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Open-label randomized trial of titrated disease management for patients with hypertension: Study design and baseline sample characteristics

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ABSTRACT

Despite the availability of efficacious treatments, only half of patients with hypertension achieve adequate blood pressure (BP) control. This paper describes the protocol and baseline subject characteristics of a 2-arm, 18-month randomized clinical trial of titrated disease management (TDM) for patients with pharmaceutically-treated hypertension for whom systolic blood pressure (SBP) is not controlled (≥140 mm Hg for non-diabetic or ≥130 mm Hg for diabetic patients). The trial is being conducted among patients of four clinic locations associated with a Veterans Affairs Medical Center. An intervention arm has a TDM strategy in which patients' hypertension control at baseline, 6, and 12 months determines the resource intensity of disease management. Intensity levels include: a low-intensity strategy utilizing a licensed practical nurse to provide bi-monthly, non-tailored behavioral support calls to patients whose SBP comes under control; medium-intensity strategy utilizing a registered nurse to provide monthly tailored behavioral support telephone calls plus home BP monitoring; and high-intensity strategy utilizing a pharmacist to provide monthly tailored behavioral support telephone calls, home BP monitoring, and pharmacist-directed medication management. Control arm patients receive the low-intensity strategy regardless of BP control. The primary outcome is SBP. There are 385 randomized (192 intervention; 193 control) veterans that are predominately older (mean age 63.5 years) men (92.5%). 61.8% are African American, and the mean baseline SBP for all subjects is 143.6 mm Hg. This trial will determine if a disease management program that is titrated by matching the intensity of resources to patients' BP control leads to superior outcomes compared to a low-intensity management strategy.

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1. Introduction

Despite its prevalence, associated morbidity and mortality, presence of evidence-based guidelines, and availability of >100 anti-hypertensive medications [1], only approximately half of American adults with hypertension (HTN) have achieved adequate blood pressure (BP) control [2,3]. Clinical trial results indicate that self-management support is critical to successful management of HTN and other chronic conditions [4–8]. Results from randomized trials would typically lead decision-makers to implement effective strategies per protocol. However, one size may not fit all. Instead, analogous to titrating medications when BP is above clinical targets [9], patients might reasonably require differing intensity of disease management depending on whether they have achieved these clinical targets. We are conducting a pragmatic clinical trial to evaluate the effectiveness of titrated disease management in which the intensity of disease management is adjusted based on an individual's systolic blood pressure (SBP).

1.1. Defining titrated disease management (TDM)

We view the process of TDM as analogous to the common process of titrating medication dosage in clinical care. For example, clinical guidelines often recommend adjusting the dosage and/or number of anti-hypertensive agents based on clinical parameters. This is often in the form of stepped care, where patient's initial medication dose is low to minimize risks of treatment (such as side effects) [10]. If patients are not responsive

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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 [11–13].

We are conducting a pragmatic trial to examine the effectiveness of titrated (not stepped) care when applied to disease management. Specifically, we are adjusting (titrating) the resource intensity (and expense) of a disease management strategy based upon the patient's clinical status. Depending on the individual's BP, resources are either intensified or reduced to achieve or maintain BP control. This resource intensity differs by: 1) who delivers disease management; 2) the complexity of the treatment (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 over time to determine if they will: 1) remain at the same level of resource intensity; 2) increase to a higher intensity level; or 3) decrease to a lower resource intensity level. This type of titration addresses a criticism about stepped care where there is no plan to reduce level of drug or other resource use for patients with improving illness severity [14].

2. Materials and methods

2.1. Study sponsorship and IRB approval

This trial is funded by the United States Department of Veterans Affairs (VA) Health Services Research and Development Service (grant # IIR 10-383; clinicaltrials.gov registration # NCT01390272). It is being conducted under the approval of the Intuitional Review Board (IRB) of the Durham VA Medical Center.

2.2. Specific aims of the pragmatic trial

The primary question of the pragmatic trial is: will the TDM intervention reduce systolic blood pressure (SBP) over 18 months compared to licensed practical nurse (LPN)-delivered behavioral support calls occurring every two months [control arm]? The primary hypothesis is that veterans randomized to TDM will have greater improvement in mean SBP over the 18 months of follow-up than veterans in the control arm. Secondary outcomes include HTN control (dichotomous), cost-effectiveness (if successful), and adherence to hypertension medications.

2.3. Setting

The study is being conducted among patients receiving primary care at clinics in four separate locations affiliated with the Durham VA Medical Center. One location is the main VA hospital, one satellite clinic is located approximately 1.5 driving miles to the north, a second clinic is located approximately 45 driving miles to the east, and a final clinic is located approximately 110 driving miles east of the hospital. In 2015, these sites had approximately 46 primary care provider (PCP) full-time equivalents for delivery of care to approximately 44,000 unique patients.

2.4. Summary of the intervention

This is a two-arm 18-month pragmatic randomized clinical trial for veterans with pharmaceutically-treated hypertension and uncontrolled SBP (defined as ≥140 mm Hg for non-diabetic or ≥130 mm Hg for diabetic patients). The intervention arm includes three levels of resource intensity targeted to improve patients' SBP (Table 1).

