Contemporary Clinical Trials 92 (2020) 105939

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

Design of a pragmatic cluster-randomized trial comparing telehealth care and best practice clinic-based care for uncontrolled high blood pressure

Karen L. Margolis[a,*], A. Lauren Crain[a], Anna R. Bergdall[a], MarySue Beran[a], Jeffrey P. Anderson[a], Leif I. Solberg[a], Patrick J. O'Connor[a], JoAnn M. Sperl-Hillen[a], Pamala A. Pawloski[a], Jeanette Y. Ziegenfuss[a], Dan Rehrauer[a], Christine Norton[a], Patricia Haugen[a], Beverly B. Green[b], Zeke McKinney[a], Amy Kodet[a], Deepika Appana[a], Rashmi Sharma[a], Nicole K. Trower[a], RaeAnn Williams[c], Benjamin F. Crabtree[d]

[a] HealthPartners Institute, Mailstop 23301A, PO Box 1524, Minneapolis, MN 55440-1524, United States of America
[b] Kaiser Permanente Washington Health Research Institute, 1730 Minor Av, Seattle, WA 98101, United States of America
[c] HealthPartners, Mailstop 31100A, PO Box 1524, Minneapolis, MN 55440-1524, United States of America
[d] Rutgers Robert Wood Johnson Medical School, Department of Family Medicine and Community Health, New Brunswick, NJ 08901, United States of America

A B S T R A C T

Background: Uncontrolled hypertension is the largest single contributor to all-cause and cardiovascular mortality in the U.S. population. Nurse- and pharmacist-led team-based care and telehealth care interventions have been shown to result in large and lasting improvements in blood pressure (BP); however, it is unclear how successfully these can be implemented at scale in real-world settings. It is also uncertain how telehealth interventions impact patient experience compared to traditional clinic-based care.

Aims/objectives: To compare the effects of two evidence-based blood pressure care strategies in the primary care setting: (1) best-practice clinic-based care and (2) telehealth care with home BP telemonitoring and management by a clinical pharmacist. To evaluate implementation using mixed-methods supported by the RE-AIM framework and Consolidated Framework for Implementation Research.

Methods: The design is a cluster-randomized comparative effectiveness pragmatic trial in 21 primary care clinics (9 clinic-based care, 12 telehealth care). Adult patients (age 18–85) with hypertension are enrolled via automated electronic health record (EHR) tools during primary care encounters if BP is elevated to ≥150/95 mmHg at two consecutive visits. The primary outcome is change in systolic BP over 12 months as extracted from the EHR. Secondary outcomes are change in key patient-reported outcomes over 6 months as measured by surveys. Qualitative data are collected at various time points to investigate implementation barriers and help explain intervention effects.

Conclusion: This pragmatic trial aims to inform health systems about the benefits, strengths, and limitations of implementing home BP telemonitoring with pharmacist management for uncontrolled hypertension in real-world primary care settings.

1. Introduction

Elevated blood pressure (BP), or hypertension, is the most common chronic condition for which patients see primary care clinicians [1]. Based on newly updated guidelines, 46% of the US adult population has hypertension, a major risk factor for heart attacks, stroke, heart failure, and kidney failure [2,3]. Compared with other modifiable cardiovascular (CV) risk factors, elevated BP is the largest single contributor to all-cause mortality (30%) and CV mortality (41%) in the U.S. population [4,5]. Achieving recommended levels of BP control has been shown to lower the risk of future CV events (heart attacks and strokes), the most common cause of death and disability worldwide [1]. However, between 2007 and 2016, about half of people with hypertension in the U.S. did not have their BP controlled to recommended levels, with disparities in rates of BP control in racial/ethnic minority and low socioeconomic status populations [6,7].

