypertension and/or CVD related quality improvement management program that the study investigators consider likely to be a co-intervention.

C.3.d. Exclusion Criteria Determined During Initial Screening Phone Call with Potential Subjects.

- Refusal or inability to consent to an in-person baseline visit.
- Planning to leave the area prior to the anticipated end of participation.
- Inability or unwillingness to come to the Durham VAMC for baseline-, 6-, 12-, and 18-month study visits.
- Does not have reasonable access to a telephone.
- Does not speak English.
- Resident in nursing home or receiving home healthcare.
- Severely impaired hearing or speech (Patients must be able to respond to phone calls.)
- Severely impaired vision (Patients must be able to read mailed material).
- At the time of potential enrollment, participating in another ongoing hypertension, diabetes, cholesterol, or cardiovascular disease clinical trial.
- Patient reports currently receiving dialysis (may or may not be at the VA).
- Type 1 diabetes, as reported by the patient.
- Patient indicates she is pregnant or planning to become pregnant in the next two years.
- Patients with class IV CHF, dialysis-requiring renal disease, and type 1 diabetes have blood pressure and/or blood sugar management that are beyond the scope of a primary care pharmacist. Exclusion of patients with COPD requiring oxygen and class IV CHF is done (similar to our exclusion of patients with metastatic cancer) to keep patients with end-stage or near end-stage illness out of the study, both because their life expectancies minimize the importance of hypertension control.

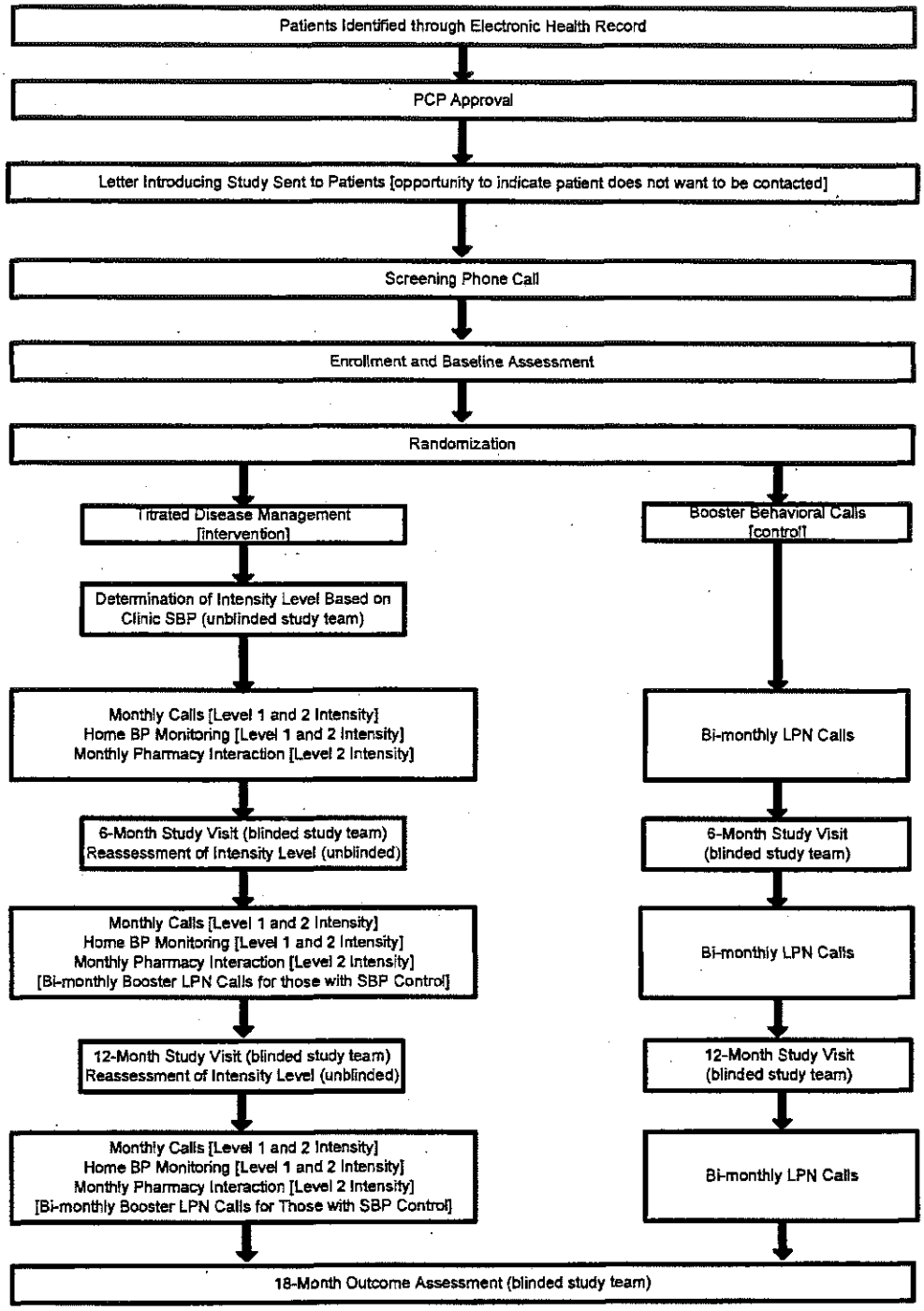
C.3.e. Exclusion Criteria Determined During the Baseline In-Person Visit with Potential Subjects.

- Refusal or inability to provide informed consent and HIPAA authorization form.
- Arm size > 50 cm
- Unable to obtain (including by arm) valid blood pressure readings
- Inadequate mental status to complete the protocol, as judged by five or more errors on the Short Portable Mental Status Questionnaire (SPMSQ).[74-76]
- Patients who indicate they have potential to become pregnant (i.e. have not reached menopause (defined as not having a period for one year or more), not had surgical sterilization such as a tubal ligation, or otherwise report they are not able to have children) will be asked to complete a urine pregnancy test (unless they report being pregnant or planning to become pregnant in the next two years). Patients who report being pregnant, planning to become pregnant in the next two years, or have a positive pregnancy test will be excluded from the study before randomization.

C.3.f. Exclusion Criteria Post Patient Enrollment and Randomization.

Before any medication management begins by a pharmacist (intervention arm) and at each study visit (control and intervention arms) the pharmacist and/or research-assistant will ask female study subjects who reported during the recruitment process that they could still have children if they are pregnant or plan to become pregnant before the end of the study (time period will vary depending on how far into the intervention the patient has progressed). Patients indicating that they are pregnant or plan to become pregnant will then be disenrolled from the study. If the pharmacist becomes aware of pregnancy during the course of the medication management, the patient may be disenrolled from the study based on the clinical judgment of the pharmacist

Figure 1. Study Flow



and study physician (i.e. if the pharmacist and study physician [or appropriately licensed backups] feel that such disenrollment does not put the patient at increased immediate risk). Any disenrolled patients will be referred to their primary care provider for follow-up.

C.4. Recruitment of Minorities and Women

Hypertension disproportionately affects African-Americans compared with Whites.[77, 78] Our research team also has a track record of successful minority recruitment. Investigators on this study have conducted numerous clinical trials and other studies that have recruited between 44% and 59% minority patients, primarily African American, at the Durham VAMC and surrounding community.[6, 9, 11, 79]

There will be no inclusion/exclusion criteria based on gender. Approximately 8% of primary care patients at the Durham VAMC are women.

C.5. Patient Enrollment

1. Potential subjects will initially be identified based upon VA electronic medical records. First, we will identify patients with pharmaceutically treated hypertension based on ICD-9 codes from encounters in the last year and pharmacy records using our inclusion/exclusion criteria. Information over the past 365 days will be used to calculate patients' mean SBP and determine the last SBP recorded. Patient eligibility at time of enrollment is based on mean SBP over the past 365 days at the time of the patient pull or subsequent prioritization of who to contact as potential subjects.

2. PCPs at Durham VAMC and at Durham affiliated clinics through which we have not begun recruiting patients for this study will be notified at the monthly PCP meetings (or through other similar venues) that we are recruiting for this study. Recruitment methods will be the same at the Durham VAMC and affiliated clinics If a PCP indicates that she or he does not want her or his assigned patients to be contacted, we will not include them in the study. If the provider wishes to review a list of her or his patients that may be contacted, she or he

will be given 14 days to do so. At the end of 14 days, it will be assumed that the provider approves the list. This procedure provides a link to primary care as suggested by the PACT/PCMH model and provides additional human subjects protection in case a provider believes that the patient is not appropriate for the protocol for some reason that is not evident from the medical record. We will approach eligible patients who have an upcoming appointment at the Durham VA or affiliated clinics. Patients will be mailed letters introducing the study. Patients can call a toll-free number to request not to be contacted by the study team or if they have any questions. Before sending these letters, the study RA and/or study coordinator will review each patient's medical recorded to determine if they match the patient eligibility and ineligibility criteria as outlined in Section C.3 (Patient Identification). This process will be repeated on a rolling basis throughout the study recruitment period. This basic process for recruiting patients has been successfully used in other clinical trials conducted at the Durham HSR&D Center of Excellence.[11]

3. Unless the patient contacts the study team to decline participation, the RA (or other authorized study staff member) may contact the patient by telephone to explain the study, ask screening questions concerning eligibility, and arrange an in-person meeting at the clinic to further describe the study, obtain informed consent, and interview the patient. During the phone call, the RA will remind patients to take medication as prescribed by their doctor. A similar reminder phone call will be made approximately a day (may be a business day) prior to the baseline and subsequent study data collection visits.

4. The baseline interview includes demographics and assesses patients' health behavior, social and medical environment, and interactions with their provider. Patients will also have baseline BP, height, weight, and pulse measurements obtained. Patients that have to end the baseline appointment early may finish the behavior and social assessment over the phone or come back to the VA to complete it in person.

5. All patients will be followed for 18 months. Trained personnel, masked to study arm assignment (if possible), will obtain the patients' outcome values (e.g., BP) and covariates at baseline, 6, 12, and 18 months using a digital sphygmomanometer and digital scale according to a standard protocol (submitted separately to the Durham VAMC IRB) [Approved June 14, 2012].

6. All study measures assume physical capability of patient to have study measures taken (e.g. if patient is an amputee certain measurements such as blood pressure or weight may not be taken) within the constraint of the location of the study visit. In addition a patient can refuse to complete any study measure. We will only exclude if the patient based on this item if we are unable to obtain valid blood pressure measurements.

C.6. Randomization

1. Once a patient has consented and completed the measurement battery, the patient will be randomized to one of the **2** study arms.

2. We will stratify randomization by diabetes status (because of differing hypertension treatment goals) and baseline SBP [SBP Low Strata = < 150mmHg and High Strata = SBP ≥ 150 mmHg for non-diabetic patients and Low Strata = SBP < 140mmHg and High Strata = SBP ≥ 140 mmHg for diabetic patients]. Diabetes is defined as having both: ICD 250.xx on ≥ 2 outpatient encounters during the prior year **and** prescription for oral hypoglycemic medication (e.g., sulfonylurea, metformin, thiazolidinedione, secretagogues, acarbose) and/or insulin during the past year. Data for the diabetes status variables will come from the data pull for evaluating inclusion/exclusion criteria and SBP is an average of study assessed readings at baseline.

3. Randomization will occur within the study computerized database. As a backup, randomization assignments by strata may be placed in sealed, consecutively numbered envelopes by a masters-level statistician before patient enrollment begins. Other similar systems for randomization, developed in consultation with study statisticians, may also be used as backup.

4. We will use blocked randomization; to prevent contamination, research assistants will be blinded to block size.

5. Patients will be told the arm to which they are assigned by the RA (or other appropriate study staff member) at the enrollment study visit. If the patient must leave the study appointment after informed consent and HIPAA Authorization have been obtained, but before randomization, the arm assignment will be revealed to the patient over the phone.

C.7. Blinding of Study Personnel

Reasonable attempts will be made to divide study personnel into two groups for the purpose of follow-up outcomes assessment: those involved with follow-up data collection and those delivering the intervention. If possible, personnel responsible for follow-up data collection will be blinded to patients' group assignment. Baseline data collection will be done before any staff members know of study arm assignment. Drs. Jackson and Edelman (or his appropriately licensed back-up/replacement) may have to respond to patient inquiries or adverse events, so they cannot be blinded. However, the research assistant (RA), and Drs. Bosworth and Weinberger (Co-Is) will be blinded throughout the study (unless conduct of the study requires blinding to be broken for any given member of the study team). The blinded study team will be responsible for all scientific judgments where knowledge of arm assignment could bias the person making the judgment. This model has worked in our previous studies.

C.8. Intervention Arm-Summary

The intervention consists of an 18-month titrated disease management intervention, assigning/triaging patients based on hypertension disease control (primary outcome) to programs of different clinical intensity and resource utilization.

C.9. Resource Intensity Titration Algorithms

This section describes the process of titrating the level of resource intensity level patients in the intervention arm will be dependent on the clinical factor of blood pressure control. This differs from the tailoring of modules received as part of behavioral phone calls relating to the health decision model as described in section B.8. That tailoring process is described in section C.10 below.

C.9.a. Baseline Titration.

No intervention subjects will **initially** be titrated to the booster (low) intensity resource level of care. Patients in the intervention arm will either receive the medium or high level of resource intensity during the first 6 months of the study. As described below, baseline titration will be based on the mean of enrollment study visit systolic BPs.

- Medium/Level 1 resource intensity – Monthly tailored **RN** delivered calls + home BP monitoring
    - Mean of enrollment study visit systolic BPs of < 150 mmHg (SBP < 140 mmHg for patients with pharmaceutically treated diabetes).
- High/Level 2 resource intensity – Monthly tailored **Pharmacist** delivered calls with additional medication management + home BP monitoring
    - Mean of enrollment study visit systolic BPs of ≥ 150 mmHg (SBP ≥ 140 mmHg for patients with pharmaceutically treated diabetes.

C.9.b. Planned Titration at 6 and 12 months.

Following the 6 and 12 month study visit, we will re-evaluate the SBP of each patient in the intervention arm and determine if that patient should have a different level of disease management program intensity (either more or less intense, depending on the SBP). We will define "SBP" as the **mean of ALL available SBP measurements** up to 31 days prior to or as a result of the titration/study visit (or from the last phone call from which home BP values were provided if > 31 days before study visit). Blood pressures contributing to this mean will be: any clinic values in VistA/CPRS (excluding emergency room or inpatient visits); the study outcome measurement SBP values; and any home SBP values reported during intervention phone calls. Because home SBP measurements have been shown across studies to be approximately 5 mmHg lower than clinic SBP measurements for treated hypertensive patients,[80] 5 mmHg will be added to home systolic BP

measurements when making this calculation. An unblinded study team member will inform intervention arm patients of any change in titrated intensity level.

- Medium/Level 1 resource Intensity
  - Mean SBP (defined above) of ≥ 140 and < 150 mmHg (SBP ≥ 130 and < 140 mmHg for patients with pharmaceutically treated diabetes).
- High/Level 2 resource Intensity
  - Mean SBP (defined above) of ≥ 150 mmHg (SBP ≥ 140 mmHg for patients with pharmaceutically treated diabetes).
- Booster level (low) resource intensity – Non-tailored **LPN** delivered calls occurring every two months
  - Mean SBP controlled; i.e. <140 mmHg (SBP <130 mmHg for patients with pharmaceutically treated diabetes).
- **NOTE:** Diabetes status will be reevaluated as part of the process of the planned titration. Diabetes status may be changed as a result of the criteria for diabetes outlined in section C.6 [number 2 in list] or a study staff member determining that the patient has been diagnosed and is being treated for diabetes by his or her healthcare team, planned titration will be based on blood pressure control definitions for patients with diabetes.

If a patient does not come in for a 6 or 12 month study visit, titration may occur based on the above protocol without having study visit BP measurements. If no BP measurements are available, the patient will continue at the same intensity level. The study physician (Dr. Edelman or his appropriately licensed back-up/replacement, which may include a mid-level provider) must approve any changes in intensity level for patients who do not have 6 or 12 month study BP measurements. If the study physician does not believe there is sufficient BP information to make a change for patients without a 6 or 12 month study visit, no changes in intensity level will be made.