- Low resource intensity: An **LPN** provides non-tailored behavioral support telephone calls every two months to patients whose SBP comes under control. The low resource intensity also serves as the control arm (described below).
- Medium resource intensity: A **registered nurse (RN)** provides monthly tailored behavioral support telephone calls **plus** home BP monitoring.
- High resource intensity: A **pharmacist** provides monthly tailored behavioral support telephone calls, home BP monitoring **and** pharmacist-directed medication management.

At the initial baseline visit patients who are randomized into the intervention arm are first titrated to either RN or pharmacist levels based on baseline blood pressure values. Subsequent titrations that include the LPN level happen at the 6 and 12 month study visits.

In the control arm (Table 1), a LPN provides behavioral support telephone calls every two months. This is identical to the low resource intensity component of the TDM intervention. This control arm differs from usual care in that patients receive additional regular contact that has been shown to enhance BP control among veterans [15] and medication adherence among North Carolina Medicaid beneficiaries [16].

2.5. Eligibility criteria

Eligible individuals included English speaking adults living in the community with access to a telephone who had been seen at a study clinic in the last year, had a VA PCP (Table 2). and had a history of pharmaceutically-treated HTN with uncontrolled SBP in the past year [17]. Specifically, based on the Seventh Report of the Joint National Commission on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC7), HTN is considered uncontrolled if SBP is ≥140 mm Hg for patients without diabetes or ≥130 mm Hg for patients with diabetes. While JNC 8 guidelines were issued during the trial [9],

Table 1
Summary of differences in intervention resource levels.

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

[a] The control arm for the study is delivery of the LPN/low intensity calls as described.

Table 2
Inclusion and exclusion criteria.

Inclusion criteria
Inclusion criteria determined by initial review of the VA electronic health record

- 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 clinics in the last year.
- Diagnosis of hypertension requiring medication, as determined by:
  - ➢ International Classification of Disease Ninth Revision (ICD-9) 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 mm Hg for non-diabetic or ≥140 mm Hg 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 mm Hg or diabetic patients with mean outpatient systolic BP of ≥130 mm Hg 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) [17]. Initial screening BP levels were 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 [51].

Inclusion Criteria Determined during the Initial Screening Phone Call

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

Exclusion criteria
Exclusion criteria determined by initial review of the VA electronic health record by chart review

- 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 (CVD) 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.

Exclusion criteria determined during the initial screening phone call

- 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.

Exclusion criteria determined during the baseline in-person visit

- Refusal or inability to provide informed consent and HIPAA authorization form.
- Arm size >50 cm in circumference
- 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) [52–54].
- Patients who report that they are pregnant or have the potential to become pregnant during the study.

BP - blood pressure; CBOC - community-based outpatient clinic; CVD - cardiovascular disease; PCP - primary care provider; VAMC - Veterans Affairs Medical Center.

we continued to utilize JNC 7 criteria so we could maintain consistent therapeutic goals throughout the study. BP control was based on mean SBP during the year prior to periodic data pulls from the VA electronic health record (described below). Because of the labile nature of blood pressure, patients were identified in the data pulls as being potentially eligible based on a SBP 10 mm Hg over JNC7 guidelines. (i.e., 150 mm Hg for patients without diabetes or 140 mm Hg for patients with diabetes).

Patients were excluded if they had known type 1 diabetes, class IV congestive heart failure, end stage renal disease, metastatic cancer, a history of solid organ or bone marrow transplantation, or a diagnosis of active psychosis at baseline. Additionally, patients were excluded if they were enrolled in any ongoing clinical trial or specific clinical program that would be expected to impact blood pressure control. Women who reported being pregnant or planning to become pregnant over the next 18 months were also excluded.

2.5.1. Change in inclusion criteria during the study

To be eligible, patients were initially required to have uncontrolled study SBP (≥140 mm Hg without diabetes; ≥130 mm Hg with diabetes) at baseline, which was assessed after the patient provided informed consent, but before randomization. While this criterion was in place, 41.3% of patients who consented did not meet the threshold for being out of control. Because these patients are likely to have been cycling in and out of control, we decided patients meeting study criteria while having baseline SBP under control would likely benefit from the intervention and, as such, should be randomized. The IRB approved this modification.

2.6. Screening and enrollment

Potential subjects were initially identified based upon data extracted from the VA electronic health record (EHR) using inclusion and exclusion criteria (above). PCPs were informed of the study and could request to review lists of potentially eligible patients to approve patients' potential participation in the study (i.e., whether individual patients could remain on the list). Providers choosing to review lists of potentially eligible patients had 14 days from receiving the list to conduct the review and contact study team with any concerns about individual listed patients participating in the study. Only one PCP chose to review patient lists.

Letters were sent from the principal investigator and study physician to potentially eligible patients allowing them to opt out of the study. For subjects who did not opt-out, study staff conducted a screening phone call to further assess inclusion and exclusion criteria and schedule baseline study visits. Given the large number of potentially eligible subjects, chart review was prioritized for patients having upcoming appointments within 4–6 weeks; doing so allowed baseline study visits to coincide with a patient's clinic visit. After approximately 7 months of enrollment, patients living within approximately 50 miles of a participating clinic were also prioritized to enhance enrollment rates.