Although access to health care remains a barrier to attaining BP control, > 80% of people with hypertension have health insurance and a regular source of health care [8,9]. Patients with hypertension average four clinician visits each year [10], which should provide ample opportunity to detect and address uncontrolled hypertension. However, clinicians are often slow to start antihypertensive drugs or increase treatment intensity with higher doses or combinations of drugs, even when BP is elevated at several clinic visits, a complex phenomenon dubbed “clinical inertia.” [11] In addition, patients face challenges implementing behavior changes related to nutrition,

* Corresponding author at: HealthPartners Institute, Mailstop 23301A, PO Box 1524, Minneapolis, MN 55440-1524, United States of America.
E-mail address: Karen.L.Margolis@Healthpartners.com (K.L. Margolis).

https://doi.org/10.1016/j.cct.2020.105939
Received 3 October 2019; Received in revised form 16 January 2020; Accepted 20 January 2020
Available online 22 January 2020
1551-7144/

exercise, stress and other lifestyle factors and difficulties with taking medications, including side effects, adherence, and costs. Since high blood pressure may not cause immediate problems for patients, they may also not understand the long-term consequences of uncontrolled hypertension [12–14].

Team-based care offers a promising approach to reduce some barriers to hypertension control [15–20]. In a 2006 meta-analysis of 28 studies, most of which included a nurse or a pharmacist team member as a care manager, average BP dropped by 10/4 mmHg, and the absolute proportion of patients achieving BP control improved by 20% [15]. A recently updated meta-analysis including 31 additional studies confirmed these findings, albeit with smaller BP reductions (5/2 mmHg, proportion achieving BP control improved by 12%) [21]. In addition, self-measured home BP monitoring has been identified as a useful, cost-saving adjunct to clinic-based care in comprehensive evidence reviews [15,16,22–28]. The combination of these interventions may be synergistic by helping patients gain insight and giving rapid feedback on response to treatment changes.

In previous work, we combined home based BP measures with pharmacist-led telephone communication in a randomized study of 450 consenting patients at 16 primary care clinics [29]. Patients with uncontrolled hypertension who received this telehealth intervention safely achieved 10/5 mmHg more BP reduction during 12 months compared with patients who continued to receive routine primary care [29]. We sought to test a larger-scale, realistic implementation of this program in primary care clinics in the same large health care system to determine whether it lowers BP more than current primary care approaches in patients with uncontrolled hypertension, and whether patients report outcomes that favor one approach over the other.

2. Methods

2.1. Study overview and aims

This cluster-randomized comparative effectiveness pragmatic trial is being conducted in 21 primary care clinics (Fig. 1). The clinic-based care approach incorporated best practices in hypertension care in 9 clinics with an enrollment goal of at least 1000 patients. It incorporated practices recommended by professional organizations for face-to-face visits, and relies primarily on the clinician-medical assistant dyad. The telehealth care approach adapted and implemented the previous successful research-tested model in 12 clinics with an enrollment goal of at least 1000 patients. It differs from clinic-based care through the addition of home BP telemonitoring and home-based telehealth care coordinated by Medication Therapy Management (MTM) pharmacists providing comprehensive medication management [30].

The study aims and hypotheses are:

Aim 1: In a pragmatic cluster-randomized trial in patients with uncontrolled hypertension, compare the effects of two evidence-based strategies on lowering blood pressure and other outcomes important to patients: best-practice clinic-based care and home-based telehealth care.

Null Hypothesis 1.1: Compared with patients in clinics assigned to clinic-based care, patients in clinics assigned to telehealth care will have no greater change in systolic blood pressure over 12 months of follow up.

Null Hypothesis 1.2: Compared with patients in clinics assigned to clinic-based care, patients in clinics assigned to telehealth care will report no differences in: a) treatment side effects; b) ratings of patient experience of hypertension care; and c) self-monitoring rates and confidence in self-care.

Aim 2: To evaluate implementation of the telehealth care and clinic-based care interventions using a mixed-methods approach supported by the RE-AIM (reach, effectiveness, adoption, implementation, and maintenance) and Consolidated Framework for Implementation Research (CFIR) frameworks.

To ensure that the study addressed the relevant questions and concerns of patients, caregivers, clinicians, and other healthcare stakeholders, the research team included two patient investigators and regularly seeks feedback from health system stakeholders, external stakeholders, and a patient advisory board.