Study visits may occur during a time period encompassing plus or minus two months around the intended study visit. In other words, the 6 month study visit may occur between 4 and 8 months following the initiation of study procedures. The 12 month study visit may occur between 10 and 14 months following the initiation of study procedures. The 18 month study visit may occur between 16 and 20 months following the initiation of study procedures.

C.9.c. Rules for Automatically Titrating Intervention Patients up to High Clinical Intensity.

If a patient reaches either of the three rules below, either at a study visit or between study visits, for close parallel to real world clinical decision-making the patient is immediately escalated to the highest level of care. If a patient is titrated to the highest level between study visits, then they must remain at the highest intensity level for at least 6 months (for example, if a patient is up stepped at month 3, they will not be reevaluated for possible down stepping until month 12).

- Mean of home systolic BPs reported during a study behavioral call ≥ 160 mmHg
  - This automatic increase in resource intensity will not include adding 5 mmHg to home systolic BP measurements. A minimum of 4 blood pressure readings considered to be validly reported by the appropriately licensed clinical interventionist will be required for automatic titrating of the intervention patients to the high clinical intensity level. Any exception to the required number would need to be approved by the study physician or an appropriately licensed clinical backup.
- Hospitalization due to stroke and/or MI. Patient will be asked at intervention phone calls if they have been hospitalized for stroke, MI and/or heart attack, we will report answers based on patient self report and/or indication of hospitalization in VA electronic health record.
- A patient triggers the safety protocol for blood pressure based on a blood pressure (see section C.19 for safety criteria) measurement considered to be valid by the appropriately licensed clinical study staff member.

C.9.d. Process for determining and communicating changes in titrated resource levels.

After completing each study visit, the interventionist to whom a patient is assigned (or other authorized unblinded study staff member if back-up is required) will access all eligible BP values for which the titration

determination will be made. BP readings will come from the following sources: 1) clinic BPs extracted nightly from the Durham VistA system (process that has been arranged by the PI for use in the HTN-IMPROVE study); 2) study BPs entered by the research assistant; and 3) home BPs reported during planned study calls. **A combined mean of these BP measurements will be calculated to produce information on the cut points upon which titration will be based.** Because measurements will have already been entered into the intervention software, the calculation will be automated. The interventionist (or other authorized unblinded study staff member if back-up is required) will inform the patient if any changes in resource intensity are indicated. The intervention software will record all titrated changes in resource intensity.

C.10. Intervention Component – Telephone Self-Management Support [medium/level 1 and high/level 2 level resource intensity]

Patients receiving medium/level1 resource intensity disease management will receive calls from a RN and those receiving high/level 2 resource intensity disease management will receive calls from a pharmacist. Because this is a pragmatic clinical trial, it is expected that some patients may not be able to be contacted or miss some portion of the scheduled telephone calls or other contacts with study personnel.

C.10.a. Tailored Telephone Calls.

Intervention requiring medium/level 1 resource intensity services will receive tailored behavioral telephone calls from an RN. Those receiving high/level 2 resource intensity services will receive tailored calls from the pharmacist. Tailoring of the calls involves delivery of scripted modules based on the needs of specific patients. The telephone scripts, questions delivered during the calls that lead to specific modules, and training of the interventionists (i.e. RN and PharmD) will be manualized so that the intervention can be replicated if it is found to be superior to the control. Tailoring will be based on questions asked during the intervention call. For example, patients who report smoking during the call will then be asked about their readiness to quit smoking. As such, the calls also take into account an individual's situation at the time of the call, not on information that could have been collected up to a year before.

C.10.a.1. Training of Personnel Making Calls. Prior to starting the intervention, the RN and pharmacist delivering the tailored calls will be **trained in motivational interviewing (MI).** A key goal of MI is to assist individuals to work through their ambivalence about behavior change. As we have done with our prior studies, we will provide didactic training on the basic principles of MI, including asking open-ended questions, learning how to use reflective listening, and learning to identify and elicit "change talk" from a patient. In addition to didactic training, we will have the RN and pharmacist role-play prior to patient recruitment. The use of MI principles will capitalize on patients' motivation and help patients overcome barriers--an essential part of self-management. The Durham HSR&D COE has two certified-trained MI trainers. In contrast to the medium and high level interventions, the **LPNs delivering booster phone calls will not receive training in MI.** Rather they will simply follow non-tailored telephone call scripts.

C.10.a.2. Mechanics of Making Calls. Within two weeks after patient randomization, the interventionist will telephone each patient in the intervention group in order to begin the phone calls. Based upon data from V-STITCH, TCYB, and TEACH-DM, the average phone call will take less than 20 minutes.

A scheduled contact will occur approximately every month. The interventionist will try at least four times to reach each patient for the scheduled monthly follow-up call, including at least one attempt off-hours. If all attempts at the scheduled call fail to reach the patient, s/he will be contacted at her/his next provider visit and/or by mail. A similar protocol will be used for patients who fail to show for a study visit. Given the frequency of contacts and patients providing ideal days/times for contact, we do not anticipate problems contacting and following patients. Among 293 individuals in the V-STITCH followed once every other month for 24 months, the average number of attempts to reach patients was 2, and retention rate for these individuals was 84%. Among patients for whom phone calls were indicated in the HINTS study, contact was made approximately 95% of the time.

Between the scheduled calls, patients may also telephone the nurse/pharmacist with questions related to their hypertension, including (but not limited to) calls relating to control of their blood pressure and the pharmacological or non-pharmacological management of hypertension. For patients in the booster resource phase, either the study interventionists [RN or PharmD] or study physician (Dr. Edelman or his appropriately licensed back-up/replacement) will assist the LPN. Information gathered during these unscheduled telephone

calls will be recorded in the intervention database. Should emergent healthcare issues arise during these calls, the RN or PharmD will immediately contact the patients' PCP (or covering provider) or refer the patient to emergent care. A message will be placed on the voice mail of the nurse and pharmacist interventionists notifying study subjects that in the case of a medical emergency, they should hang up and dial 911.

The interventionist will use software already developed for HINTS and needing only minimal adaptation for the current study, to guide tailored patient components of the intervention during telephone calls, including manualized scripts and questions for patients. This software adheres to current VA information security standards. A secure computer database will be used to inform the software seen by the interventionist; it will update vitals, medications etc so the interventionist can see current clinical data. Tailored intervention materials (algorithms, standardized scripts, etc.), will be available for dissemination at the end of the study.

C.10.a.3. Content of Calls. The specific content of each call will be determined by activating modules that pertain to each of the barriers to control described below (section C.10.b). The modules will be "activated" (introduced as a topic in a specific phone call) when a patient shows a barrier that the module is designed to address. The modules can be activated on a different schedule, each consistent with the content and goals of the specific module. Each module is either (1) a health behavior (e.g., exercise) that is desirable for control of blood pressure or (2) a modifiable patient factor that can lead to improved control (e.g., knowledge, memory). Patient factor modules will only be activated once unless there is a problem with that factor (e.g., poor social support, poor memory). The patient initiated phone call module can, of course, be activated at anytime. Patients requesting previously developed written information in follow-up will be provided material approved by the study physician (Dr. Edelman or his appropriately licensed back-up/replacement), pharmacist (Dr. Melnyk or her appropriately licensed back-up/replacement who could be the intervention pharmacist), RN interventionist, and pharmacist interventionist. All calls from the study pharmacist will be indicated with a note in the Durham VAMC electronic health record.

C.10.b. Topics Covered in Intervention Phone Calls.

A major emphasis of the program is initiating and maintaining specific health behaviors related to hypertension/diabetes. The intervention is organized as telephone encounters that occur approximately every 4 weeks. At each telephone encounter, a core group of modules are potentially activated. Table 4 shows a sample of a module schedule. A summary of module content is below. Scripts for specific topics covered have been submitted for IRB approval. Only approved IRB scripts will be used for each intervention.

Table 4: Sample Module Schedule (for illustrative purposes only, exact order based on specific patient)

Encounter 1	Encounter 2	Encounter 3	Encounter 4	Encounter 5	Encounter 6	Encounter 7
Opening Intro call Med mgmt Home monitoring Closing	Opening Med mgmt Side effects Home monitoring Memory Closing	Opening Med mgmt Side effects Home monitoring Diet Closing	Opening Med mgmt Side effects Home monitoring Exercise Closing	Opening Med mgmt Side effects Home monitoring Weight Closing	Opening Med mgmt Side effects Home monitoring Knowledge Closing	Opening Med mgmt Side effects Home monitoring Stress Closing
Encounter 8	**Encounter 9**	**Encounter 10**	**Encounter 11**	**Encounter 12**	**Encounter 13**	**Encounter 14**
Opening Med mgmt Side effects Home monitoring Depression Closing	Opening Med mgmt Side effects Home monitoring Social support Closing	Opening Med mgmt Side effects Home monitoring Smoking Closing	Opening Med mgmt Side effects Home monitoring Alcohol Closing	Opening Med mgmt Side effects Home monitoring Memory Closing	Opening Med mgmt Side effects Home monitoring Social support Closing	Opening Med mgmt Side effects Home monitoring Exercise Closing
Encounter 15	**Encounter 16**	**Encounter 17**	**Encounter 18**	**Encounter 19**		
Opening Med mgmt Side effects Home monitoring Knowledge Closing	Opening Med mgmt Side effects Home monitoring Social support Closing	Opening Med mgmt Side effects Home monitoring Smoking Closing	Opening Med mgmt Side effects Home monitoring Weight Closing	Opening Med mgmt Side effects Home monitoring Final closing		

Open module/medication management. Each encounter begins with an opening session which involves the interventionist reviewing the patients' currently prescribed BP medication, assessing if the participant is familiar with the purpose of the medication, and whether there have been any changes in the use of the their hypertensive medications. If the patient does not understand the purpose of their hypertension medication in any encounter or how to take the medication, the interventionist explains the purpose of each medication prescribed for that individual. If the patient reports that there has been a change in their BP medications, the interventionist queries if their PCP is aware of the change. If not, the interventionist discusses the importance of informing their PCP of changes in their BP medication regimens.

Adverse effects of antihypertensive medication. The interventionist queries patients at every phone call about any specific BP medication side effects they may have. If a patient is having a hypertension-medication related adverse effect, the interventionist discusses the problem with the patient. The interventionist also reminds the patient to discuss any adverse effects with their PCP. Any potentially life threatening adverse effect is reported immediately to the PCP. The goal is to prevent medication nonadherence by informing patients of common adverse effects and help to facilitate medication change when necessary.

Memory. Patients who report they have difficulties remembering to take their medication are provided various mnemonic strategies such as setting an alarm or using a weekly pillbox.[45] The interventionist conveys the need and importance of taking BP medication consistently and in a timely manner to both the patient and family/friends identified by the patient.

Knowledge/risk perception. All patients will receive information and counseling from the interventionist on the importance of maintaining BP control by underscoring the association between hypertension and diseases that come about from poor control. Counseling is tailored to individuals who are diabetic,[81-83] African-American,[84, 85] recently diagnosed with hypertension, and/or have hypertensive relatives[86, 87] because these factors confer specific risks for worse health outcomes.

Participatory decision making/patient/physician communication. The nature of hypertension requires substantial responsibility by the patient for implementing treatment regimens agreed on during the provider-patient visit. Patients identified as having poor provider relationships receive information on ways to empower patients to interact more productively with their providers.

Diet. The diet module begins with the interventionist asking the patient to talk about foods they eat in a typical day. This leads to a discussion of sodium and sources of where high levels of sodium may be found, followed by having individuals think of ways they can reduce their sodium intake. In addition, the interventionist discusses how individuals can determine the sodium contents of food and remind patients of how much sodium they should ingest in a day. This material includes the Dietary Approaches to Stop Hypertension (DASH) diet, which has been found to lower BP.[88-90]

Weight. The interventionist emphasizes the importance of maintaining a healthy weight and queries individuals as to what stage they are in terms of initiating weight loss (not ready, thinking about it, preparing, or taking action). In intervention levels 1 and 2, weight loss information is then tailored to individuals' readiness to change.

Exercise. The interventionist reviews the benefits of exercise and assesses current physical activity and whether individuals have increased their level of physical activity since enrolling in the study. In intervention levels 1 and 2, the interventionist determines their exercise activity readiness to change and information is then tailored to the patient's readiness. The interventionist also helps the individual to determine the intensity level of their planned activities as well as setting realistic goals.

Social and medical environment/access to care. If barriers to care (e.g., lack of transportation, medical costs, social isolation) are identified, the interventionist assists patients in identifying and using available resources to overcome barriers (e.g., community resources, inexpensive medications).

Stress, mental health, insomnia and sleep apnea. While there is more evidence that stress increases blood pressure in the short-term, the long-term implications of stress are not clear.[91] This module involves the interventionist querying patients about their knowledge of the relationship between stress and hypertension as well as how individuals know when they are stressed. The interventionist provides some suggestions on how to potentially reduce stress, monitor their sleep habits and if appropriate be referred to the sleep apnea clinic. Among individuals who screen positive on Patient Health Questionnaire (PHQ)-2[92, 93] [2 item screening instrument for depression] (questions part of intervention software), the interventionist will discuss various treatments available (e.g., medication, therapy), the importance of seeking treatment, and how to access these resources as a VA patient.

Smoking. Among smokers, the interventionist highlights the benefits of smoking cessation for those who report they are current smokers. The interventionist then determines the individual's stage in terms of considering smoking cessation.

Closing module. At each encounter's closure, the interventionist asks patients to report their most recent blood pressure. If they are not aware of it, the interventionist reiterates the importance of knowing one's blood pressure. For those who know their blood pressure, the interventionist provides feedback for those with inadequate blood pressure control and further reinforcement for those with adequate blood pressure control.

C.11. Intervention Component – Booster Level Phone Calls

Patients whose systolic blood pressure comes under control at 6 or 12 months will be switched to booster level resource intensity LPN phone calls (based on procedures described in section C.9.b). The calls will occur every two months instead of monthly and be conducted by a LPN instead of an RN. The number of contacts will depend on the point in the study when LPN calls begin and changes made during titrations. Unlike the RN and pharmacist, the LPN will not receive training in motivational interviewing. Further, specific behavioral modules that are activated will not be tailored to the patient and the LPN will not ask for information about any home BP measurements. The goal is to identify stable patients and reduce the resources they use to minimize cost of our intervention.

LPNs [known as licensed vocational nurses (LVNs) in California and Texas] differ from RNs in several important dimensions. While both are nurses, LPNs focus on providing specified services under the direction of another licensed clinician, often a RN. While RNs can assess patients and develop plans for nursing care, LPNs cannot independently assess and take action in relation to patient care. As we propose for this study, LPNs can complete assigned patient care tasks, observe patients, and report observations to other clinicians. Further, RNs have training in areas such as educating patients about health issues. As a result of their greater responsibilities, RNs are paid significantly more than LPNs.[94, 95]

Because this is a pragmatic clinical trial, it is expected that some patients may not be able to be contacted or miss some portion of the scheduled telephone calls or other contacts with study personnel.

C.12. Intervention Component – Home BP Monitoring [medium/level 1 and high/level 2 resource intensity]

All patients randomized to the intervention arm who do not currently have a VA approved home BP monitor will receive one. All intervention patients will receive training in its use at their baseline study visit according to a protocol developed in our prior studies.[96] If a patient must leave the study visit before receiving training or randomization must be revealed over the phone, the study team may either schedule a follow-up appointment for training or walk the patient through use of the home BP monitor over the phone. Patients will use BP monitors every other day to check their BP, using a defined protocol similar to the one in previous studies. We will request individuals to provide their BP values for at least the two weeks prior to the monthly intervention phone calls so that the interventionist [RN or PharmD] can comment on BP control. Patients will be reminded to record their blood pressures as part of the intervention telephone calls. Examinations of the agreement between self-reported and electronically stored blood pressure has generally been good, with one study of agreement indicating that 68% of reported home systolic BP measurements were identical to those stored electronically.[97] In a previous study, we were able to maintain an 84% home BP monitor compliance rate over 24 months (instructions submitted separately to the Durham VAMC IRB). [Submitted for approval with this protocol]

Because this is a pragmatic clinical trial, it is expected that some patients may choose not to obtain a home BP monitor from the VA. Clinical judgment will be utilized in determining which home blood pressure readings will be recorded and utilized as part of study intervention.