2.7. Patient compensation

Patients receive $15 for each of the four data collection visits (baseline, 6, 12, and 18-months), for a total potential payment of $60 for participating in the study.

2.8. Protocol for measuring baseline and outcome systolic blood pressure (SBP)

At each study visit (including baseline), the SBP outcome is based on the mean of three BP measures obtained 30 seconds apart after the patient has sat for 5 minutes. All BP measurements are performed using electronic BP cuffs, which have been shown to be equivalent to (and ecologically safer) than the gold standard of random zero sphygmomanometers [18]. The same type of electronic BP cuff is being used for all clinic locations in the study (Omron Digital Blood Pressure Monitor HEM-907XL).

2.9. Randomization

We used blocked randomization stratified by diabetes status (because of differing HTN treatment goals) and baseline SBP [up to moderately out of control: SBP < 150 mm Hg for non-diabetic patients (or <140 mm Hg for diabetic patients); significantly out of control: SBP ≥ 150 mm Hg for non-diabetic patients (or ≥140 mm Hg for diabetic patients)]. Research assistants were blinded to randomization block size. Diabetes was defined from EHR data as having both: ICD-9 diagnosis code 250.xx on ≥2 outpatient encounters during the prior year and a prescription for oral hypoglycemic medication (e.g., sulfonylurea, metformin, thiazolidinedione, secretagogues, acarbose) and/or insulin during the past year.

It was not feasible to blind personnel who collected study outcome data to the assigned study arm. To minimize bias, baseline outcome data were collected prior to randomization and SBP measurement outcome data collection utilized an electronic blood pressure machine and standard protocol, which is described above.

2.10. Intervention

2.10.1. Titration algorithms

The protocol for titrating resource intensity of the intervention depended on BP control. Titration algorithms are detailed in Table 3.

2.10.2. Intervention component — telephone self-management support [medium- and high-level resource intensity]

Patients receiving medium resource intensity disease management receive calls from a RN; patients receiving high resource intensity disease management receive calls from a pharmacist (PharmD). The calls combine tailored information and feedback that address aspects of hypertension management specifically relevant to a particular patient

Table 3
Intervention titration algorithm.

Baseline titration
Based on mean baseline study visit SBP values:

- Medium resource intensity — Monthly tailored RN delivered calls + home BP monitoring
  - ➢ Mean of enrollment study visit SBPs of <150 mm Hg (<140 mm Hg for patients with diabetes)
- High resource intensity — Monthly tailored pharmacist delivered calls with additional medication management + home BP monitoring
  - ➢ Mean of enrollment study visit SBPs of ≥150 mm Hg (≥140 mm Hg for patients with diabetes)

Planned titration at 6 and 12 months
Based on the mean of all available SBP values up to 31 days prior to the patients study visit, including study visit BP values, any clinic BP values, and/or any home BP values provided to during the intervention:

- Low resource intensity – non-tailored LPN delivered calls occurring every two months
  - ➢ Mean SBP controlled; i.e. <140 mm Hg (SBP <130 mm Hg for patients with diabetes).
- Medium resource Intensity
  - ➢ Mean SBP (defined above) of ≥140 mm Hg and <150 mm Hg (≥130 mm Hg and <140 mm Hg for patients with diabetes)
- High resource Intensity
  - ➢ Mean SBP (defined above) of ≥150 mm Hg (SBP ≥ 140 mm Hg for patients with diabetes)

Unplanned titration between 6 and 12 months

- Mean of home SBPs reported during a study behavioral call ≥160 mm Hg
  - ➢ This automatic increase in resource intensity will not include adding 5 mm Hg to home systolic BP measurements. A minimum of 4 blood pressure readings considered to be validly reported by the appropriately licensed clinical interventionist was required. 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 myocardial infarction. Patient will be asked at intervention phone calls if they have been hospitalized for stroke, myocardial infarction and/or heart attack. We will also make unplanned titrations due to hospitalizations that are noted by interventionists as having been recorded in the VA electronic health record.
- A patient triggers the safety protocol based on a blood pressure.

If a patient is titrated to the highest level between study visits, 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).

BP – blood pressure; mm Hg – millimeters of mercury; LPN – licensed practical nurse; RN – registered nurse; SBP – systolic blood pressure; VA – Veterans Affairs.

[19]. Drawing on stages of change [20,21], and a revised Health Decision Model (HDM) that considers how patients' beliefs, environment, and characteristics impact decisions concerning health behaviors [21–23], the intervention addresses how to: 1) set realistic, healthy goals that reflect patient preferences and readiness to change and support self-efficacy for achieving those goals [24–27], 2) implement healthful behaviors and monitor performance, and 3) maintain the behaviors and associated hypertension control over time. To further tailor the intervention, callers use scripted modules based on patients' specific needs identified from questions asked during the call. For example, patients who report they are current smokers are asked about their readiness to quit smoking.

2.10.2.1. Training personnel making calls. Prior to starting the intervention, the RNs and pharmacist delivering the calls were trained in motivational interviewing (MI). MI is a tool that can assist individuals work through ambivalence about behavior change. Interventionists were provided 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. The LPN delivering low resource intensity calls did not receive training in MI and followed non-tailored telephone call scripts.