2.2. Setting

HealthPartners is a nonprofit integrated health system in Minnesota and western Wisconsin serving 1.8 million health plan members and 1.2 million patients. It includes a multispecialty group practice of > 1800 physicians, 25 MTM pharmacists, eight hospitals, and 55 primary care clinics. The HealthPartners care group accepts all forms of commercial insurance, Medicaid, and Medicare, and the patients are diverse by age, race/ethnicity, and socioeconomic status.

2.3. Recruitment and randomization of clinics

Clinics were eligible to participate if they had an MTM pharmacist onsite at least one half-day per week and used standardized methods to measure BP with validated oscillometric BP monitors at the time of clinic recruitment in early 2017. All 21 eligible clinics agreed to participate and these clinics had 15 MTM pharmacists on staff. Two pairs of clinics were each randomized as a single unit due to co-location with shared MTM and clinic management, resulting in a total of 19 randomized units.

We conducted a 3-month pilot test of study procedures in four vanguard clinics prior to full implementation at all study clinics. Clinics were randomized within each of four strata defined by 1) their status as a vanguard or non-vanguard clinic, and 2) among non-vanguard clinics, the proportion of clinic patients whose systolic BP (SBP) and diastolic BP (DBP) met the criteria for BP control in the month prior to randomization [31]. The four vanguard clinics were randomized in stratum 1. The 15 non-vanguard clinics were grouped into tertiles of their pre-randomization BP control rates (strata 2–4). The study statistician used a random number generator to assign a randomly selected number from a normal distribution (M = 0, SD = 1, seed = 20,170,531) to each clinic. Within each stratum, clinics with below-median numbers were assigned to the Best Practice Clinic-based care intervention, and those with above-median numbers to the Telehealth care intervention. The randomized assignment of clinics to intervention group was concealed from study staff until clinic trainings were scheduled. For practical reasons, intervention group assignment was not concealed from clinic staff and patients.

2.4. Inclusion and exclusion criteria for patients

Eligibility was evaluated using automated real-time algorithms that were applied upon BP entry during primary care office encounters in randomized clinics. Patients were eligible if they 1) were age 18 to 85; 2) had two or more qualifying encounters with a hypertension diagnosis code within the last 24 months; 3) had a visit with their assigned primary care provider (PCP) in the last 12 months with or without a hypertension diagnosis code; 4) met high BP study criteria at the current encounter; 5) met high BP study criteria at their most recent previous qualifying encounter and 6) were currently in the clinic where their assigned PCP practices.

According to the nursing protocol for BP measurement, BPs were repeated if the first BP was elevated, defined as a SBP ≥ 140 mmHg or DBP ≥ 90 mmHg. Study criteria for uncontrolled BP for patients were defined as SBP ≥ 150 mmHg or DBP ≥ 95 mmHg in the first BP and in a repeated BP within the same encounter. A previous qualifying encounter is defined as an office visit with a medical assistant, nurse, physician, nurse practitioner, or physician assistant in internal medicine, family medicine, geriatric medicine, cardiology, endocrinology, or nephrology clinics. We selected study criteria for uncontrolled BP based