C. 13. Intervention Component – Pharmacist-Directed Algorithmic Medication Management [high/level 2 resource intensity]

Many patients require medication intensification to achieve targets for BP. Appropriate medication management requires accurate and timely information on the patient's current level of disease control, treatment adherence, evidence-based recommendations, and potential barriers to successful implementation. Patients who meet criteria for high/level 2 resource intensity disease management will receive medication management from a clinical pharmacist, who will be backed up by an MD (Dr. Edelman or his appropriately licensed back-up/replacement who could be a mid-level provider). Pharmacists are authorized to make medication changes according to accepted treatment algorithms and based on their scope of practice. Via CPRS, the pharmacist will also communicate these changes to the patient's PCP. While pharmacists may collaborate with the patients' providers when clinically indicated, they do not have to rely on providers to make the changes. The goal of the medication component of the intervention is not to replace clinic based management, but rather to supplement it based on home BP readings in order to more efficiently implement interventions that may otherwise be left until the next provider appointment. The pharmacist will attempt to contact patients every month while they are in the high-intensity titration level of the intervention. At the pharmacist's discretion, patients may be asked to come to the Durham VAMC for an in-person meeting, however, most interactions will be conducted over the phone. During each encounter, the pharmacist will have information from both CPRS and the behavioral-telephone calls conducted as part of the intervention so information on such topics as patient medication and barriers to adherence can be available. During the initial encounter the pharmacist will assess the patient's medication adherence, review all BP related medications, discuss the purpose of each medication, and the appropriate administration of each medication. While not explicitly planned, the pharmacist (or appropriately licensed clinical backup) may discuss other medicines if he or she feels that this is needed to appropriately manage BP medication. At subsequent contacts the pharmacist will review any medication changes with the patients and update patients' medication lists. All calls will be indicated with a note in the Durham VAMC electronic health record.

For patients who require a change in their prescription, the pharmacist will communicate the change to the VA pharmacy and the patient's PCP using standard clinic procedures. At the next monthly telephone contact, the pharmacist will assess any new symptoms (e.g., hypotension). This will allow adequate time for the patient to obtain the medication and to get accustomed to the medication change. Any medication change that requires additional testing or follow-up (e.g., assessment of serum potassium, sodium and creatinine following the addition of an ACE-I or diuretic) will be ordered and followed-up. In cases where a medication change is made, a note will be generated for the patient's medical record and co-signed by the patient's PCP. This algorithm and methods of communication of changes to the PCP and follow-up of required labs has all been developed and tested in the HINTS study. If any significant adverse events occur, the pharmacist will consult with the patients' provider along with the study physician (Dr. Edelman or his appropriately licensed back-up/replacement who could be a mid-level provider or other appropriate clinician) to take appropriate action and/or make further recommendations. Patients will also be provided with a toll-free number to call the pharmacist to report any adverse events or ask questions. All medication changes will be indicated with a note in the Durham VAMC electronic health record. Medications algorithms are being submitted separately to the Durham VAMC IRB. [approved by IRB on August 24,2011]

Because this is a pragmatic clinical trial, it is expected that patients may not be able to be contacted or miss some portion of the scheduled telephone calls or other contacts with study personnel.

C.13.a. Hypertension Medication Management.

We have previously developed a set of clinical rules, based on VA practice guidelines to facilitate telephone management of BP medications. Many of the clinical rules are based on the following treatment principles:

a. Encourage use of diuretics as first-line agents, which have established effectiveness in reducing long-term morbidity and mortality.
b. Select drug partners with favorable interactions, for example, diuretic and ACE inhibitor.
c. Avoid drug partners with potential adverse interactions (e.g., ACE inhibitor and potassium-sparing diuretic (increases risk of hyperkalemia).
d. Avoid drug partners that do not have added efficacy (e.g., ACE inhibitors and angiotensin II receptor antagonists).

e. In patients with additional diseases, select drugs that are appropriate for dual effects, for example, ACE inhibitor in a diabetic patient in an effort to preserve renal function.
f. Avoid drugs that may aggravate other health problems (e.g., avoid calcium channel antagonists in patients with gastroesophageal reflux disease since these agents may lower pressure in the lower esophageal sphincter).
g. Encourage appropriate intervals before assessing the impact of the drug (e.g., waiting one month for the full effect of hydrochlorothiazide as compared with several days for the full effect of calcium channel antagonists).
h. Be aware of potential withdrawal syndromes (e.g., change from beta receptor antagonists or clonidine).

C.14. Procedures for Assessing Immediate Patient Risks.

During each scheduled encounter between a patient and study interventionist, immediate patient risks will be assessed via brief clinical questions asked by the interventionist. Emergent concerns will require referral to emergency care for immediate medical attention, usually by having the patient call 911. These include active chest pain, typical cardiac chest pain of duration > 10 minutes within the last 24 hours, dyspnea, SBP ≥ 220 mmHg, DBP ≥ 120 mmHg, SBP ≤ 90 with lightheadedness, heart rate ≥ 120, heart rate ≤ 50 with lightheadedness, new severe generalized or focal weakness, and altered mental status. In response to all other concerns not related to blood pressure the patient will be urged to contact his/her PCP. This same basic procedure was used during our recently completed Diabetes Group Visits Trial. Only one patient was referred for emergency care among over 600 patient-visits to that study. In addition, section C.19 outlines safety parameters for the primary outcome (BP).

C.15. Measuring Components and Fidelity of the Intervention.

At each intervention encounter, the interventionists (i.e. nurse or pharmacist) will review a checklist of issues pertinent to that particular patient. The checklist will be maintained in the intervention database, which the interventionist will use while s/he is conducting intervention calls. The database will facilitate ascertainment of compliance with this intervention.

All telephone calls initiated by the interventionist will be conducted while s/he is logged on to the intervention database created for the study. This will record the number and duration of calls and the type of intervention components delivered for each patient that will be used for cost analyses. The database will also contain a standardized script. In the intervention software, the interventionists will maintain a log for calls initiated by patients and calls to providers. Further, a log of all consultations by study interventionists/clinicians on patient clinical issues will be maintained in the intervention software. This includes any contacts with a patient's PCP. All pharmacist-made medication changes will be recorded in the intervention software (in addition to CPRS). The project coordinator will review all logs weekly to assure that the components that were due at the scheduled call were in fact recorded as delivered. Drs. Jackson and Edelman (or his appropriately licensed back-up/replacement) will meet with the interventionists approximately monthly to discuss any possible problems with the scheduled delivery of the intervention. A member of the unblinded study team will listen to approximately 1 phone call approximately every 2 weeks to ensure that what is being recorded in the databases is actually being covered on the calls. The process may become less frequent if consistent quality is observed. In addition, more phone calls may be listened to if necessary to ensure quality.

C.16. Control Arm

Patients in the control arm will receive the booster level resource intensity LPN phone calls that will also be received by patients in the intervention arm whose hypertension comes into control (described in section C.11). Control patients will be contacted at 6, 12, and 18 months after randomization in order to come to an in-person study visit to complete the same outcome measures as the intervention group.

This process differs from usual care and emulates phone calls based on those that have been shown to be effective at improving blood pressure control and patient medication adherence in both clinical trial and implementation settings. Phone calls used in the V-STITCH study were not-tailored based on the patient's stage of change for a specific concern (e.g. all smokers received the same information on smoking regardless of how ready they were to quit smoking).[45, 52] Further, the calls only occurred every two months. Despite these

limitations, receiving the phone calls was associated with a significant increase in hypertension control compared to not receiving the phone calls.[6] In addition to this trial evidence, the implementation of bi-monthly calls using scripts provided by Dr. Bosworth in a purely quality improvement project was associated with significant improvement in patient adherence to hypertension medication.[7] As a result, we are proposing a control arm that would be expected to lead to modestly reduced systolic BP and do it at a low cost per patient.[6, 51]

C.17. Evaluation of the Intervention to Inform Future Translation into Practice

All telephone calls initiated by the study interventionists will be conducted while they are using the intervention software, which will record the number and duration of calls and the type of intervention components delivered for each patient. The schedule for telephone calls between interventionists and patients will be closely monitored and intervention sessions will be randomly reviewed to ensure intervention fidelity.

Measuring process data is an important component of any well-designed intervention trial, with results used to help understand why an intervention was or was not effective. The process research proposed here is designed with a focus on enhancing the readiness of the interventions for translation. Successful translation into real-world settings has three components: 1) adoption of these interventions by practice settings outside of the research context, 2) successful implementation of the interventions in these settings, and 3) effective use of the interventions by the populations accessed or served through these settings. Greenhalgh et al describe the diffusion of innovations into service organizations as conditioned by characteristics of: the innovation (in this case, the interventions), individual adopters and their service systems, the sources of innovation and mechanisms of diffusion and dissemination, and the larger inter-organizational context.[98] Changing service system readiness for adoption and implementation of innovations is clearly beyond the scope of this project. However, making the intervention more ready for effective adoption, implementation, and use in practice settings is a natural extension of this work that helps fulfill the mandate to promote translation.

Reasons for increased likelihood that the intervention will be ready for effective translation into practice include: 1) the behavioral modules are standardized, consistent and tailored to patients' needs. Thus, the modules are only activated for those with problems (e.g., side effects) and when activated, the modules are tailored to the patient's current stage of change. As a result, each phone call encounter is less than 20 minutes. 2) The medication algorithm for diabetes, hypertension, and lipids has been developed. In addition, the algorithm focuses on generic and low cost medications. 3) The intervention software package is extremely adaptable and can function in a paper and electronic medical record environment. The software allows the integration of patient, medical records, and provider information and can be easily changed to update medication or guidelines changes. 4) The various components of the material have been tested in over 2500 patients in 6 diverse clinics.

C.17.a. Semi-Structured Qualitative Interviews.

To better understand both the specific intervention components that may impact outcomes and potential issues in implementation, we may utilize semi-structured interview methods to study implementation processes.[99, 100] Our sample will consist of the study interventionists (pharmacist, RN, LPN), a sample of approximately 5-10 Durham VAMC PCPs, which may include providers at Durham affiliated community-based clinics, (depending on data saturation) [to examine issues involved in future implementation], and a sample of approximately 15-25 patients (depending on data saturation) who were in the intervention group. To better understand differences in attributes of the intervention that may impact implementation in parent medical centers and community outpatient clinics, we will seek patients who have primary care providers at both the Durham VAMC/Hillandale clinics (i.e. parent VAMC) and in Durham affiliated community based clinics (primarily Greenville, where we actively physically enrolled patients in the study). Our goal is that patients that have had a variety of experience with the titration process. For example, this may include: 1) patients who started and remained at the level 2 (pharmacist delivered) resource intensity level, 2) patients who started at the level 2 (pharmacist delivered) resource intensity level and were down stepped to another intensity at some time during the study, 3) patients who started and remained at the level 1 (RN delivered) resource intensity level; 4) patients who started at the level 1 (RN delivered) resource intensity level and were down stepped to another intensity at some point during the study and; 5) patients who started at the level 1 (RN delivered) resource intensity level and were up stepped to another intensity at some point during the study. The staff

interviews will be guided by an implementation framework developed by Weiner.[101] The framework suggests that implementation is a function of the clinics' readiness for change, the quality of the implementation policies and practices, climate for implementation, extent to which intended users of the innovation perceive that innovation use fosters the fulfillment of their values, and extent to which the innovation fits with task requirements. Patient interviews will be designed to examine perceptions of intervention effectiveness based on domains of the Chronic Care Model that are observable by patients: patient activation, delivery system design, goal setting/tailoring, problem solving, and follow-up/coordination.[102]

C.17.a.1. Interview Procedures. The following procedures will be followed for interviews for staff members.

1. Interviews will only be conducted by research study team staff of the Durham VA Medical Center Health Services Research & Development Center of Excellence.

2. Study interventionists and Durham VAMC PCP's interviews will be conducted over the telephone. A waiver of documentation of informed consent is being requested. However, a staff member may request an in person interview if he or she prefers.

3. Interviews of the patients will also be conducted either by telephone or in person.

4. Patients will have already gone through an informed consent process and signed VA form 10-3203 prior to participating in the interviews.

5. **Staff contact** information will be obtained through VA Outlook and/or the VA phone book on the VHA intranet

6. **Patient Contact information** will be obtained from study records and/or the VHA electronic health record.

7. **Selected PCP's and staff interventionists** will be contacted via email using the attached text.

8. **Selected PCP's and staff interventionists** may decline to participate (opt-out) upon receiving the email.

9. **Selected PCPs and staff interventionists** may write back to schedule a time to talk that meets within their schedule. We will make clear that our interview does not supersede any work events that may arise and can be interrupted and resumed later if necessary.

10. If the If the **selected PCP or staff interventionist** does not respond to the email, study staff will call the staff member using the attached telephone script.

11. The telephone script for **Selected PCPs and staff interventionists** contains the elements of informed consent. A waiver of documentation of informed consent is being requested form the IRB.[Waiver of Documentation of Informed Consent for interventionist/providers approved August 24, 2011]

12. **Staff members** may decline to participate at any point.

13. **Patients** may decline to participate at any point.

14. Interviews will be conducted using a semi-structured interview guide. This guide will be sent to the IRB before it is used. **No interviews will be conducted until the IRB has approved the structured interview guides.**

15. **There will be no exclusions based on staff member race, ethnicity, or gender.**

C.17.a.2. Additional Procedures to Protect Confidentially of Employees. The following additional procedures will be followed to provide additional protection of employee confidentiality.

1. PCP supervisors will not be told whether or not an individual has agreed to participate in an interview.

2. PCP supervisors will not be told whether or not an individual has participated in an interview.

3. As with all studies, there will be no sharing individual responses to interviews with individuals not on the study staff list on file with the Durham VAMC IRB.

4. All names will be redacted from final transcripts of interviews that will be used for qualitative analysis

5. As described in section on data handling, extensive efforts are being made to maintain the security of data.

6. An experienced staff member who had not previously been involved in this study will be asked to complete the interviews of the study interventionists.

C.18. Primary Outcome – Blood Pressure

Continuous change in systolic blood pressure will be measured as the primary outcome. BP will be measured at baseline and at the 6-, 12-, and 18- month study visits. At each study visit, three measures will be obtained. The final outcome will be the average of the three measures. All BP measurements will be performed using electronic blood pressure cuffs, which have been shown to be equivalent to (and ecologically safer than) the gold standard of random zero sphygmomanometers.[103] Study personnel will be trained and certified in correct measurement technique using established methods.[104] These are currently the methods that a Co-I of the proposed study (Bosworth) is using in his currently funded NHLBI trial. In addition to blood pressure, pulse will also be measured.

Systolic BP has been chosen as the primary outcome because it is far more likely to be out of control than diastolic BP. Fewer than 2% of patients with HTN on medications have isolated poor diastolic BP control.[105]

We are proposing examining systolic BP as the primary outcome, as opposed to changes in control, because equal incremental improvements lead to greater reduction in complications at the higher end of the scale (i.e. higher BP). That is, there is a greater health impact in lowering someone's SBP from 160 to 150 mmHg than there is from lowering it from 145 to 135, even though the latter crosses a threshold and brings the patient "under control." As argued for HbA1c for Pogach et al. (2006),[106] we therefore felt that continuous SBP was a more clinically relevant primary outcome than control, given that patients lowered from 160 to 150 would be considered "failures" using the latter, dichotomous outcome. Extensive epidemiological data have confirmed the importance of SBP as a primary determinant of risk.[107] The relationship between BP and CVD risk is relatively continuous and SBP reductions of 6 mmHg translate to reduction in clinical events and all-cause mortality.[8]

Study visits may occur during a time period encompassing plus or minus two months around the intended study visit. In other words, the 6 month study visit may occur between 4 and 8 months following the initiation of study procedures. The 12 month study visit may occur between 10 and 14 months following the initiation of study procedures. The 18 month study visit may occur between 16 and 20 months following the initiation of study procedures.