2.10.2.2. Mechanics of making calls. The interventionist calls patients within two weeks after randomization. Subsequent contacts are scheduled approximately monthly. Between scheduled calls, patients are encouraged to telephone the interventionist with questions related to their hypertension, including (but not limited to) control of their BP and the pharmacological or non-pharmacological management of HTN. Should emergent healthcare issues arise during these calls, the study contacts the patient's PCP (or covering provider) via a note in the EHR or refers the patient to emergency care.

2.10.2.3. Content of calls. The interventionist utilizes computerized software to guide tailored patient modules during the intervention calls. Each module addresses either (1) a health behavior (e.g., exercise) that is desirable for BP control or (2) a modifiable patient factor that can improve control (e.g., hypertension knowledge, memory) that may impact medication adherence. The modules are "activated" (introduced as a topic) when a patient reports a barrier that the module was designed to address.

A major emphasis of the intervention is initiating and maintaining specific health behaviors related to HTN. During each monthly call, a core group of modules were available. All RN and PharmD phone calls addressed medication management, side effects (with the exception of the first call) and home BP monitoring. An additional health behavior or modifiable patient factor was also addressed. Topics covered in calls can be found in Table 4. The call schedules for the RN, pharmacist, and LPN (control arm) calls can be found in Table 5.

2.10.3. Intervention component — booster level phone calls

Patients whose SBP comes under control at 6 or 12 months are switched to low resource intensity LPN phone calls. Low resource intensity calls occur every two months instead of monthly and follow a standardized script with no tailoring or probing about BP measurements.

2.10.4. Intervention component — home BP monitoring: medium and high resource intensity

All patients randomized to the intervention arm who do not currently have a VA approved home BP monitor were eligible to receive one. They receive training in its use at their baseline study visit according to a protocol developed in our prior studies [28]. Patients are instructed to check their BP every other day using a defined protocol similar to previous studies [29]. We request individuals to provide their BP values for the two weeks prior to the monthly intervention calls so that the

Table 4
Intervention arm module content – medium (RN) and high (pharmacist) resource levels.[a]

Topic	Module content
Opening module/medication management [delivered during each call]	1. Review of 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. 2. 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. 3. 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 [delivered during each call]	1. Patients are queried at every scheduled phone call about any specific BP medication side effects they may have. 2. 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	1. 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 [55]. 2. The interventionist conveys the need and importance of taking BP medication consistently and in a timely manner.
Knowledge/risk perception	1. 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 [56–58], African American [59,60], recently diagnosed with hypertension, and/or have hypertensive relatives [61,62] because these factors confer specific risks for worse health outcomes.
Participatory decision-making and patient-provider communication	1. Patients identified as having poor provider relationships receive information on ways to empower patients to interact more productively with their providers.
Diet	1. Patients are asked to choose a topic of interest for them for information on low sodium diet, healthy carbohydrates, or heart healthy choices and portion control. 2. Patients are also asked to talk about foods they eat in a typical day. 3. There is 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. 4. 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)

(*continued on next page*)

Table 4 (*continued*)

Topic	Module content
	diet, which has been found to lower BP [63–65].
Weight	1. 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). 2. Weight loss information is then tailored to individuals' readiness to change.
Exercise	1. 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. 2. The interventionist determines their exercise activity readiness to change and information is then tailored to the patient's readiness. 3. 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.	1. 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.	1. Patients are asked about their knowledge of the relationship between stress and hypertension as well as how individuals know when they are stressed. 2. 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 [66,67] [2 item screening instrument for depression], 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. 3. Patients are asked the Berlin Questionnaire (for sleep apnea) during the 6 month study visit to identify patients at risk for the sleep apnea syndrome. 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. High Risk patients trigger a module where the interventionist discusses the result and encourages participant to discuss a referral for diagnostic polysomnogram (PSG) evaluation for sleep apnea with their PCP.
Smoking	1. Among smokers, the interventionist highlights the benefits of smoking cessation for those who report they are current smokers. 2. The interventionist then determines the individual's stage in terms of considering smoking cessation.
Closing module [delivered during each call]	1. 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. 2. For those patients 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.

BP - blood pressure; PCP - primary care provider.

[a] LPN calls provide knowledge-based information on these topics, with the exception of diet, exercise, mental health, and sleep apnea based on the schedule in Table 5.

interventionist (RN or pharmacist) could assess their BP control. Patients are reminded to record their BP as part of the intervention calls.

2.10.5. Intervention component — pharmacist-directed algorithmic medication management [high resource intensity only]

Patients who meet criteria for high resource intensity disease management receive medication management from a clinical pharmacist, who will be backed up by a study physician. Pharmacists are authorized to make medication changes according to accepted treatment algorithms and based on their scope of practice. Via the VA EHR, the pharmacist will also communicate these changes to the patient's PCP. While pharmacists in the VA may collaborate with the patients' providers when clinically indicated, they do not have to rely on them to make the changes. The study pharmacist attempts to contact patients every month while they are in the high-intensity titration level of the intervention. During each contact, the pharmacist has information from both the VA EHR and the behavioral support 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 call, the pharmacist assesses the patient's medication adherence, reviews all BP-related medications, and discusses the purpose and appropriate administration of each medication. 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 reviews any medication changes with the patients and updates patients' medication lists. For patients who require a change in their prescription, the pharmacist writes the prescription, and then communicates the change to the patient's PCP using standard clinic procedures.