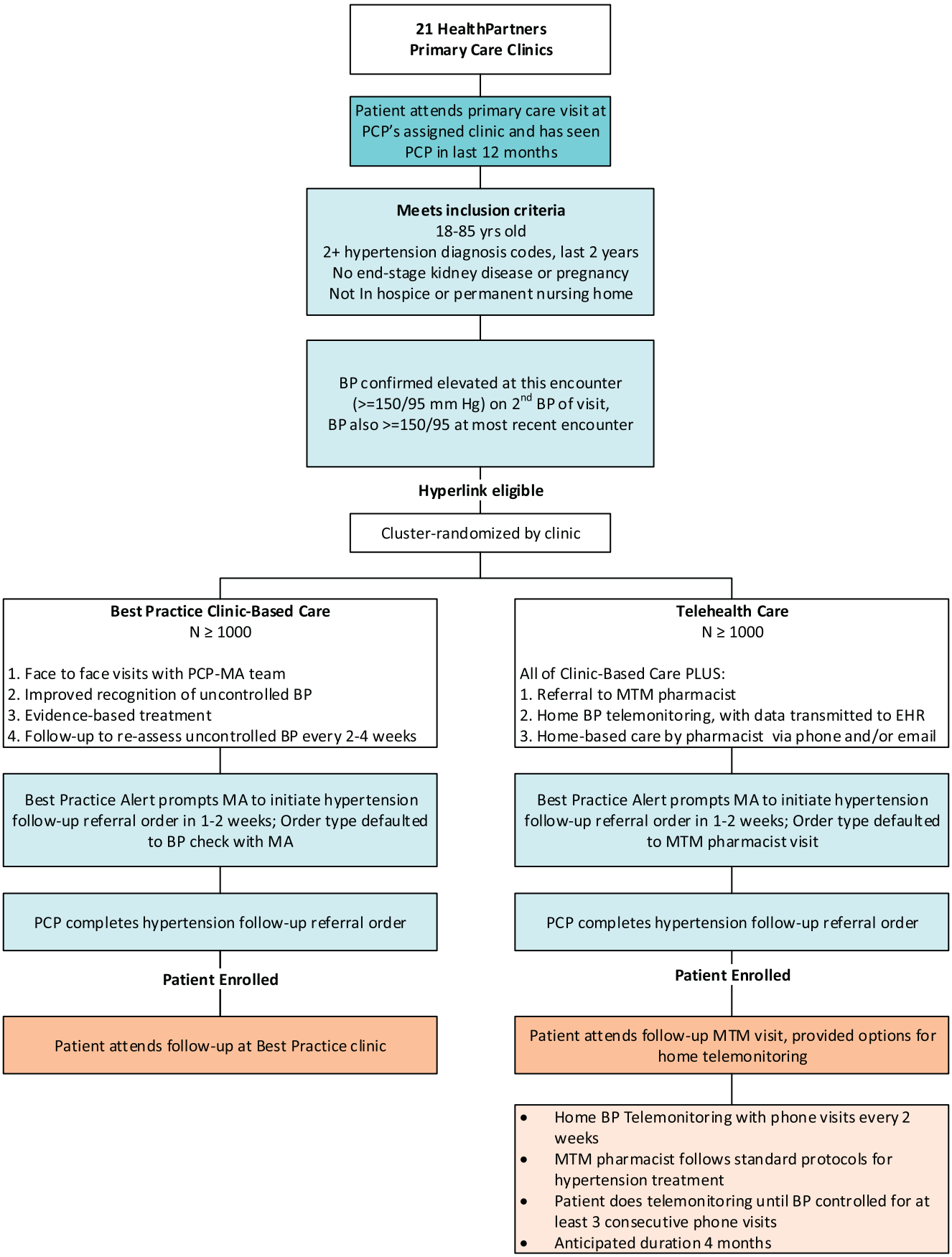

Fig. 1. Study design overview
Abbreviations: BP (blood pressure), EHR (electronic health record), MA (Medical Assistant), MTM (Medication Therapy Management), PCP (primary care physician).

on the estimated sample size, the estimated number of eligible patients per clinic, and the capacity of MTM pharmacists in telehealth care clinics to accommodate additional follow-up referrals.

The study excluded 1) pregnant patients, since they require specialized obstetric care, 2) patients with end-stage renal disease, who need specialized care from kidney disease specialists, 3) patients in hospice care, and 4) patients who permanently reside in a nursing home. The population of interest was intended to represent patients who were included in national hypertension quality measures and had persistently uncontrolled hypertension.

2.5. Enrollment of patients

For eligible patients, a best practice alert automatically prompted the medical assistant to set up a referral order for hypertension follow-up in primary care for the clinician to review and sign. The referral order defaulted to a provider/visit type depending on the clinic's randomization status (medical assistant BP check for clinic-based care and MTM pharmacist for telehealth care clinics). Other follow-up options included the PCP, cardiology, or nephrology. Follow-up urgency was set to 2 weeks, unless the BP $\geq$180/110 mmHg, in which case it was set to 1 week. Clinicians were able to change the provider type or timing of follow-up from the defaulted choice on the referral order if they felt that a different choice was best for an individual patient, but telehealth care with home BP telemonitoring was only available for patients in telehealth clinics. Enrollment in the trial was defined by an eligible patient having a signed hypertension referral order. The primary care encounter during which this occurred was referred to as the index visit from which follow-up time is calculated. Patients were enrolled over an 18-month period, with the goal of recruiting at least 2000 patients.