C.19. Safety Parameters for Primary Outcome

Certain extreme BP values, both high and low, carry an urgent risk of major complication. As a result, if the most recent BP measurement is reported during a patient phone call, at a study data collection visit, or during other contact between study clinical staff and a patient is at one of these extremes, we will advise patients to take specific actions to minimize those risks. For SBP ≥ 180 mmHg or DBP ≥110mmHg, we will advise the patient to contact her/his triage nurse (or other similar position) within 24-48 hours. If a patient is advised to contact the triage nurse, a note will be placed in the patient's medical record. For participants that have moved care to a different VA facility (as described in section C.3.b) we will advise patient to go to the emergency room or urgent care facility but not put a note that requires PCP co-signature in their medical record (because it is not possible to require co-signatures of providers from another facility). This level corresponds to JNC 7

classification of Stage 3 hypertension and are the safety criteria currently used by our data safety monitoring board in TCYB and TEACH-DM. For SBP ≥ 210 mmHg or DBP ≥ 120 mmHg, or SBP ≤90 mmHg and/or DBP ≤40, we will advise the patient to seek immediate care. For all instances in which we recommend seeking immediate care, we will put a note that requires PCP co-signature in the patient's medical record. For participants that have moved care to a different VA facility (as described in section C.3.b) we will advise patient to go to the emergency room or urgent care facility but not put a note that requires PCP co-signature in their medical record (because it is not possible to require co-signatures of providers from another facility).

C.20. Secondary Outcomes

C.20.a. Systolic Blood Pressure Control.

As a secondary analysis, we will examine the difference in the degree of systolic BP control over the 18 months of the study between the intervention and control arms. Control will be defined as SBP ≤ 130mmHg for hypertensive patients with diabetes and ≤ 140mmHg for patients without diabetes.

C.20.b. Intervention Cost Measurement.

We will assess intervention-related costs and resource-utilization costs to create a complete picture of the costs that would be incurred if the intervention were adopted system-wide. We will examine outcomes over 18 months, matching the timing of the measurement of the primary outcome. Intervention costs include labor and capital costs. Labor will include interventionist time, assessed using VA Human Resources data for salaries and carefully tracked study data on time spent per task. LPN, RN and PharmD time on calls, clinic time devoted to the study, and training costs to implement the study will all be included at the relevant wage and fringe benefit rates. We do not anticipate that the interventions will place additional time burden on physicians. We will assume that capital costs such as overhead costs, office space and supply costs, and telephone services costs will be neutral because implementation would use existing capitol. In addition, equipment costs of the electronic home BP monitoring units (and batteries) will be included, using current market prices.

C.20.c. Patient Cost and Utilization.

All resource utilization and cost data will come from Decision Support System (DSS) data (or equivalent database if the VA data storage locations change before the end of the study), including the DSS Outpatient (OPAT) National Data Extract (NDE), the DSS NDE SAS Pharmacy Dataset, and the DSS Inpatient Discharge Extract File (DISCH).[108, 109] We will measure VA outpatient and inpatient utilization and costs by treatment or control over 18 months. Outpatient encounters will be categorized using clinic stop codes into primary care visits, specialty care visits, and other outpatient care (laboratory, radiology, surgery, nursing, and all other clinical visit and ancillary services and encounters not already mentioned), as well as a count of total encounters (unique CLSTOPS) and total costs (OCST_TOT). We will also examine hypertension-related outpatient pharmacy prescription counts and costs using an identification method developed in the HINTS study (SAS algorithm of HTN-related outpatient drugs developed by Mark Perkins, Puget Sound VA),[110] in order to compare them to total outpatient pharmacy costs (DISP_COST plus ACT_Cost). The utilization most likely to be affected by the intervention will be outpatient and pharmacy-related. For comparability with other studies, however, we will also examine inpatient utilization and costs.[48, 51] Inpatient encounters will include whether there was any inpatient care in the study period, total days in the hospital (DISDAY minus ADMITDAY, DAYS), and total inpatient costs (DCST_TOT). We will also use diagnostic codes to categorize inpatient stays that are hypertension related. The analysis will focus on differences in utilization and costs in the study period but we also will examine costs in the 18 months pre-intervention to check for temporal trends. Specific variables outlined above represent applicable variables as of the time of the initial protocol submission. Because of changing VA data structures, the precise variable names may change over the course of the study. In addition we will evaluate costs from the perspective of both patient and society.

C.20.d. Adherence to Blood Pressure Medication.

We will assess adherence using **prescription refill data**. These data will be extracted from the Durham VistA (electronic health record) system or national VA pharmacy databases that contain pharmacy information

from the VA electronic health record. Commonly used in pharmacoepidemiology, refill data are used to estimate the supply of medications patients have and are often expressed as a Medication Possession Ratio (MPR). In this study, we will use ReComp,[111-113] which was developed and validated using pharmacy refill data. ReComp is more flexible than previous measures in handling longer prescription periods for chronic cardiovascular medications. ReComp also accounts for multiple dimensions of adherence behavior (e.g., late fills, use of overstocked medication) and is more precise than previous refill approaches when used in repeated measures over short time periods. We will utilize ReComp to measure adherence with antihypertensive medication [considered together for adherence]. An aggregate ReComp-based MRP measure will be calculated for each patient by averaging ReComp MPR for individual drug classes covering six month time intervals beginning 1 year prior to patient randomization and continuing during the 18 months of the intervention or booster control. Other methods for calculating medication adherence using prescription refill data may also be examined using the same data.

C. 21. Measures to Increase Understanding of Intervention Mechanisms/Potential Covariates

C.21.a. Self Reported Medication Adherence.

For **self-reported medication adherence** , we selected a modification of a 4-item measure developed by Morisky et al.[114] Respondents are asked to rate their medication-taking behaviors on a scale ranging from 1 (strongly agree) to 4 (strongly disagree). Higher scores reflect lower adherence. The measure will be administered at baseline and at the 6-, 12-, and 18-month study visits. Self-reported adherence is complementary to the secondary outcome measure of medication adherence based on prescription refill data.[115] Endorsing any of the items is considered to indicate nonadherence.

C.21.b.Self-efficacy.

Self-efficacy involves a "judgment of one's abilities to produce given attainments." In the Health Decision Model as discussed in section B.8., individuals who believe they possess the skills necessary to achieve goals are more likely to adopt healthy behaviors.[116] Additionally, self-efficacy has been well studied and applied to diabetes interventions, usually through fostering confidence in behavior change (e.g., weight reduction, physical activity) that enhance outcomes such as glucose control.[117-123] We expect the intervention will improve patients' self-efficacy to change behaviors related to BP control. Thus, we will measure both behavior change and self-efficacy at baseline, 6-, 12-, and 18-month study visits. Self-efficacy for hypertension will be measured using the measures utilized in V-STITCH.[52]

C.21.c. Exercise.

One of the goals of the intervention will be to increase the amount of leisure-time exercise performed by those patients who are not exercising to appropriate standards. Leisure-time activity will be measured by the Short International Physical Activity Questionnaire (IPAQ).[124] The measure will be administered at baseline and at the 6-, 12-, and 18-month study visits.

C.21.d. Body Mass Index.

The sentinel impact of diet on control of both glucose and blood pressure is weight loss,[8, 125] which leads to significant improvement in both those parameters. Therefore, we will use weight as a proxy for success in changing diet, and we will measure weight at baseline, 6-, 12-, and 18-month study visits. We will measure height at baseline, allowing us to use body mass index as an estimate of appropriateness of weight for each individual.

C.21.e. Literacy.

At baseline we will measure health-related literacy by using the Rapid Estimate of Adult Literacy in Medicine (REALM),[126] a brief, well-validated measure of health-related literacy that correlates >0.9 with the criterion standard measure. REALM is associated both with gold standard reading evaluations[126] and, in a recent meta-

analysis, with a number of chronic disease outcomes.[127] If a patient is unable (e.g. patient did not have his or her reading glasses with them) or wishes not to complete the REALM (requires reading a series of words) at baseline, we will offer the REALM at a subsequent study visit.

C.21.f. Social Support.

At baseline, two questions previously used in clinical trials at the Durham VA Medical Center will be used to measure overall social support, which is associated with better chronic illness self-management[128] and BP control.[129]

C.21.g. EQ-5D -5L– is a standardized measure of health status. It provides a simple descriptive profile and a single index value that addresses: mobility, self-care, usual activities, pain/discomfort, anxiety/depression.

C.21.h. Demographics.

We will measure a number of demographic factors that may affect response to the intervention, including race, ethnicity, age, marital status, education level, gender, adequacy of annual income, and number of people living in the household. All will be measured at baseline by patient self-report. If over the course of the study a patient notes a change in this information (e.g. marital status changes), that information may be recorded and used in study analyses.

C.21.i. Comorbidities for Risk Adjustment, Pharmaceuticals, and Smoking Status.

Medical comorbidities and presence of end-stage organ damage influence BP and glycemic control in many ways. The presence of comorbid illnesses will increase patients' medical regimen complexity. This increase in complexity results in patients' increased difficulty remembering and adhering to their medication regimens. Additionally, certain medical comorbidities and end-stage organ damage are indicators of severity of both diabetes and hypertension. Thus, we will assess comorbidities by using the Deyo modification of the Charlson comorbidity index [or equivalent risk adjustment index] (calculated for the year prior to enrollment),[130] utilizing data obtained from **Inpatient and Outpatient Medical SAS Datasets** housed at the VA Austin Information Technology Center [or other equivalent centralized VA data system or the VHA electronic health record]. We will also measure self-reported smoking and alcohol use at baseline, 6-, 12-, and 18-month study visits.

C.21.j. Patient Perception of Organization of their Primary Care.

We will assess patient perception of provision of chronic care with the Patient Assessment of Chronic Illness Care (PACIC). The PACIC is a validated 20-item instrument that measures specific actions or qualities of care that patients report they have experienced in the delivery system. Patients grade each item along a 5-point Likert Scale. The PACIC produces five subscales corresponding to five components of the CCM: 1) patient activation; 2) delivery system design/decision support; 3) goal setting; 4) problem-solving/contextual counseling; and 5) follow-up/coordination.[102, 131, 132] Six items will be added to measure delivery of the 5-As of patient-centered counseling (ask, advise, agree, assist, and arrange) which represents hypothesized optimum self-management support.[102, 132] The measure will be administered at baseline and 18-month study visits.

C.21.k. Berlin Questionnaire – Evaluation of risk of having sleep apnea.

We will use the Berlin questionnaire at the 6 month study visit. For participants who miss their 6 month study visit the interventionist will conduct it prior to the sleep apnea encounter. The questionnaire consists of 3 categories related to the risk of having sleep apnea. Patients can be classified into High Risk or Low Risk based on their responses to the individual items and their overall scores in the symptom categories. Use of the questionnaire is described in the following paper: (Netzer NC, Stoohs RA, Netzer CM, et al. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. Ann Intern Med. 1999; 131: 485–491).

C.22. Data Quality

Use of the electronic data management system, described in section J.1 below, will aid the research assistant (RA) conducting study visit to monitor which data collection instruments and questions have been completed by the patient. Though the computerized auditing procedure, the RA will determine if all questions have been answered. If not, the subject will be given the opportunity to answer questions. As with all study components, the study patient will have the opportunity to decline to answer any questions. Before the end of the study visit, the RA will complete a checklist to ensure that all measurements are completed.

Study implementation and quality assurance methods that we will be employed include: 1) careful scheduling and thorough, timely monitoring of the planned visit schedule to be certain that complete visits do occur; 2) collection of contact information for each participant at each visit; 3) prompt contact and rescheduling of missed study visits; and 4) review and documentation of the reasons for missed visits that do occur. We will also review individual patient data promptly to identify problems or missing values that can be completed by follow-up.

C.23. Patient Compensation

Participants will be paid $15 for participation in each in person study data collection visits (total of 4). This payment may come in the form of cash reimbursement, electronic fund transfer, a VA check, or another form of payment through the VA. If the patient completes all in-person interviews they will receive a total payment of $60. If a patient attends what would be the baseline study visit but cannot be enrolled because he or she has baseline blood pressure indicate hypertension is in control, the patient will be paid $15 that corresponds to the baseline study data collection visit. Patients will not receive reimbursement for other contacts with study staff, including if they choose to participate in a qualitative interview at the end of the study. This payment is comparable to compensation in other related studies conducted at the Durham VAMC.

D. DATA ANALYSIS.

The analysis plans outlined below will be used to addresses the study objectives. Specific statistical methods may be altered based on emerging understanding of statistical science.

D.1. Data Summary

Descriptive statistics, including graphical displays (i.e., frequency distributions and box plots), will be used to summarize all study variables. We will construct individual and mean trajectory plots of the longitudinal outcome variables to understand their general trends over the study period. In addition, we will explore the variability and correlation structure of the longitudinal outcome variables.

D.2. Analysis of Primary Hypothesis

Veterans randomized to the titrated disease management intervention arm will have greater improvement in mean systolic blood pressure over the 18 months of follow-up than veterans randomized to the control arm.

The purpose of the Primary Aim is to examine the impact of titrated disease management on mean systolic blood pressure over 18 months, and the trial is powered to detect a 5 mmHg difference between the two treatment arms (see sample size section D.3 below). As described above, blood pressure will be measured on all patients at baseline, 6, 12, and 18 months of follow up. A general linear model will be used to estimate changes in mean systolic blood pressure over time and test the primary hypothesis.[133] Linear models are a flexible and powerful analytic tool for repeated continuous measures, such as systolic blood pressure.

The predictors in the model will include a time effect and the intervention-by-time interaction. We will use the results from our exploratory graphical methods as well as AIC and BIC fit indices to select the most appropriate way to model time for the two treatment groups over the 18 month follow up.[133] In previous studies, we have generally observed a quadratic trend over time in the intervention group, where patients in the intervention group improve the first half of the study and sustain improvement for the remainder of the study. Other possibilities include a linear trend or categorical (i.e., dummy coded) time. The stratification

variables of baseline level of blood pressure control and diabetes status will also be included. A model with categorical time is shown below in equation (1):

$$SBP = \beta_0 + 6month*\beta_1 + 12month*\beta_2 + 18month*\beta_3 + 6month*IntArm*\beta_4 + 12month*IntArm*\beta_5 + 18month*IntArm*\beta_6 + baselineBPcontrol*\beta_7 + diabetes*\beta_8 + \varepsilon$$

We will use our exploratory descriptive and graphical methods for variability and correlation as well as AIC and BIC fit indices to determine an appropriate covariance structure for to take into account the within-patient correlation between repeated measures over time. [134] In previous studies, we have found that either a random intercept-slope (i.e., growth curve model) specification for the random effects or an unstructured covariance matrix has been most appropriate.

We will estimate the parameters in the model using the SAS procedure MIXED and contrasts will be written in the context of this model to test the treatment difference at month 18. Furthermore, if the intervention-by-time terms in the model are significant, this provides evidence that the difference in systolic blood pressure between the two treatment groups over the 18 months of follow up is not constant, that is, it is time-dependent. This is an omnibus test contrasting the two treatment groups at the 6, 12, and 18 month time points. If this interaction test is significant and if it represents a qualitative , rather than a quantitative effect, this will provide insight into the different time-dependent patterns for each intervention group.[135] As a summary, model estimated means and confidence intervals of systolic blood pressure will be generated at each time point for both treatment groups. Additionally, simultaneous confidence intervals on the treatment group differences will be generated for each time point.

D.3. Sample Size and Power Considerations

The sample size estimate is based on the primary hypothesis: veterans randomized to titrated disease management will have lower mean systolic blood pressure at 18 months than veterans randomized to bi-monthly LPN-delivered telephone calls. A **5 mmHg** improvement at 18 months will be the definition of a minimally clinically significant difference. This represents the differential between the two treatment groups at 18 month; therefore, the power and sample size considerations, apply even if the control group also improves over the 18 month study period (i.e., "placebo" effect). For example, if the control group improves from 145 mmHg to 142 mmHg, we will have adequate power to detect a 5 mmHg differential improvement – the intervention group improves from 145 to 137 mmHg.