2.11. Control arm

Control patients receive the low resource intensity intervention, which is described above, for the entire study period.

2.12. Outcomes and study measures

Table 6 lists all study measures and time points at which information is being collected.

2.12.1. Primary outcome — continuous change in systolic blood pressure

SBP is the primary outcome because it has greater association with cardiovascular disease risk than diastolic BP among patients with pharmaceutically-treated hypertension [30–32]. The procedure for measuring SBP at all study visits is described above in Section 2.8.

2.12.2. Secondary outcome — SBP control

This is a dichotomous outcome in which control is defined as SBP ≤ 130 mm Hg for hypertensive patients with diabetes and ≤140 mm Hg for patients without diabetes.

2.12.3. Secondary outcome — adherence to blood pressure medication

Adherence is measured as the supply of medications patients have, expressed as a medication possession ratio (MPR). We use the ReComp MPR algorithm [33,34], which was developed and validated using

Table 5
TDM Trial module schedule.

RN & PharmD encounters with module topic

Encounter 1	**Encounter 7**	**Encounter 13**
Opening/closing	Opening/closing	Opening/closing
Medications/side effects	Medications/side effects	Medications/side effects
CVD knowledge	Weight loss	Weight loss goal f/u
Memory	Alcohol	Adverse events
Adverse events	Adverse events	
	Encounter 8	**Encounter 14**
Encounter 2	Opening/closing	Opening/closing
Opening/closing	Medications/side effects	Medications/side effects
Medications/side effects	Diet	Alcohol
Tobacco use	Tobacco use goal f/u	Adverse events
Social support	1 mo weight loss f/u	
Adverse events	Adverse events	**Encounter 15**
	Encounter 9	Opening/closing
Encounter 3	Opening/closing	Medications/side effects
Opening/closing	Medications/side effects	Insomnia
Medications/side effects	Insomnia	Apnea
Mental health	Apnea	Adverse events
1 mo f/u tobacco use	Adverse events	
Adverse events	**Encounter 10**	**Encounter 16**
	Opening/closing	Opening/closing
Encounter 4	Medications/side effects	Medications/side effects
Opening/closing	CVD knowledge	Diet
Medications/side effects	Memory	Adverse events
Diet	Adverse events	
Pt-physician interaction	**Encounter 11**	**Encounter 17**
Adverse events	Opening/closing	Opening/closing
	Medications/side effects	Medications/side effects
Encounter 5	Pt-physician interaction 6 mo f/u	Stress
Opening/closing	Adverse events	Adverse events
Medications/side effects		
Exercise	**Encounter 12**	**Encounter 18**
Adverse events	Opening/closing	Opening/closing
	Medications/side effects	Medications/side effects
Encounter 6	Diet	Adverse events
Opening/closing	Mental health	Final call summary
Medications/side effects	Adverse events	
Stress		
1 mo f/u exercise		
Adverse events		

LPN encounters with module topic

Encounter 1 (maps to Enc. 1 & 2 of RN/PharmD schedule):	**Encounter 5 (maps to Enc. 9 & 10 of RN/PharmD schedule):**	*HTN knowledge is similar to the RN/PharmD script for CVD Knowledge
Opening/closing	Opening/closing	*Decision making is similar to the RN/PharmD script for patient-physician interaction
Medications	Medications	
HTN knowledge*	Memory	
Memory	HTN knowledge*	
Tobacco use	Adverse events	
Adverse events		
	Encounter 6 (maps to Enc. 11 & 12 of RN/PharmD schedule without goal follow–up):	
Encounter 2 (maps to Enc. 3 & 4 of RN/PharmD schedule without goal follow–up):	Opening/closing	
Opening/closing	Medications	
Medications	Decision making*	
Social support	Adverse events	
Decision making*		
Adverse events	**Encounter 7 (maps to Enc. 13 &.14 of RN/PharmD schedule):**	
Encounter 3 (maps to Enc. 5 & 6 of RN/PharmD schedule without goal follow–up):	Opening/closing	
Opening/closing	Medications	
Medications	Alcohol	
Stress	Adverse events	
Adverse events		
	Encounter 8 (maps to Enc. 15 & 16 of RN/PharmD schedule):	
Encounter 4 (maps to Enc. 7 & 8 of RN/PharmD schedule without goal follow–up):	Opening/closing	
Opening/closing	Medications	
Medications	Adverse events	
Alcohol		
Tobacco use	**Encounter 9 (maps to Enc. 17 & 18 of RN/PharmD schedule):**	
Adverse events	Opening/closing	
	Medications/side effects	
	Stress	
	Adverse events	

Enc. - encounter; LPN – licensed practical nurse; PharmD - doctor of pharmacy (pharmacist); RN - registered nurse; HTN – hypertension, Pt – Patient, f/u – follow-up.

pharmacy refill data to measure adherence with antihypertensive medication (considered together for adherence).

2.13. Planned data analysis

Our pre-specified primary and secondary hypotheses will be tested with two-sided p-values at the $p < 0.05$ level; intent-to-treat basis; we analyze all data up to the 18-month follow-up (or last available prior to exclusion or dropout) [35]. Statistical analyses will be performed using SAS for Windows (version 9.4: SAS Institute, Cary, NC) and R (http://www.R-project.org).

2.13.1. Planned analysis

To examine the impact of TDM on mean SBP over 18 months, we will use a linear mixed model [36]. Baseline, 6-, 12- and 18-month values in the response vector will be used to estimate changes in SBP over time and test the primary hypothesis. The predictors in the model will include time and the intervention-by-time interaction. This constrained longitudinal model (cLDA) assumes the study arms have equal baseline means, which is appropriate for a randomized control trial and is equivalent in efficiency to an ANCOVA [37]. Results from exploratory graphical methods as well as model selection criteria will be used to select the most appropriate way to model time over the 18 month follow-up.

We will fit models using the SAS procedure MIXED (Cary, NC), which handles dropout in a principled manner. However, 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 [38]. Secondary analyses will be conducted in a similar manner, testing for differences in medication adherence as a continuous outcome. For BP control and dichotomous adherence, similar modeling procedures will be followed using generalized linear mixed models using PROC GLIMMIX with adaptive quadrature [36].

2.13.2. Sample size considerations

We estimated that 400 subjects (200 per arm) would be required to detect a 5 mm Hg difference in SBP at 18 months with 80% power and a type-I error of 5%. We used a method based on ANCOVA type analyses [39] where we assumed an expected mean baseline mean SBP of 145 mm Hg, standard deviation of 17.5 mm Hg, correlation between repeated measurements of 0.4, and attrition rate of 15% by 18 months.

2.13.3. Planned analysis of secondary outcome — cost effectiveness

The primary objective of the cost-effectiveness analysis is to estimate the cost per unit difference in effectiveness (if intervention is effective). The incremental cost effectiveness ratio (ICER) will be calculated as the difference in the average cost per patient between

Table 6
Study measures.

	Baseline	6 month	12 month	18 month
Outcome				
Blood pressure	X	X	X	X
Adverse events				
Adverse events[a]		X	X	X
Falls, lightheadedness, fatigue		X	X	X
Assessment of cognitive ability for determination of eligibility				
Short Portable Mental Status Questionnaire (SPMSQ) [52–54]	X			
Demographics and socioeconomic status				
Gender	X			
Age	X			
Race	X			
Ethnicity	X			
Educational level (highest completed grade)	X			
Marital Status	X	X	X	X
Number of people living in the patient's household	X	X	X	X
Adequacy of income	X	X	X	X
Employment status	X	X	X	X
Help with tasks	X	X	X	X
Components of body mass index				
Height	X	X	X	X
Weight	X	X	X	X
Additional measures				
Self-reported medication adherence – modification of the Morisky measure [68]	X	X	X	X
Self-efficacy for management of hypertension [69]	X	X	X	X
Exercise – Short International Physical Activity Questionnaire (IPAQ) [70]	X	X	X	X
Literacy – Rapid Estimate of Adult Literacy in Medicine (REALM) [71]	X			
Social support – presence of a close personal relationship	X			
Quality of Life – EuroQol (EQ)-5D-5L [72]	X	X	X	X
Organization of Primary Care – Patient Assessment of Chronic Illness Care (PACIC) [73–75]	X			X
Risk of having sleep apnea - Berlin questionnaire [76]		X		
Health behavior (smoking & alcohol use)	X	X	X	X
Health (years living with hypertension; home use of BP monitor; diagnosis of sleep apnea and subsequent use of CPAP machine)	X	X	X	X
Family history of hypertension	X			

[a] Adverse events reported during study phone calls are also collected and reported.

the treatment and control arm divided by the difference in mm Hg between the treatment and control arms. Salaries specific to LPN, RN, and pharmacist will be used to calculate cost of interventionist time. This time includes preparing for intervention calls, attempting to make calls, and delivering the intervention. We will account for the amount of time that patients spend at the high, medium, and low resource levels of the intervention (including actions taken). Sensitivity analyses will also be performed on types of costs: intervention, resource utilization, and total (intervention 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 constant dollars (e.g. 2016), using the Consumer Price Index for Medical Care for medical items or Consumer Price Index for other items.

3. Results of enrollment procedures

Chart review eligibility assessments were performed on 5812 patients (Fig. 1). Patients may have been found to be ineligible during the recruitment process (2185), not prioritized for further screening based on operating procedures described above (1246), unable to contact for or fully complete a recruitment process [e.g., not able to complete a screening call in the time allotted] (605), not attending the baseline study visit (123) or have declined to participate when the recruitment letter was sent, during the screening telephone call, or at the baseline/consent study visit (1268). In total, 385 veterans were enrolled and randomized between November 6, 2012 and April 9, 2015, 192 to the intervention arm and 193 to the control arm.

Reflecting the VA patient population as a whole, subjects are predominately men (92.5%). Their mean age was = 63.5 years. The majority of patients are black (61.8%), with 33.8% being white and 4.5% being of another race or multiple races; 3.4% are of Latino(a) or Hispanic origin or decent. The majority are married (57.0%) and approximately one-quarter have a low level of literacy. More than half have diabetes (57.1%) and mean baseline SBP of 143.6 mm Hg. Detailed baseline characteristics by arm can be found in Table 7. The two arms were similar at baseline.