Sample size calculations are based on ANCOVA methods as presented in Borm et al.[136] We used data from previous studies to estimate quantities needed for the sample size calculation. We anticipate a common mean systolic blood pressure of 145 mmHg, a standard deviation of 17.5 mmHg in both treatment groups at baseline, and a correlation between time points equal to 0.4. Finally, based on previous studies, we estimate a 15% attrition rate by 18 months. From the calculation, we determined that **we will need to enroll until we randomize 400 patients (200 randomized in each group)** to detect a 5mmHg difference at 18 months with 80% power and a type-I error of 5%. Based on our prior recruitment experience, we consider this to be feasible given the 18 months timeframe (on average 6-7 patients per week), the potential for over 3,800 eligible individuals in Durham and a total of ~7,900 in all Durham affiliated clinics, and the requested resources. We note that these calculations do not reflect that stratification variables will be included in the final analysis model described above. Stratification variables are expected to account for variability in the outcome. The projected sample size analysis is therefore conservative, and we anticipate that there will be greater power to detect between-group differences with this study size.

D.4. Analysis of Secondary Hypothesis – Systolic Blood Pressure Control

Systolic BP control (< 140 mmHg for patients without diabetes and < 130 mmHg for patients with diabetes (different definitions may be modeled as part of sensitivity analyses) will be determined at the 6, 12, and 18 month study visits based on study BP measurements (process described in section C.18). We plan to model the probability of having controlled systolic BP over time and test this secondary hypothesis using generalized linear mixed models as applied in PROC GLIMMIX with adaptive quadrature.[137] The mixed model will include time, the treatment by time interaction (with time dummy coded), and the stratification variables. To account

for the within-patient correlation over time, we have found that either a random intercept-slope (i.e., growth curve model) specification for the random effects or an unstructured covariance matrix is most appropriate.

D.5. Analysis of Secondary Hypothesis - Adherence

Do veterans randomized to the titrated disease management arm have greater medication adherence than veterans randomized to the control arm?

As described in the measures section C.20.d, medication adherence will be calculated by applying the ReComp algorithm to local VA pharmacy records (i.e., medication name, date dispensed, the number of days supply dispensed). ReComp values can be any value greater than or equal to 0, with the range between 0 and 1 representing the proportion of days that a medication was available to the patient, and values over 1 representing oversupply of medication. Medication adherence will be calculated for each veteran at baseline and each month of follow up, so the unit of analysis is the person-month. We will operationalize adherence as both a continuous and dichotomous variable as described above under measures. Examining adherence as a continuous variable (as opposed to dichotomizing adherent vs. not adherent) will allow for assessment of over-supply and the association between over-supply and systolic blood pressure.[115]

The impact of the intervention upon continuous medication adherence will be tested with a general linear model as described above for systolic blood pressure. Again, we will use the SAS procedure MIXED to estimate the model and test the difference in medication adherence at 18 months. We plan to model the probability of being adherent over time and test this secondary hypothesis using generalized linear mixed models as applied in PROC GLIMMIX with adaptive quadrature.[137] The mixed model will include time, the treatment by time interaction (with time dummy coded), and the stratification variables. To account for the within-patient correlation over time, we have found that either a random intercept-slope (i.e., growth curve model) specification for the random effects or an unstructured covariance matrix is most appropriate.

D.6. Health Economic Analyses

If the intervention is found to be effective, is it cost effective?

D.6.a. Effectiveness Measurement.

A continuous outcome measure, reduction in units of mmHg from baseline to 18 months, will be employed to measure the effectiveness of the intervention (see description of the BP measure in section C.18).

D.6.b. Analysis.

The primary objective of the cost-effectiveness analysis will be to estimate the cost per unit difference in effectiveness. The incremental cost effectiveness ratio (ICER) will be calculated as the difference in the average cost per patient between the treatment and control arm divided by the difference in the units of mmHg between the treatment and control arms:

$$ICER = \frac{AVERAGE\ COST_{t=x} - AVERAGE\ COST_{t=0}}{Average\ \text{Re}duction\ mmHg_{t=x} - Average\ \text{Re}duction\ mmHg_{t=0}}$$

Because we will take an all-cost approach, that is, we assume that any costs unrelated to blood pressure or the intervention will be neutral between the treatment and control group, we will carefully examine the data for outliers. For example, there may be high inpatient costs for patients in the intervention group that are attributable to non-hypertension related comorbidities, necessitating a consideration of this in the analysis. As such, in addition to a consideration of all resource utilization costs described, we will run sensitivity analysis in which we will (1) use diagnostic codes in the inpatient files in order to attribute inpatient utilization to treatment of comorbidities associated with chronic hypertension and/or diabetes, running a sub analysis only on this type of inpatient care; (2) remove patients who are outliers and (3) consider outpatient costs and outpatient HTN-related pharmacy costs exclusively. In addition, we will also perform sensitivity analysis of the ICER calculated on two samples: all patients randomized (complying with the intention to treat principles and a subset of all patients who completed the intervention. Sensitivity analyses will also be performed on types of costs: intervention costs, resource utilization costs, and total costs (intervention costs plus resource utilization costs). If there are no differences in resource utilization across arms, we will simply include the intervention

costs in the ICER calculation. All dollars will be expressed in 2011 dollars, using the Consumer Price Index for Medical Care for medical items or Consumer Price Index for other items.

We will use stochastic methods to evaluate variability associated with the cost-effectiveness ratio. If the difference in SBP is significantly higher in an intervention arm relative to the standard care arm, the 95% confidence interval for the base-case cost-effectiveness ratio will be computed with nonparametric bootstrapping using the bias-corrected percentile method (1,000 repetitions).[138, 139] The bootstrapping procedure will allow us to use limited information to estimate the sampling distribution of mean costs per patient, which then will allow us to make inference about the true population sampling distribution of mean costs without making strong distributional assumptions .[140] Using bootstrapped confidence intervals will help us bind our estimates in a way that reduces the influence of outliers. This procedure is relevant for thinking about implementation effects of the intervention, when there will be much larger sample sizes and a ICER not limited by small sample properties.

D.7. Missing Data

Because the main predictors of interest, treatment group and demographics, are collected at baseline, we do not anticipate much missing data in these variables. There may be missing values in the outcome measures due to drop-out, a missed interim assessment, or item non-response. Given a thorough understanding of the missing data mechanism, it is possible to use all of the available information in analysis, rather than using only subjects with completely observed information. Our main analysis technique, general linear models via maximum likelihood estimation, implicitly accommodates missing data when the response is Missing At Random (MAR) [141]; that is, when missing data is due either to treatment, to prior outcome, or to other baseline covariates included in the model. Therefore, inferences will be valid even if we have differential dropout by treatment group. Depending on the type and scope of missing data, we will also explore multiple imputation as a strategy to use in conjunction with our primary analytic tools. Finally, following recent guidelines published by the National Research Council's Panel on Handling Missing Data in Clinical Trials, we will conduct sensitivity analyses with sets of pattern-mixture models to examine the degree to which our primary analyses and inferences are dependent upon missing data assumptions.[142]

D.8. Intention-to-Treat Analysis

All of the proposed primary and secondary analyses focus on the effect of the intervention group as compared to the control group. We, therefore, plan to use the Intention-to-treat assumption for all analyses. In this assumption, patients are analyzed as part of the group to which they are randomized, regardless of treatment compliance.

D.9. Exploratory Analyses

We will also examine predictors/covariates that may explain for which individuals the intervention is more effective. For example, prior work suggests that African Americans are more likely to have greater improvements in SBP/DBP than whites participating in diseases management studies.[143] These analyses may include examining the impact of the intervention on additional clinical outcomes available through the VA electronic health record or related linked administrative data (e.g. impact of the intervention of hemoglobin A1c for patients with diabetes).

We will also collect data via the VA electronic health record or related linked administrative data on healthcare events for the full sample from the study. While we are not likely to be powered to detect differences in healthcare events, these analyses may provide preliminary data and power calculations for future studies. These data will also allow for long-term examination of the impact of the intervention on clinical and economic outcomes. With appropriate informed consent and HIPAA authorization, clinical and utilization data from VA electronic health record or related linked administrative data may be obtained for the period prior to or after study enrollment.

Linked data that may be obtained with appropriate informed consent and HIPAA authorization includes information from linked Medicare and/or Medicaid files for patients with corresponding healthcare coverage.

E. POTENTIAL DIFFICULTIES AND LIMITATIONS

We are proposing to randomize 400 individuals. However, based upon our prior experience, we will be able to achieve our recruitment goals using multiple techniques established in our prior studies: 1) the Durham VAMC has a large pool of potentially eligible patients (~7,900 patients, including ~3,800 in Durham based on most recent quality improvement figures); 2) the COE's research assistants have experience working with veterans and have worked with the VAMC clinics previously; 3) all material has been examined for culturally sensitivity. These methods and past experience have led to very high recruitment rates in previous studies and surpass the proportion of minorities and vulnerable individuals found in the local community. An additional challenge is the number of intervention components that individuals may receive including both behavioral and medication management. In general, evidence does not suggest 'one size fits all' and in the context of hypertension, there are a number of behaviors involved that patients need to address. We propose to examine the use of specific components of the intervention.

F. STUDY STRENGTHS

Although several clinical trials have demonstrated the efficacy of utilizing various combinations of behavioral phone calls, home monitoring, and pharmaceutical management in reducing systolic blood pressure, these previous studies relied on single protocols for all patients in the studies that did not vary based on patient outcomes during the study.[6, 9-11] While very appropriate for efficacy studies aimed at establishing evidence for new interventions, these traditional methods do not necessarily answer the key question of whether it is possible to titrate the resource intensity of such disease management components as would be done in clinical practice. As a result, we are proposing a pragmatic clinical trial of titrated disease management. In a pragmatic trial, clinicians must follow a specific protocol (e.g., titration algorithm, standardized scripts for phone calls, medication management algorithms). However, specific patients will receive services that are in line with the protocol, not specifically the same exact services or drugs. This more closely approximates clinical care.

As described in section B.7, the study team has extensive experience conducting disease management trials. Previous projects demonstrate an ability to: 1) recruit patients; 2) follow patients through the intervention, and 3) analyze results. We look forward to extending previous work through a pragmatic trial aimed at addressing a question critical to the VA: can we develop a system for titrating the resource intensity of disease management so that patients receive appropriate care within resource constraints?

G. DISSEMINATION OF STUDY RESULTS

The proposed research recognizes that healthcare systems have limited resources to meet the many goals involved in helping patients. The purpose is to examine whether having a titrated disease management program based on clinically reasonable triaging criteria leads to better disease control than booster behavioral telephone calls conducted on top of usual care. As a result, the proposed research is designed with potential implementation in mind and holds promise for improving patients' CVD control and meeting the VA's BP goals. For the research to have an impact, stakeholders, and those in position to effect change based on the work, must be aware of projects from initiation through publication. This sets the stage for rapid more widespread implementation of resulting innovations in care. In the case of the proposed study, like others conducted by this research team, ongoing dissemination throughout the project will allow other researchers engaged in intervention research to learn from experiences of the research team.

We have attached letters of support from representatives of the Stroke, Diabetes, and Ischemic Heart Disease QUERIs and Durham VAMC Associate Chief of Staff for Ambulatory Care. In addition, the Co-Clinical Coordinator of the IHD QUERI is a co-investigator (Dr. Ho). The established relationship with these groups will allow us to consult with QUERI leadership on the process of implementing study and actively building relationships with VA stakeholders should the intervention under study prove to be effective. In our own facility, we will work with the ACOS for Ambulatory Care to plan for how our project may impact to workflow of the clinic, increasing both the likelihood of successful conduct of the trial and future implementation. We have also attached a letter of support from the national director of VA clinical cardiology supporting the intervention as one that should be considered for widespread implementation should it be effective/cost-effective.

The study team has a great deal of implementation experience in and outside of the VA. For example, the PI served as served as the Project Director for the treatment measurement aspects of the Colorectal Cancer

Care Collaborative (C4). C4 was a partnership between Health Services Research & Development, Office of Quality and Performance, Systems Redesign (formerly Advance Clinic Access) program, Office of Patient Care Services, and Office of the Deputy Under Secretary for Operations and Management.[144, 145] Dr. Jackson also conducted analysis of data for a special study of the VA External Peer Review Program (EPRP) on the quality of colorectal cancer care. In addition, Drs. Bosworth and Jackson are conducting the Hypertension Telemedicine Nurse Implementation Project for Veterans (HTN-IMPROVE) project which is seeking to understand the process of implementing nurse-delivered telephone self-management support in three VA Medical Centers (funding of surveys and qualitative interviews via RRP-09-198, Dr. Jackson, PI; Dr. Bosworth, Co-PI).[146] We are also conducting a study to examine longer-term outcomes of previous clinical trials so that we can better understand potential patient needs that may surface during the implementation of self-management support programs (funded via RRP-09-407, Dr. Jackson PI; Drs. Edelman and Bosworth, Co-Is).

Results from this grant will be disseminated in journal articles, other written reports, and presentations at national, state, and local conferences and meetings.

H. PROJECT MANAGEMENT PLAN

H.1. Resources and Facilities Required

This team already has the majority of resources and facilities needed. We have identified the sites and have begun developing relationships with these locations.

H.2. Overview of Administration Plan

The proposed study will be administered through the Durham HSR&D Center of Excellence. The investigators have an extensive history working together and hold various academic appointments in the Duke Division of General Internal Medicine, Departments of Psychiatry and Biostatistics and Bioinformatics, and School of Nursing at Duke University Medical Center and Department of Health Policy and Management in the School of Public Health at the University of North Carolina at Chapel Hill. Prior to beginning the study, IRB approval will be obtained.

H.3. Anticipated Time Table for Funded Grant

We propose a **four-year** study. Work on how to select potential subjects, abstract appropriate data, developing training material has already occurred. There will be 6 months to hire and train staff, 15 months for enrollment, and 18 months of intervention follow-up. The final 9 months of the grant will be devoted to data analysis. The first 3 of these months will be devoted to examining clinical and adherence outcomes. Cost data analysis as well as preparing reports will occur in the final 6 months of the study.

Table 5: Study Gantt Chart (i.e. anticipated study timeline during grant funding)

	YEAR 1				YEAR 2				YEAR 3				YEAR 4			
	Q 1	Q 2	Q 3	Q 4	Q 1	Q 2	Q 3	Q 4	Q 1	Q 2	Q 3	Q 4	Q 1	Q 2	Q 3	Q 4
Project Start Up																
Higher Study Staff	X	X														
Train staff	X	X														
Finalizing computerized intervention modules	X	X														
Intervention Implementation																
Pilot process for enrolling patients ~ 10 patients			X													
Enrolling Patients in Intervention			X	X	X	X	X									
Delivery of 18-Month Intervention				X	X	X	X	X	X	X	X	X	X			
Data Analysis																
Planning for data analysis													X			
Data analysis and paper preparation														X	X	X

I. HUMAN SUBJECTS

The study will be conducted according to Good Clinical Practice guidelines, the U.S. Code of Federal Regulations (CFR) Title 21 CFR (Part 16 – Protection of Human Subjects and Part 56 – Institutional Review Boards), VHA Handbook 1200.05, the Declaration of Helsinki, and other applicable regulations and laws. **This protocol will be submitted to the Durham VA Medical Center Institutional Review Board for approval.** The informed consent of each subject will be obtained in accordance with 21 CFR Part 50 and the Declaration of Helsinki before protocol-specified procedures are carried out.

Informed consent and **waiver of HIPAA authorization** will be obtained using an informed consent form and waiver of HIPAA authorization form that will be used after approval of the Durham VA Medical Center Institutional Review Board. A copy of the informed consent will be scanned into the VA electronic medical record.

I.1. Sources of Materials

The procedures for obtaining research material for the study include anthropometric and BP measurements, medical records, interviews, and self-completed questionnaires. Trained and certified professional staff will obtain all data according to detailed study protocols. Data will be collected directly from study participants, medical records, and used specifically for research purposes.

I.2. Potential Risks

Blood pressure. All participants will have HTN and receive regular medical care from clinics affiliated with the Durham VA Medical Center. The study intervention is likely to lower BP. However elevated BP or low BP may be noted by study personnel as a result of study measurements or home BP monitoring.

Physical activity. Patients receiving the disease management intervention are encouraged to increase their physical activity, raising the possibility of musculoskeletal injury or unmasking of heart disease.

Food. Participants receiving information though the diet phone call module will be encouraged to try new foods, raising the possibility of allergic reactions. In addition, participants will be encouraged to increase intake of dairy products, possibly leading to symptoms of lactose intolerance.