4. Discussion

The TDM Trial is a pragmatic trial designed to test interventions in "real world" practices so that, if effective, they can be more rapidly implemented. In this particular study intervention patients have the intensity of their care titrated based upon their BP control [40–42]. By reserving the most intensive and expensive strategies to veterans with greatest clinical need, this titrated strategy can potentially lead to more efficient use of resources. 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, the VA's version of the Patient Centered Medical Home (PCMH) [43–45]. Further, the study will provide evidence concerning whether the titrated disease management process may be used as a method for healthcare systems to enhance the allocation of scarce resources.

The TDM Trial recognizes that LPNs, RNs, and clinical pharmacists have varying scopes of practice, as well as differing salaries. LPNs [known as licensed vocational nurses (LVNs) in California and Texas] differ from RNs in several important dimensions. While both are nurses,

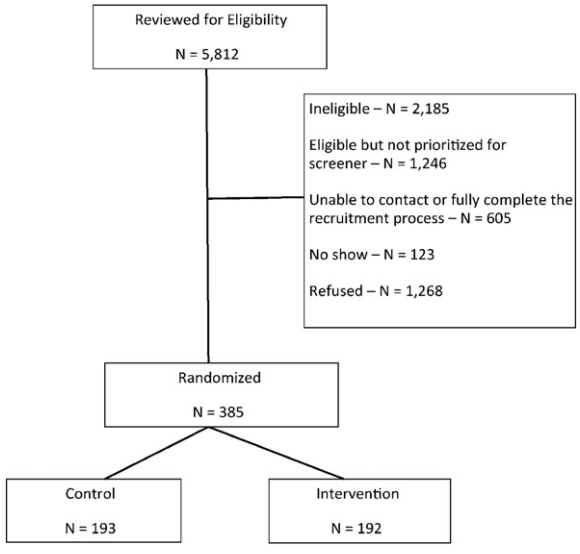

Fig. 1. Study flow through randomization.

Table 7
Baseline study characteristics.

	Overall N = 385	TDM intervention N = 192	Control N = 193
Age, mean (SD)	63.5 (8.8)	64.2 (9.0)	62.9 (8.5)
Gender, observed			
Male	356 (92.5)	176 (91.7)	180 (93.3)
Female	29 (7.5)	16 (8.3)	13 (6.7)
Marital status[d]			
Married	219 (57.0)	115 (60.2)	104 (53.9)
Living together, committed relationship	6 (1.6)	2 (1.0)	4 (2.1)
Divorced/separated	110 (28.6)	50 (26.2)	60 (31.1)
Widowed	17 (4.4)	8 (4.2)	9 (4.7)
Single, never married	32 (8.3)	16 (8.4)	16 (8.3)
Latino(a) or Hispanic origin/descent[d]			
Yes	13 (3.4)	9 (4.8)	4 (2.1)
No	366 (96.6)	179 (95.2)	187 (97.9)
Race[d]			
White	129 (33.8)	68 (35.6)	61 (31.9)
Black	236 (61.8)	111 (58.1)	125 (65.4)
Other	17 (4.5)	12 (6.3)	5 (2.6)
Highest level of education			
Less than high school graduate	27 (7.0)	14 (7.3)	13 (6.7)
High school graduate or GED	108 (28.1)	60 (31.3)	48 (24.9)
Some college or technical school	160 (41.6)	78 (40.6)	82 (42.5)
College graduate	59 (15.3)	26 (13.5)	33 (17.1)
Post college education	31 (8.1)	14 (7.3)	17 (8.8)
REALM[d]			
Less than 60	93 (24.5)	40 (21.3)	53 (27.7)
60 or more	286 (75.5)	148 (78.7)	138 (72.3)
Household financial situation[d]			
After paying the bills, you still have enough money for special things that you want	142 (37.3)	74 (38.9)	68 (35.6)
You have enough money to pay the bills, but little spare money to buy extra or special things	155 (40.7)	68 (35.8)	87 (45.5)
You have money to pay the bills, but only because you have to cut back on things	47 (12.3)	27 (14.2)	20 (10.5)
You are having difficulty paying the bills, no matter what you do	37 (9.7)	21 (11.1)	16 (8.4)
Current living situation			
Own home/apartment	364 (94.5)	184 (95.8)	180 (93.3)
No stable residence	21 (5.5)	8 (4.2)	13 (6.7)
Blood relative(s) with high blood pressure			
Yes	305 (79.2)	150 (78.1)	155 (80.3)
No	36 (9.4)	16 (8.3)	20 (10.4)
Don't know	44 (11.4)	26 (13.5)	18 (9.3)
Ever smoked or used tobacco products			
Yes	283 (73.5)	142 (74.0)	141 (73.1)
No	102 (26.5)	50 (26.0)	52 (26.9)
Smoked or used tobacco products in past 6 months[d]			
Yes	108 (28.1)	49 (25.7)	59 (30.6)
No	276 (71.9)	142 (74.3)	134 (69.4)
Current smoker[d]			
Yes	94 (24.5)	45 (23.6)	49 (25.4)
No	290 (75.5)	146 (76.4)	144 (74.6)
Diabetes			
Yes	220 (57.1)	109 (56.8)	111 (57.5)
No	165 (42.9)	83 (43.2)	82 (42.5)
Satisfied with BP control[a,d], mean (SD)	6.2 (2.8)	6.1 (2.7)	6.2 (2.8)
Average systolic BP[b], mean (SD)	143.6 (17.6)	143.5 (17.7)	143.7 (17.5)
Average diastolic BP[b], mean (SD)	79.9 (13.6)	79.4 (14.6)	80.3 (12.4)
Systolic BP status[e]			
Significantly out of control	180 (46.8)	88 (45.8)	92 (47.7)
Moderately out of control	115 (29.9)	57 (29.7)	58 (30.1)
In control	90 (23.4)	47 (24.5)	43 (22.3)
Have someone to help with tasks, if needed[d]			
Yes	337 (88.2)	163 (85.3)	174 (91.1)
No	45 (11.8)	28 (14.7)	17 (8.9)
Medication adherence on modified BP medication adherence[c]			
Non-adherent	164 (42.6)	82 (42.7)	82 (42.5)
Adherent	221 (57.4)	110 (57.3)	111 (57.5)
Health professionals control my health[d]			
Strongly agree	66 (17.2)	37 (19.4)	29 (15.1)
Agree	148 (38.6)	73 (38.2)	75 (39.1)
Disagree	131 (34.2)	60 (31.4)	71 (37.0)
Strongly disagree	38 (9.9)	21 (11.0)	17 (8.9)