Breach of patient confidentiality. There is a small risk that unauthorized persons could get access to personal or study-related patient information.

I.3. Adequacy of Protection Against Risks

The specific risks of participation in this study are noted above; procedures for protection follow. Study personnel will not be responsible for the clinical care of the participants and participants will be made aware of this delineation of responsibility. Participants will be referred to their primary provider if any clinical problem is detected.

Blood Pressure.

Certain extreme BP values, both high and low, carry an urgent risk of major complication. As a result, if the most recent BP measurement is reported during a patient phone call, at a study data collection visit, or during other contact between study clinical staff and a patient is at one of these extremes, we will advise patients to take specific actions to minimize those risks. For SBP ≥ 180 mmHg or DBP ≥110mmHg, we will advise the patient to contact her/his triage nurse (or other similar position) within 24-48 hours. If a patient is advised to contact the triage nurse, a note will be placed in the patient's medical record. For participants that have moved care to a different VA facility (as described in section C.3.b) we will advise patient to contact her/his triage nurse (or other similar position) but not put a note in their medical record. This level corresponds to JNC 7 classification of Stage 3 hypertension and are the safety criteria currently used by our data safety monitoring board in TCYB and TEACH-DM. For SBP ≥ 210 mmHg or DBP ≥ 120 mmHg, or SBP ≤90 mmHg and/or DBP

≤40, we will advise the patient to seek immediate care. For all instances in which we recommend seeking immediate care, we will put a note that requires PCP co-signature in the patient's medical record. For participants that have moved care to a different VA facility (as described in section C.3.b) we will advise patient to go to the emergency room or urgent care facility but not put a note that requires PCP co-signature in their medical record (because it is not possible to require co-signatures of providers from another facility).

Physical Activity. Risks from increased physical activity will be minimized by encouraging moderate rather than vigorous activity. If an exercise-related symptom is reported to the interventionist during phone calls, the interventionist advise participants to get clearance from their primary care provider before they can restart physical activity.

Food. Risks from trying new food as a result of diet suggestions will be minimized by encouraging individuals who have previously become sick after eating dairy products or other specific foods mentioned to patients not to resume eating such items without consulting their primary care provider. Further, patients will be told not to continue eating new foods if they become sick or experience an allergic reaction.

Data Confidentiality. The Durham HSR&D COE conducts computer operations in its secure Centralized Computing Facility managed by VA OI&T network and server administrators. In the Center's computing facility, all research data are stored on VA-Administered servers which are physically secured in a Durham VAMC server room. VA network access to research data is controlled in accordance with the Center's Standard Operating Procedures and VA policies and in cooperation with the Durham VAMC IRB. The utilization data will be downloaded directly from national files to the VA network and servers administered by the Durham HSR&D COE. The master's statistician will have exclusive access to these files and they will not be moved from this secured folder and network environment.

Confidentiality will be assured through several mechanisms. First, each participant will be assigned an anonymous study ID which will be used on all study forms. Second, all study records that contain participant information will be kept in secured, locked areas when not in use. In addition, such materials, when in use, will be kept away from public scrutiny. Third, access to all participant data and information will be restricted to authorized personnel. In the case of computerized study data, access to data will be password protected, and staff members will be assigned individualized passwords and permissions that allow them access to only those elements of the data management system to which they are authorized. In addition, all study personnel will maintain certification with the Durham VAMC IRB that they have completed training in research ethics and confidentiality. Finally, participants will not be identified by name in any reports or publications, nor will data be presented in such a way that the identity of individual participants can be inferred.

I.4. Anticipated Adverse Events

Because of the increased risk of these patients for cardiovascular and other diseases, it is expected that these patients will have a variety of episodes related to cardiovascular and related diseases such as diabetes. Such complications would be expected to occur in the absence of the intervention. These may include, but are not limited to, heart attack, stroke, and complications of diabetes among those patients with the disease. Because of the advanced age of many patients enrolled in clinical trials in the VA setting, it can be expected that other conditions related to aging may occur that would occur without the presence of the intervention. This includes, but is not limited to, the diagnosis of cancer and dementia. Further, while patients will be encouraged to not smoke and limit alcohol intake, those patients who smoke, drink alcohol, or take illicit drugs would be expected to have related complications. This includes, but is not limited to, development of disease of the lung or liver.

I.5. Procedures for Assessing Immediate Patient Risks.

During each scheduled encounter between a patient and study interventionist, immediate patient risks will be assessed via brief clinical questions asked by the interventionist. Emergent concerns will require referral to emergency care for immediate medical attention, usually by having the patient call 911. These include active chest pain, typical cardiac chest pain of duration > 10 minutes within the last 24 hours, dyspnea, SBP ≥ 220

mmHg, DBP ≥ 120 mmHg, SBP ≤ 90 with lightheadedness, heart rate ≥ 120, heart rate ≤ 50 with lightheadedness, new severe generalized or focal weakness, and altered mental status. In response to all other concerns not related to blood pressure the patient will be urged to contact his/her PCP.

I.6. Potential Benefits to Subjects and Others.

Potential benefits for study participants include improved lifestyle, improved control of BP, and consequent reduction in cardiovascular risk. An additional benefit for some participants may be personal satisfaction in being part of a study that may have major public health implications for the VA and community. No benefit from participation can be guaranteed. Potential benefits to others include the possibility that this research will lead to a better understanding of how to match resources for disease management programs to the clinical needs of patients.

I.7. Importance of Knowledge to be Gained.

The proposed research would examine whether a disease management program that is titrated by matching the intensity of resources to patients' disease control leads to superior outcomes compared to a low-intensity management strategy. Using a pragmatic clinical trial, this study would provide important evidence of a clinically-sensible disease management program that has the potential for widespread implementation, especially as the VA adopts the patient-centered medical home.

I.8. Data and Safety Monitoring Plan.

During the course of the study the investigators will monitor the integrity of data collection and monitor for adverse events. We do not anticipate any real harm to patients, but adverse event forms will be used to report all unanticipated events. The following information will be included in the report: date of event, attribution to intervention, and outcome of adverse events. Death will be reported within 24 hours. Unanticipated adverse events will be reported within 5 business days. Reports will be submitted via overnight courier or facsimile to the Durham VAMC IRB and VA HSR&D. A written follow-up will be submitted within 30 calendar days. All adverse events (serious or not, related or unrelated, anticipated or unanticipated) will be reported in the annual report to the Durham VAMC IRB and VA HSR&D.

I.9. Inclusion of Women.

The study has a target of enrolling until we randomizing 400 patients. The 400 number is based on the potential number of patients to be randomized. The intervention will be delivered to both male and female patients. There will be no inclusion/exclusion criteria based on gender. Approximately 8% of primary care patients at the Durham VAMC are women. We expect that this will be the approximate percentage of female patients that will be enrolled in the study.

I.10. Inclusion of Minorities.

There will be no inclusion or exclusion criteria based on race or ethnicity. Our research team also has a track record of successful minority recruitment. Investigators on this study have conducted numerous clinical trials and other studies that have recruited between 44% and 59% minority patients, primarily African American, at the Durham VAMC and surrounding community.

I.11. Inclusion of Children.

An eligibility criterion for the study is being ≥ 18 years of age. Children are excluded from this study for two primary reasons. First, although we acknowledge the importance of lifestyle modification for preventing and treating hypertension in children, diagnostic and therapeutic approaches are different in this group. Second,

there is insufficient evidence that tailored lifestyle modification programs such as the one proposed are appropriate for children (e.g., calorie restriction for weight loss).

I.12. Intended/Potential Use of Data and Study findings.

The proposed research recognizes that healthcare systems have limited resources to meet the many goals involved in helping patients. The purpose is to examine whether having a titrated disease management program based on clinically reasonable triaging criteria leads to better disease control than booster behavioral telephone calls conducted on top of usual care. As a result, the proposed research is designed with potential implementation in mind and holds promise for improving patients' CVD control and meeting the VA's BP goals.

These data will also allow for long-term examination of the impact of the intervention on clinical and economic outcomes. With appropriate informed consent and HIPAA authorization, clinical and utilization data from VA electronic health record or related linked administrative data may be obtained for the period prior to or after study enrollment.

Results from this grant will be disseminated in journal articles, other written reports, and presentations at national, state, and local conferences and meetings. In addition, study investigators will work with officials of the Veterans Health Administration to ensure that lessens from this study are disseminated to the VA healthcare system.

J. INFORMATION SECURITY, DATA MANAGEMENT, DATA USE, AND PRIVACY

J.1. Data Management Procedures

The information technology solution that will serve to facilitate research activity will be based on a series of asynchronously connected database applications over which a comprehensive data model will be deployed. Each database application will function independently as a discrete system. All data transactions within and between subsystems will run through controlled, secure transactions to ensure the preservation of database integrity and privacy. Study data will be maintained on secure servers for the duration of the study and for a period of time after the completion of the study that will be compliant the VA regulations at the time of study closure. All study data will be backed up on a nightly, monthly, and annual schedule. These provisions are made in compliance with VHA Handbook 1200.05 and VHA Handbook 1605.1. Data will be used for screening purposes, evaluating treatment arm titratrations and for study analysis.

All server hardware has built-in redundant systems. Technicians will constantly monitor server hardware, operating system and database service performance. Workstations, laptops, and any other mission-critical devices will receive periodic booster support in order to ensure high performance and secure operation. The primary database engine technology will be a Microsoft SQL Server. All automated systems will be implemented in DTS and run using the Microsoft SQL Server Management Agent. Automated processes will be monitored daily. The system will be configured to notify the HSR&D IT Group if an automated process fails to run successfully. The data collected during in-person interviews will be entered directly into our third party survey application named "DatStat Illume" running on an encrypted, password-protected laptop (www.datstat.com/). This survey application has been developed using Microsoft Visual Studio Visual Basic Net. On the laptop, data will be stored in a series of XML files until it is synchronized with the Illume server. We have chosen DatStat Illume because of industry standard acceptance as a reliable and flexible method for collecting and storing research survey information. DatStat Illume is a computer product used throughout the Durham HSR&D Center of Excellence. If the HSR&D Center of Excellence works with appropriate VA authorities to change to another software package with equivalent security features, this study would make the change as required by the Durham HSR&D Center of Excellence.

All data collected can be exported into a number of standard formats such as SAS, MS Access, and SQL Server. Laptop data will be synchronized with the server a daily basis. Also, server data will be backed up on a daily basis as well. We have used similar methods of data entry in our prior studies, and internal audits show excellent reliability.

The **data collection for the qualitative interviews** will be conducted from an office/meeting room at the Durham VAMC. The phone call will be recorded on a VA owned and configured computer that is connected to the Durham VAMC computer network. This will allow data to be stored directly on a Durham VAMC HSR&D

server. Voice recorder has no ability to store information. Data will be stored on a VA HSR&D server that is compliant with regulations described in VA Directive 6500 and located on the VA FISMA certified network. The servers are located within the VA protected environment (i.e. behind the VA fire wall). Physical access to the servers is limited to authorized VA OI&T personnel in accordance with VA directive 6500. Only HSR&D study staff at the Durham VAMC will have access to data stored on the server. Research records will be maintained only for the period of time required by VHA regulations. Information from this study will be shredded in accordance the VA requirements for destruction of sensitive information in accordance with the record control schedule and information from this study in electronic format will be deleted or purged from data files in accordance with the VA record control schedule. The storage capacity of the data storage device is 2.7 TB and the size of individual electronically stored record is approximately 500mb.

J.1.a. Primary Data Extraction.

The initial patient sample for the study will be extracted by an automated request from the VA electronic health record. The Durham VAMC MUMPS programmer or other member of the study staff with appropriate credentials will write code necessary to develop a list of patients meeting initial screen criteria outline above. It will be used to identify and screen participants to participate in the primary study. The data extract and all related patient level information is stored on a secure computer server located in the offices of the Durham VAMC HSR&D Center of Excellence. The authorized study staff will have exclusive access to these files and they will not be moved from this secured folder and network environment.

For patients enrolled in the intervention arm of the study, clinic blood pressures will be extracted nightly from the Durham VAMC electronic health record or other appropriate data base (such as the VISN data warehouse). The MUMPS programmer or other member of the study staff with appropriate credentials will write code necessary to capture BP readings of enrolled patients so that appropriate disease management titration can occur. The blood pressures will be placed on a secure server at the Durham VAMC located behind the VA firewall. Data will then be moved into the study intervention software with all data stored on a secure computer server behind the VA firewall located in the offices of the Durham HSR&D Center of Excellence.

J.1.b. Primary Data Collection.

Blood pressure and survey data will be collected by an authorized member of the study staff using VA issued laptops or desktops that meet applicable regulations for updates, encryption and information security. Data collection will occur at the Durham VAMC or affiliated CBOC, clinic location, or research location. When network connectivity is available, survey answers are recorded directly to the HSR&D servers. When connectivity is not available, the "Remote Data Collection" option of the HSR&D owned Illume software (or similar option available in software used by the Durham HSR&D Center at the time of data collection), which requires a password for access, will be used to record survey answers on a VA issued laptop or desktop that meet applicable regulations for updates, encryption and information security, after which the data is uploaded to the HSR&D servers at the earliest practicable opportunity. If computer resources are not available during the study visits, applicable data collection may occur using paper forms, after which the data will be entered into a database on the HSR&D computer servers at the earliest practicable opportunity. Paper records/forms created at interviews are transported back to the office of the Durham HSR&D Center, where they will be stored in a locked location.

The qualitative interview will be collected using voice recorders directly connected to VA issued laptops or desktops that meet applicable regulations for updates, encryption and information security. The "Sparky" USB audio recorder is a pass through audio recorder which does not store any data. Software is required for this device which is installed and configured by VA OI&T personnel after sanctuary exemptions have been obtained. Transcription of the qualitative interviews will be conducted utilizing VA approved software installed and configured by VA OI&T personnel after sanctuary exemptions have been obtained.

All research paper and electronic records, including interviews, and audio recordings, will be in the care of Dr. Jackson. They will be safeguarded under lock and key at locations managed by the Durham VA Medical Center . Data could be stored at any of the following locations where records are maintained by HSR&D: Legacy Tower, Durham, NC floors 6 and/or 7, the E-Wing of the Durham VAMC, and in HSR&D office space currently located in room 1C214 at the Greenville HCC. HSR&D administrative staff and OI&T maintain a log

of where all study files are kept and can provide specific locations for paper records upon request. Study data storage involves computer files that are password protected and saved on the p drive in an electronic folder named TDMTrial.

Files containing names and addresses have separate passwords and will be accessible only to personnel who need to contact subjects. All survey data will be obtained using a VA owned and configured encrypted laptop or desktop computer that is connected to the Durham VAMC computer network. This will allow all data to be stored directly on the Durham VAMC HSRD server that is compliant and with regulations and located on the VA Federal Information Security Management Act (FISMA) certified network. In the Center's computing facility, all research data are stored on VA-Administered servers which are physically secured in a Durham VAMC server room. VA network access to research data is controlled in accordance with the Center's Standard Operating Procedures and VA policies and in cooperation with the Durham VAMC IRB.

J.1.c. Intervention Software.

The interventions will conduct the intervention calls and/or make medication changes using a Durham VAMC HSR&D created intervention application. The survey answers are recorded directly to Durham VAMC HSR&D computer servers located behind the VA firewall. This survey application has been developed using Microsoft Visual Studio Visual Basic .Net. This intervention tool provides a reliable and flexible method for collecting and storing research survey information. All data collected can be exported into a number of standard formats including SAS, MS Access, and SQL Server. Also, server data will be backed up on a daily basis as well.

J.1.d. Supplemental Data Extraction.

In order to complete health economic, medication adherence, and exploratory analyses, we will extract data from the VA electronic health record or related linked administrative data on healthcare events for the full sample from the study. With appropriate informed consent and HIPAA authorization, clinical and utilization data from VA electronic health record or related linked administrative data may be obtained for the period prior to study enrollment.