SD = standard deviation, BP = blood pressure, REALM = Rapid Estimate of Adult Literacy in Medicine.
Note. n (%) unless otherwise indicated.
[a] Scale of 1–10, with 1 = definitely not satisfied and 10 = definitely satisfied
[b] Average of three blood pressure measurements taken at baseline
[c] Assessed using Morisky self-reported adherence measure. A positive response to at least one question indicated non-adherence.
[d] Missing data: note, unless otherwise indicated, responses of 'don't know' or 'refused' were considered missing. Information is missing as follows: marital status-1, race-3, Latino(a)/Hispanic origin-6, household finances-4, smoker, current and 6 mo-1, satisfaction with blood pressure control-1, REALM-6, Help with tasks-3, Health professionals control my health-2
[e] Significantly out of control: systolic BP ≥ 140 for diabetics and ≥150 for those without diabetes; Moderately out of control: systolic BP ≥ 130 for diabetics and ≥140 for those without diabetes; In control: systolic BP < 130 for diabetics and <140 for those without diabetes

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 have done, LPNs 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 and time in training, RNs are paid significantly more than LPNs [46,47].

Clinical pharmacists have been studied as part of clinical teams managing hypertension to improve BP control [7,48]. They are trained in medication management and, in that role, can provide clinical assessments of patients. In the VA and many states, clinical pharmacists can directly prescribe medications within their scope of practice. Even in settings where prescribing is not permitted pharmacists can recommend pharmaceutical management to prescribing providers. However, there are far fewer clinical pharmacists than nurses available to participate in disease and self-management programs in most clinical settings, making use or RNs and LPNs appealing, when clinically appropriate. Additionally, clinical pharmacists have significantly higher salaries due to their greater scope of practice.

The TDM Trial is testing a disease management program that 1) matches the resources intensity and skill set of clinicians to the clinical needs of patients and 2) allows the intensity to be adjusted up or down over the course of the program. The strategy is appealing because most health systems do not have the human resources necessary to provide the highest intensity resources to all patients who could potentially benefit from disease management programs and patients' clinical needs likely vary over time. Finally, the decision was made to test the intervention against a type of non-tailored telephone intervention that has been previously shown to improve blood pressure control because we believed that organizations would need to see superiority over such a low intensity program to consider the potential for utilizing resources to implement a TDM approach.

The TDM Trial has limitations and considerations that may impact the study. The participants are predominantly older men, which reflects the VA population as a whole [49]. Further, the trial is being conducted among patients receiving primary care from one of four locations affiliated with only one VA medical center. Although our participants are racially diverse and are socioeconomically vulnerable, these factors limit generalizability. Second, we did not have the study personnel needed to maintain blinding among those collecting study outcomes. However, baseline outcomes were obtained before randomization, and we used a standardized protocol for measuring BP and implemented procedures to audit and maintain data quality. These processes have been employed to reduce the potential of bias resulting from the inability to maintain blinding during the study. Third, we lack the resources to examine whether any differences in results will continue after the study ends. However, we recently evaluated clinical benefits of calls similar to those in the TDM Trial and home BP monitoring after the trial concluded. The positive effect of the intervention, which did not include titration of resource intensity, was sustained 18 months following study conclusion [50]. Finally, we were not able to maintain our original goal of only including patients who had uncontrolled SBP at baseline. In the final sample, 23.4% of patients had blood pressure under control based on measurements collected at the baseline study visit.

5. Conclusion

The TDM Trial is a pragmatic health services research clinical trial testing an 18-month intervention titrating the resource intensity of disease management based on the clinical status of patients. The 385 individuals randomized in the trial represent a diverse group of veterans treated by the VA. The VA, like all healthcare organizations, must make the best use of available resources to enhance the health of those who receive care within the system. The TDM Trial will provide additional evidence concerning how to organize population-health interventions to lead to maximum benefit of patients.

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