The extracted data will be stored on a VA HSR&D server that is compliant with regulations described in VA Directive 6500 and located on the VA FISMA certified network. The servers are located within the VA protected environment (i.e. behind the VA fire wall) and are physically located within the secured server room at the offices of the Durham VAMC HSR&D Center of Excellence. Physical access to the servers is limited to authorized VA OI&T personnel in accordance with VA directive 6500. Only HSR&D study staff at the Durham VAMC will have access to data stored on the server. All staff has and maintain VA required training, maintain study data exclusively on HSR&D servers, follow accepted security practices such as locking computer with CTRL-ALT-DEL when not at the computer, and adhere to other regulations laid out in VA Directive 6500. Destruction of data will be done in accordance with all VA and VHA records disposition requirements.

J.2. Data Security and Confidentiality

The Durham VAMC HSR&D Center of Excellence has developed Standard Operating Procedures for data security which have been designed to protect against data loss and maintain patient confidentiality. These procedures have been used in many studies and we will adhere to these procedures for the proposed study. The Durham HSR&D COE conducts computer operations in its secure Centralized Computing Facility managed by VA OI&T network and server administrators. In the Center's computing facility, all research data are stored on VA-Administered servers which are physically secured in a Durham VAMC server room. VA network access to research data is controlled in accordance with the Center's Standard Operating Procedures and VA policies and in cooperation with the Durham VAMC IRB. The utilization and other centralized data will be downloaded from national files or the local electronic health record to the VA network and servers administered by the Durham HSR&D COE and/or Durham OI&T. The authorized study personnel will have exclusive access to these files and they will not be moved from this secured folder and network environment.

Confidentiality will be assured to the greatest degree possible through several mechanisms. First, each participant will be assigned an anonymous study ID which will be used on study forms that do not require the

using of the patient name and/or Social Security Number (e.g. informed consent form). Second, all study records that contain participant information will be kept in secured, locked areas when not in use. In addition, such materials, when in use, will be kept away from public scrutiny. Third, access to all participant data and information will be restricted to authorized personnel. In the case of computerized study data, access to data will be password protected, and staff members will be assigned individualized permissions that allow them access to only those elements of the data management system to which they are authorized. In addition, all study personnel will maintain certification with the Durham VAMC IRB that they have completed training in research ethics and confidentiality. Finally, participants will not be identified by name in any reports or publications, nor will data be presented in such a way that the identity of individual participants can be inferred.

J.3. Data Storage Location

All research paper and electronic records, including interviews, and audio recordings, will be in the care of Dr. Jackson. They will be safeguarded under lock and key at locations managed by the Durham VA Medical Center . Data could be stored at any of the following locations where records are maintained by HSR&D: Legacy Tower, Durham, NC floors 6 and/or 7, the E-Wing of the Durham VAMC, and in HSR&D office space currently located in room 1C214 at the Greenville HCC. HSR&D administrative staff and OI&T maintain a log of where all study files are kept and can provide specific locations for paper records upon request. Study data storage involves computer files that are password protected and saved on the p drive in an electronic folder named TDMTrial.

Study data storage involves computer files that are password protected. Files containing names and addresses have separate passwords and will be accessible only to personnel who need to contact subjects. All survey data will be obtained using a VA owned and configured encrypted laptop or desktop computer that is connected to the Durham VAMC computer network. This will allow all data to be stored directly on the Durham VAMC HSRD server that is compliant and with regulations and located on the VA Federal Information Security Management Act (FISMA) certified network.

When computer connectivity is not available, the "Remote Data Collection" option of the HSR&D owned Illume software (or similar option available in software used by the Durham HSR&D Center at the time of data collection), which requires a password for access, will be used to record survey answers on a VA issued laptop or desktop that meet applicable regulations for updates, encryption and information security, after which the data is uploaded to the HSR&D servers at the earliest practicable opportunity. If computer resources are not available during the study visits, applicable data collection may occur using paper forms, after which the data will be entered into a database on the HSR&D computer servers at the earliest practicable opportunity. Paper records/forms created at interviews are transported back to the office of the Durham HSR&D Center, where they will be stored in a locked location.

To provide the greatest possible assurance that inadvertent disclosure will NOT take place, analytic data files are organized by study ID number and have no names or social security numbers attached. The linking file will be stored separately. During the intervention, authorized study staff will need to have access to patient contact information, name, and Social Security to conduct and support the intervention. The number of individuals having access to this data will be minimized.

All databases are secured with password protection to prevent unauthorized access and paper copies of information are kept in locked file cabinets. The paper research records will be shredded in accordance with the VA record control requirements for destruction of sensitive information. Information in the electronic format will be deleted or purged from data files in accordance with VA record control requirements It is not anticipated that research data will be removed from the VA protected environment; however research forms and information may need to be transported between VA medical centers (e.g. from Raleigh CBOC to HSR&D offices).

K. REFERENCES

1. Roland M, Torgerson DJ. What are pragmatic trials? *BMJ.* Jan 24 1998;316(7127):285.
2. Thorpe KE, Zwarenstein M, Oxman AD, et al. A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. *J Clin Epidemiol.* May 2009;62(5):464-475.
3. Maclure M. Explaining pragmatic trials to pragmatic policymakers. *J Clin Epidemiol.* May 2009;62(5):476-478.
4. Program Announcement: HSR&D Priorities for Investigator-Initiated Research. http://www.hsrd.research.va.gov/funding/HSRD-IIR-Priorities-2011.pdf. Accessed October 29, 2010.
5. IOM. *Initial National Priorities for Comparative Effectiveness Research.* Washington, DC: The National Academies Press; 2009.
6. Bosworth HB, Olsen MK, Dudley T, et al. Patient education and provider decision support to control blood pressure in primary care: a cluster randomized trial. *Am Heart J.* Mar 2009;157(3):450-456.
7. Bosworth HB, DuBard CA, Ruppenkamp J, Trygstad T, Hewson DL, Jackson GL. Evaluation of a self-management implementation intervention to improve hypertension control among patients in Medicaid. *Translational Behav Med.* in press.
8. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA.* May 21 2003;289(19):2560-2572.
9. Bosworth HB, Olsen MK, Grubber JM, et al. Two self-management interventions to improve hypertension control: a randomized trial. *Ann Intern Med.* Nov 17 2009;151(10):687-695.
10. Piette JD, Weinberger M, McPhee SJ, Mah CA, Kraemer FB, Crapo LM. Do automated calls with nurse follow-up improve self-care and glycemic control among vulnerable patients with diabetes? *Am J Med.* Jan 2000;108(1):20-27.
11. Edelman D, Fredrickson SK, Melnyk SD, et al. Medical clinics versus usual care for patients with both diabetes and hypertension: a randomized trial. *Ann Intern Med.* Jun 1 2010;152(11):689-696.
12. Yu W, Ravelo A, Wagner TH, et al. Prevalence and costs of chronic conditions in the VA health care system. *Med Care Res Rev.* Sep 2003;60(3 Suppl):146S-167S.
13. Jackson GL, Edelman D, Weinberger M. Simultaneous control of intermediate diabetes outcomes among veterans affairs primary care patients. *J Gen Intern Med.* Oct 2006;21(10):1050-1056.
14. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet.* Jun 13 1998;351(9118):1755-1762.
15. Adler AI, Stratton IM, Neil HA, et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. *BMJ.* Aug 12 2000;321(7258):412-419.
16. Standards of medical care in diabetes--2009. *Diabetes Care.* Jan 2009;32 Suppl 1:S13-61.
17. Von Korff M, Tiemens B. Individualized stepped care of chronic illness. *West J Med.* Feb 2000;172(2):133-137.
18. McFarland KF. Type 2 diabetes: stepped-care approach to patient management. *Geriatrics.* Oct 1997;52(10):22-26, 35, 39.
19. Von Korff M, Gruman J, Schaefer J, Curry SJ, Wagner EH. Collaborative management of chronic illness. *Ann Intern Med.* Dec 15 1997;127(12):1097-1102.
20. Radin AM, Black HR. Hypertension in the elderly: the time has come to treat. *J Am Geriatr Soc.* May 1981;29(5):193-200.
21. Gjerdingen D, Katon W, Rich DE. Stepped care treatment of postpartum depression: a primary care-based management model. *Womens Health Issues.* Jan-Feb 2008;18(1):44-52.
22. Zatzick D, Roy-Byrne P, Russo J, et al. A randomized effectiveness trial of stepped collaborative care for acutely injured trauma survivors. *Arch Gen Psychiatry.* May 2004;61(5):498-506.

23. Lin EH, VonKorff M, Russo J, et al. Can depression treatment in primary care reduce disability? A stepped care approach. *Arch Fam Med.* Nov-Dec 2000;9(10):1052-1058.
24. Katon W, Von Korff M, Lin E, et al. Stepped collaborative care for primary care patients with persistent symptoms of depression: a randomized trial. *Arch Gen Psychiatry.* Dec 1999;56(12):1109-1115.
25. Wagner EH. Chronic disease management: what will it take to improve care for chronic illness? *Eff Clin Pract.* Aug-Sep 1998;1(1):2-4.
26. Gilbody S, Bower P, Fletcher J, Richards D, Sutton AJ. Collaborative care for depression: a cumulative meta-analysis and review of longer-term outcomes. *Arch Intern Med.* Nov 27 2006;166(21):2314-2321.
27. Walsh JM, McDonald KM, Shojania KG, et al. Quality improvement strategies for hypertension management: a systematic review. *Med Care.* Jul 2006;44(7):646-657.
28. Tsai AC, Morton SC, Mangione CM, Keeler EB. A meta-analysis of interventions to improve care for chronic illnesses. *Am J Manag Care.* Aug 2005;11(8):478-488.
29. Laragh JH. Modification of stepped care approach to antihypertensive therapy. *Am J Med.* Aug 20 1984;77(2A):78-86.
30. Glynn LG, Murphy AW, Smith SM, Schroeder K, Fahey T. Interventions used to improve control of blood pressure in patients with hypertension. *Cochrane Database Syst Rev.* 2010;3:CD005182.
31. Boulware LE, Daumit GL, Frick KD, Minkovitz CS, Lawrence RS, Powe NR. An evidence-based review of patient-centered behavioral interventions for hypertension. *Am J Prev Med.* Oct 2001;21(3):221-232.
32. Schroeder K, Fahey T, Ebrahim S. How can we improve adherence to blood pressure-lowering medication in ambulatory care? Systematic review of randomized controlled trials. *Arch Intern Med.* Apr 12 2004;164(7):722-732.
33. Weinberger M. Telephone-based interventions in outpatient care. *Ann Rheum Dis.* Apr 1998;57(4):196-197.
34. Stead LF, Perera R, Lancaster T. Telephone counselling for smoking cessation. *Cochrane Database Syst Rev.* 2006;3:CD002850.
35. Eakin EG, Lawler SP, Vandelanotte C, Owen N. Telephone interventions for physical activity and dietary behavior change: a systematic review. *Am J Prev Med.* May 2007;32(5):419-434.
36. American Community Survey, 2003, Selected Housing Characteristics. http://factfinder.census.gov. Accessed October 7, 2009.
37. Edmonds D, Foerster E, Groth H, Greminger P, Siegenthaler W, Vetter W. Does self-measurement of blood pressure improve patient compliance in hypertension? *J Hypertens Suppl.* Apr 1985;3(1):S31-34.
38. Pickering TG, Miller NH, Ogedegbe G, Krakoff LR, Artinian NT, Goff D. Call to action on use and reimbursement for home blood pressure monitoring: a joint scientific statement from the American Heart Association, American Society Of Hypertension, and Preventive Cardiovascular Nurses Association. *Hypertension.* Jul 2008;52(1):10-29.
39. Papadopoulos DP, Makris TK. Masked hypertension definition, impact, outcomes: a critical review. *J Clin Hypertens (Greenwich).* Dec 2007;9(12):956-963.
40. Bobrie G, Chatellier G, Genes N, et al. Cardiovascular prognosis of "masked hypertension" detected by blood pressure self-measurement in elderly treated hypertensive patients. *Jama.* Mar 17 2004;291(11):1342-1349.
41. Chabot I, Moisan J, Gregoire JP, Milot A. Pharmacist intervention program for control of hypertension. *Ann Pharmacother.* Sep 2003;37(9):1186-1193.
42. Borenstein JE, Graber G, Saltiel E, et al. Physician-pharmacist comanagement of hypertension: a randomized, comparative trial. *Pharmacotherapy.* Feb 2003;23(2):209-216.
43. Vivian EM. Improving blood pressure control in a pharmacist-managed hypertension clinic. *Pharmacotherapy.* Dec 2002;22(12):1533-1540.
44. Rothman RL, Malone R, Bryant B, et al. A randomized trial of a primary care-based disease management program to improve cardiovascular risk factors and glycated hemoglobin levels in patients with diabetes. *Am J Med.* Mar 2005;118(3):276-284.
45. Bosworth HB, Olsen MK, Goldstein MK, et al. The veterans' study to improve the control of hypertension (V-STITCH): design and methodology. *Contemp Clin Trials.* Apr 2005;26(2):155-168.

46. Bosworth HB, Olsen MK, Dudley T, et al. The Take Control of Your Blood pressure (TCYB) study: study design and methodology. *Contemp Clin Trials.* Jan 2007;28(1):33-47.
47. Bosworth HB, Olsen MK, Neary A, et al. Take Control of Your Blood Pressure (TCYB) study: a multifactorial tailored behavioral and educational intervention for achieving blood pressure control. *Patient Educ Couns.* Mar 2008;70(3):338-347.
48. Reed SD, Li Y, Oddone EZ, et al. Economic evaluation of home blood pressure monitoring with or without telephonic behavioral self-management in patients with hypertension. *Am J Hypertens.* Feb 2010;23(2):142-148.
49. Bosworth HB, Olsen MK, McCant F, et al. Hypertension Intervention Nurse Telemedicine Study (HINTS): Testing a multifactorial tailored behavioral/educational and a medication management intervention for blood pressure control. *Am Heart J.* Jun 2007;153(6):918-924.
50. Fredrickson S, Coffman CJ, Weinberger M, et al. Group medical visits improve lipid profiles in patients with diabetes and hypertention. *J Gen Intern Med.* Apr 2009 2009;24(S1):S80-S81.
51. Datta SK, Oddone EZ, Olsen MK, et al. Economic analysis of a tailored behavioral intervention to improve blood pressure control for primary care patients. *Am Heart J.* Aug 2010;160(2):257-263.
52. Bosworth HB, Olsen MK, Gentry P, et al. Nurse administered telephone intervention for blood pressure control: a patient-tailored multifactorial intervention. *Patient Educ Couns.* Apr 2005;57(1):5-14.
53. Eraker SA, Kirscht JP, Becker MH. Understanding and improving patient compliance. *Ann Intern Med.* Feb 1984;100(2):258-268.
54. Becker MH, Maiman LA. Sociobehavioral determinants of compliance with health and medical care recommendations. *Med Care.* Jan 1975;13(1):10-24.
55. Bosworth HB, Oddone EZ. A model of psychosocial and cultural antecedents of blood pressure control. *J Natl Med Assoc.* Apr 2002;94(4):236-248.
56. Bosworth HB, Voils CI. Theoretical models to understand treatment adherence. In: Bosworth HB, Oddone EZ, Weinberger M, eds. *Patient Treatment Adherence: Concepts, Interventions, and Measurement.* Mahwah, NJ: Lawrence Erlbaum Associates; 2006:13-48.
57. Prochaska JO, DiClemente CC. Stages and processes of self-change of smoking: toward an integrative model of change. *J Consult Clin Psychol.* Jun 1983;51(3):390-395.
58. Woolf B. *Customer Specific Marketing.* New York, NY: Rand McNally; 1992.
59. Prochaska JO, DiClemente CC. Stages of change in the modification of problem behaviors. *Prog Behav Modif.* 1992;28:183-218.
60. Bandura A. Health promotion from the perspective of social cognitive theory. *Psychology & Health.* 1998;13:623-649.
61. Bandura A, Adams NE, Beyer J. Cognitive processes mediating behavioral change. *J Pers Soc Psychol.* Mar 1977;35(3):125-139.
62. Bodenheimer T, Lorig K, Holman H, Grumbach K. Patient self-management of chronic disease in primary care. *JAMA.* Nov 20 2002;288(19):2469-2475.
63. Lorig KR, Ritter P, Stewart AL, et al. Chronic disease self-management program: 2-year health status and health care utilization outcomes. *Med Care.* Nov 2001;39(11):1217-1223.
64. Reid RJ, Fishman PA, Yu O, et al. Patient-centered medical home demonstration: a prospective, quasi-experimental, before and after evaluation. *Am J Manag Care.* Sep 2009;15(9):e71-87.
65. Ko JM, Rodriguez HP, Fairchild DG, Rodday AC, Safran DG. Paying for enhanced services: Comparing patients' experiences in a concierge and general medicine practice. *The Patient: Patient-centered outcomes research* 2009;2(2):95-103.
66. Rosenthal TC. The medical home: growing evidence to support a new approach to primary care. *J Am Board Fam Med.* Sep-Oct 2008;21(5):427-440.
67. Bodenheimer T, Wagner EH, Grumbach K. Improving primary care for patients with chronic illness: the chronic care model, Part 2. *JAMA.* Oct 16 2002;288(15):1909-1914.
68. Jackson GL, Yano EM, Edelman D, et al. Veterans Affairs primary care organizational characteristics associated with better diabetes control. *Am J Manag Care.* Apr 2005;11(4):225-237.

69. Jackson GL, Weinberger M. A decade with the chronic care model: some progress and opportunity for more. *Med Care.* Sep 2009;47(9):929-931.
70. Damush TM, Jackson GL, Powers BJ, et al. Implementing evidence-based patient self-management programs in the Veterans Health Administration: perspectives on delivery system design considerations. *J Gen Intern Med.* Jan 2010;25 Suppl 1:68-71.
71. Bosworth HB, Powers BJ, Olsen MK, et al. Can home blood pressure management improve blood pressure control: Results from a randomized controlled trial. *Arch Intern Med.* 2011:(in press).
72. Rothman AA, Wagner EH. Chronic illness management: what is the role of primary care? *Ann Intern Med.* Feb 4 2003;138(3):256-261.
73. Jackson GL, Weinberger M, Hamilton NS, Edelman D. Racial/ethnic and educational-level differences in diabetes care experiences in primary care. *Primary Care Diabetes.* February 2008;2(1):39-44.
74. Pfeiffer E. A short portable mental status questionnaire for the assessment of organic brain deficit in elderly patients. *J Am Geriatr Soc.* Oct 1975;23(10):433-441.
75. Callahan CM, Hendrie HC, Tierney WM. Documentation and evaluation of cognitive impairment in elderly primary care patients. *Ann Intern Med.* Mar 15 1995;122(6):422-429.
76. Hanlon JT, Horner RD, Schmader KE, et al. Benzodiazepine use and cognitive function among community-dwelling elderly. *Clin Pharmacol Ther.* Dec 1998;64(6):684-692.
77. *National Healthcare Disparities Report, 2008.* AHRQ Publication No. 09-0002 ed. Rockville, MD: Agency for Health Research and Quality; 2009 March.
78. *Health, United States, 2008.* DHHS Pub No. 2009-1232 ed. Hyatsville, MD: Centers for Disease Control and Prevention, National Center for Health Statistics; 2009 March.
79. Edelman D, Edwards LJ, Olsen MK, et al. Screening for diabetes in an outpatient clinic population. *J Gen Intern Med.* Jan 2002;17(1):23-28.
80. Verberk WJ, Kroon AA, Kessels AG, de Leeuw PW. Home blood pressure measurement: a systematic review. *J Am Coll Cardiol.* Sep 6 2005;46(5):743-751.
81. Nicolucci A, Carinci F, Ciampi A. Stratifying patients at risk of diabetic complications: an integrated look at clinical, socioeconomic, and care-related factors. SID-AMD Italian Study Group for the Implementation of the St. Vincent Declaration. *Diabetes Care.* Sep 1998;21(9):1439-1444.
82. Jamerson K, DeQuattro V. The impact of ethnicity on response to antihypertensive therapy. *Am J Med.* Sep 30 1996;101(3A):22S-32S.
83. Tuck ML. Role of salt in the control of blood pressure in obesity and diabetes mellitus. *Hypertension.* Jan 1991;17(1 Suppl):I135-142.
84. Hutchinson RG, Watson RL, Davis CE, et al. Racial differences in risk factors for atherosclerosis. The ARIC Study. Atherosclerosis Risk in Communities. *Angiology.* Apr 1997;48(4):279-290.
85. Svetkey LP, George LK, Tyroler HA, Timmons PZ, Burchett BM, Blazer DG. Effects of gender and ethnic group on blood pressure control in the elderly. *Am J Hypertens.* Jun 1996;9(6):529-535.
86. Kornitzer M, Dramaix M, De Backer G. Epidemiology of risk factors for hypertension: implications for prevention and therapy. *Drugs.* May 1999;57(5):695-712.
87. Cooper R, Rotimi C. Hypertension in populations of West African origin: is there a genetic predisposition? *J Hypertens.* Mar 1994;12(3):215-227.
88. Svetkey LP, Moore TJ, Simons-Morton DG, et al. Angiotensinogen genotype and blood pressure response in the Dietary Approaches to Stop Hypertension (DASH) study. *J Hypertens.* Nov 2001;19(11):1949-1956.
89. Moore TJ, Conlin PR, Ard J, Svetkey LP. DASH (Dietary Approaches to Stop Hypertension) diet is effective treatment for stage 1 isolated systolic hypertension. *Hypertension.* Aug 2001;38(2):155-158.
90. Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *N Engl J Med.* Jan 4 2001;344(1):3-10.
91. Rozanski A, Blumenthal JA, Davidson KW, Saab PG, Kubzansky L. The epidemiology, pathophysiology, and management of psychosocial risk factors in cardiac practice: the emerging field of behavioral cardiology. *J Am Coll Cardiol.* Mar 1 2005;45(5):637-651.

92. Kroenke K, Spitzer RL, Williams JB. The Patient Health Questionnaire-2: validity of a two-item depression screener. *Med Care.* Nov 2003;41(11):1284-1292.
93. Lowe B, Kroenke K, Grafe K. Detecting and monitoring depression with a two-item questionnaire (PHQ-2). *J Psychosom Res.* Feb 2005;58(2):163-171.
94. NCIOM. *Task Force on the North Carolina Nursing Workforce*. Durham, NC: North Carolina Institute of Medicine; 2004, May.
95. Beverage PA. How LPNs can be part of the solution. *N C Med J.* Mar-Apr 2004;65(2):96-97.
96. Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med.* Jun 12 2008;358(24):2545-2559.
97. Johnson KA, Partsch DJ, Rippole LL, McVey DM. Reliability of self-reported blood pressure measurements. *Arch Intern Med.* Dec 13-27 1999;159(22):2689-2693.
98. Greenhalgh T, Robert G, Macfarlane F, Bate P, Kyriakidou O. Diffusion of innovations in service organizations: systematic review and recommendations. *Milbank Q.* 2004;82(4):581-629.
99. Miles MB, Huberman AM. *Qualitative Data Analysis: An Expanded Sourcebook.* Second ed. Thousand Oaks, CA: Sage Publications; 1994.
100. Van de Ven AH, Polley DE. *The Innovation Journey*. New York, NY: Oxford University Press; 1999.
101. Weiner BJ, Lewis MA, Linnan LA. Using organization theory to understand the determinants of effective implementation of worksite health promotion programs. *Health Educ Res.* Apr 2009;24(2):292-305.
102. Glasgow RE, Whitesides H, Nelson CC, King DK. Use of the Patient Assessment of Chronic Illness Care (PACIC) with diabetic patients: relationship to patient characteristics, receipt of care, and self-management. *Diabetes Care.* Nov 2005;28(11):2655-2661.
103. Kim JW, Bosworth HB, Voils CI, et al. How well do clinic-based blood pressure measurements agree with the mercury standard? *J Gen Intern Med.* Jul 2005;20(7):647-649.
104. Sacks FM, Obarzanek E, Windhauser MM, et al. Rationale and design of the Dietary Approaches to Stop Hypertension trial (DASH). A multicenter controlled-feeding study of dietary patterns to lower blood pressure. *Ann Epidemiol.* Mar 1995;5(2):108-118.
105. Lloyd-Jones DM, Evans JC, Larson MG, O'Donnell CJ, Roccella EJ, Levy D. Differential control of systolic and diastolic blood pressure : factors associated with lack of blood pressure control in the community. *Hypertension.* Oct 2000;36(4):594-599.
106. Pogach LM, Rajan M, Aron DC. Comparison of weighted performance measurement and dichotomous thresholds for glycemic control in the Veterans Health Administration. *Diabetes Care.* Feb 2006;29(2):241-246.
107. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet.* Dec 14 2002;360(9349):1903-1913.
108. Phibbs CS, Barnett PG, Harden C, King SS. *Research Guide to Decision Support System National Cost Extracts*. Menlo Park, CA: Health Economics Resource Center of Health Service R&D Service, Veterans Health Administration 2008.
109. *VIReC Research User Guide: VHA Pharmacy Prescription Data, 2003*. Hines, IL: Veterans Affairs Information Resource Center, Edward J. Hines, Jr. VA Hospital; 2003, September.
110. Maciejewski ML, Bryson CL, Perkins M, et al. Increasing copayments and adherence to diabetes, hypertension, and hyperlipidemic medications. *Am J Manag Care.* Jan 2010;16(1):e20-34.
111. Bryson CL, Au DH, Young B, McDonell MB, Fihn SD. A refill adherence algorithm for multiple short intervals to estimate refill compliance (ReComp). *Med Care.* Jun 2007;45(6):497-504.
112. Chernew M, Gibson TB, Yu-Isenberg K, Sokol MC, Rosen AB, Fendrick AM. Effects of increased patient cost sharing on socioeconomic disparities in health care. *J Gen Intern Med.* Aug 2008;23(8):1131-1136.
113. Pan F, Chernew ME, Fendrick AM. Impact of fixed-dose combination drugs on adherence to prescription medications. *J Gen Intern Med.* May 2008;23(5):611-614.
114. Lowry KP, Dudley TK, Oddone EZ, Bosworth HB. Intentional and unintentional nonadherence to antihypertensive medication. *Ann Pharmacother.* Jul-Aug 2005;39(7-8):1198-1203.
115. Thorpe CT, Bryson CL, Maciejewski ML, Bosworth HB. Medication acquisition and self-reported adherence in veterans with hypertension. *Med Care.* Apr 2009;47(4):474-481.

116. Bandura A. Self-efficacy: toward a unifying theory of behavioral change. *Psychol Rev.* Mar 1977;84(2):191-215.
117. Anderson RM, Funnell MM, Butler PM, Arnold MS, Fitzgerald JT, Feste CC. Patient empowerment. Results of a randomized controlled trial. *Diabetes Care.* Jul 1995;18(7):943-949.
118. Johnston-Brooks CH, Lewis MA, Garg S. Self-efficacy impacts self-care and HbA1c in young adults with Type I diabetes. *Psychosom Med.* Jan-Feb 2002;64(1):43-51.
119. Howorka K, Pumprla J, Wagner-Nosiska D, Grillmayr H, Schlusche C, Schabmann A. Empowering diabetes out-patients with structured education: short-term and long-term effects of functional insulin treatment on perceived control over diabetes. *J Psychosom Res.* Jan 2000;48(1):37-44.
120. Piette JD, Weinberger M, McPhee SJ. The effect of automated calls with telephone nurse follow-up on patient-centered outcomes of diabetes care: a randomized, controlled trial. *Med Care.* Feb 2000;38(2):218-230.
121. Norris SL, Engelgau MM, Narayan KM. Effectiveness of self-management training in type 2 diabetes: a systematic review of randomized controlled trials. *Diabetes Care.* Mar 2001;24(3):561-587.
122. Ogedegbe G, Mancuso CA, Allegrante JP, Charlson ME. Development and evaluation of a medication adherence self-efficacy scale in hypertensive African-American patients. *J Clin Epidemiol.* Jun 2003;56(6):520-529.
123. Williams GC, Freedman ZR, Deci EL. Supporting autonomy to motivate patients with diabetes for glucose control. *Diabetes Care.* Oct 1998;21(10):1644-1651.
124. Craig CL, Marshall AL, Sjostrom M, et al. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc.* Aug 2003;35(8):1381-1395.
125. Buse JB, Ginsberg HN, Bakris GL, et al. Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. *Circulation.* Jan 2 2007;115(1):114-126.
126. Davis TC, Long SW, Jackson RH, et al. Rapid estimate of adult literacy in medicine: a shortened screening instrument. *Fam Med.* Jun 1993;25(6):391-395.
127. Dewalt DA, Berkman ND, Sheridan S, Lohr KN, Pignone MP. Literacy and health outcomes: a systematic review of the literature. *J Gen Intern Med.* Dec 2004;19(12):1228-1239.
128. van Dam HA, van der Horst FG, Knoops L, Ryckman RM, Crebolder HF, van den Borne BH. Social support in diabetes: a systematic review of controlled intervention studies. *Patient Educ Couns.* Oct 2005;59(1):1-12.
129. Carels RA, Blumenthal JA, Sherwood A. Effect of satisfaction with social support on blood pressure in normotensive and borderline hypertensive men and women. *Int J Behav Med.* 1998;5(1):76-85.
130. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol.* Jun 1992;45(6):613-619.
131. Glasgow RE, Wagner EH, Schaefer J, Mahoney LD, Reid RJ, Greene SM. Development and validation of the Patient Assessment of Chronic Illness Care (PACIC). *Med Care.* May 2005;43(5):436-444.
132. Glasgow RE, Emont S, Miller DC. Assessing delivery of the five 'As' for patient-centered counseling. *Health Promot Int.* Sep 2006;21(3):245-255.
133. Verbeke G, Molenberghs, G. *Linear Mixed Models for Longitudinal Data.* New York: Springer-Verlag; 2000.
134. Singer J, Willett, JB. . *Applied Longitudinal Data Analysis.* . New York: Oxford University Press; 2003.
135. Gail M, Simon R. Testing for qualitative interactions between treatment effects and patient subsets. *Biometrics.* Jun 1985;41(2):361-372.
136. Borm GF, Fransen J, Lemmens WA. A simple sample size formula for analysis of covariance in randomized clinical trials. *J Clin Epidemiol.* Dec 2007;60(12):1234-1238.
137. Olsen MK, DeLong ER, Oddone EZ, Bosworth HB. Strategies for analyzing multilevel cluster-randomized studies with binary outcomes collected at varying intervals of time. *Stat Med.* Dec 20 2008;27(29):6055-6071.
138. Chaudhary M, Stearns, SC. Estimating confidence intervals for cost-effectiveness ratios: an example from a randomized trial. *Statistics in Medicine.* 1996;15:1447-1458.

139. Efron B, Tibshirani, RJ. Bootstrap methods for standard errors, confidence intervals, and other measures of statistical accuracy. *Stat Sci.* 1986;1:54-77.
140. Mooney CZ, Duval RD. *Bootstrapping: A Nonparametric Approach to Statistical Inference, A SAGE University Paper in the Quantitative Application in the Social Sciences Series, 07-095*. Thousand Oaks, CA: SAGE Publications; 1993.
141. Rubin DB, Wiley. *Multiple Imputation for Nonresponse in Surveys.* New York: Wiley; 1987.
142. NRC. *The Prevention and Treatment of Missing Data in Clinical Trials. Panel on Handling Missing Data in Clinical Trials*. Washington, DC: National Academy Press for National Research Council; 2010.
143. Bosworth HB, Olsen MK, Grubber JM, Powers BJ, Oddone EZ. Racial differences in two self-management hypertension interventions. *Am J Med.* May 2011;124(5):468 e461-468.
144. Jackson GL, Powell AA, Ordin DL, et al. Developing and sustaining quality improvement partnerships in the VA: the Colorectal Cancer Care Collaborative. *J Gen Intern Med.* Jan 2010;25 Suppl 1:38-43.
145. Chao HH, Schwartz AR, Hersh J, et al. Improving colorectal cancer screening and care in the Veterans Affairs Healthcare system. *Clin Colorectal Cancer.* Jan 2009;8(1):22-28.
146. Bosworth HB, Almirall D, Weiner BJ, et al. The implementation of a translational study involving a primary care based behavioral program to improve blood pressure control: The HTN-IMPROVE study protocol (01295). *Implement Sci.* Jul 16 2010;5(1):54.