2.6. Interventions

2.6.1. Best practice clinic-based care

The best practice clinic-based care intervention was based on practices recommended by professional organizations at the time the study was designed and affirmed in subsequent national guidelines (Table 1) [3,32–36]. Infrastructure and policies in place at HealthPartners that promote high quality care included the following components: 1) accurate BP measurement using validated oscillometric BP monitors (Omron HEM 907XL) [37] according to a standard nursing protocol; 2) a hypertension registry to identify and track the patient population with hypertension and systematically engage those with uncontrolled BP in additional BP checks with a medical assistant; 3) PCP and clinic performance measurement on BP control with monthly feedback; 4) an evidence-based hypertension treatment protocol that promotes low-cost generic medication and single-pill combination therapy; and 5) no-cost BP check visits with a medical assistant with a standing order protocol for registered nurses to adjust hypertension treatment when BP is uncontrolled. Interpreters were available for all non-English speaking patients for both clinic and telephone encounters. The best practice clinic-based intervention reflects standard workflows to the extent they were followed by each clinic. All clinicians and clinic received monthly reports on BP control in their attributed patients, and the study provided additional feedback reports to clinic leadership to support optimal delivery of these standards of care.

Eligible patients in clinics randomized to best practice clinic-based care were recommended to follow up with a medical assistant for a BP check within 1 or 2 weeks depending on the severity of their elevated BP. Patients could schedule their follow-up visit in the clinic or by phone. Follow-up referral orders were added to a "referral work queue" used by clinic assistants to conduct scheduling outreach. This work queue contained many types of referrals back to primary care for various purposes. Clinic assistants placed up to two phone calls to reach non-scheduled patients and then sent a letter to non-responders. All attempts to reach the patient were noted in the EHR. All enrolled patients were also contacted by staff from either the clinic or a centralized resource to schedule BP checks through the hypertension registry, which was a standard process for all hypertension patients with uncontrolled BP in the care system. If BP remained uncontrolled at the initial post-enrollment visit, HealthPartners policies promoted follow-up at 2–4 week intervals with either a clinician or medical assistant until BP is controlled.

2.6.2. Telehealth care

The telehealth care intervention was based on and adapted from our previous research [38]. Telehealth clinics offered best-practice clinic-based care as described above, with the added components of systematic home BP telemonitoring and BP management by an MTM pharmacist. Although for simplicity we refer to MTM pharmacists carrying out the telehealth care management, telehealth care was designed to be adaptable for shared coordination by other qualified members of primary care teams, e.g., nurse practitioners, registered nurses, and health coaches. For example, one eligible large clinic had limited MTM pharmacist capacity, and in this clinic the telehealth care management was done by nurse practitioners with some assistance by registered nurses. Eligible patients in clinics randomized to telehealth care were recommended to follow up with an MTM pharmacist within 1 or 2 weeks depending on the severity of the elevated BP. This method fit with patient feedback from our previous study to strengthen the clinician-pharmacist connection by having the clinician place the initial referral order for telehealth care. Follow-up scheduling was completed

Table 1
Components of best-practice clinic-based care and telehealth care.

Component	Measurement of intervention fidelity in primary care clinics
Best practice clinic-based care	
Accurate BP measurement	% all primary care SBPs ending in 0 or 8
Repeat elevated BP	% of elevated 1st BPs with a repeat BP in primary care encounters
Recognition of uncontrolled BP	% of encounters with confirmed elevated BP with ICD-10 hypertension diagnosis code
Action taken for uncontrolled clinic BP	% of encounters with elevated clinic BP with antihypertensive medication class added
Referral follow-up completion with MA	% of enrolled patients with MA BP check within 6 weeks
Re-assess elevated BP after 2–4 weeks	% of enrolled patients with any follow-up within 6 weeks
Ad hoc home BP monitoring, no data transmitted	Patient survey
PCP and clinic performance measurement and feedback	Field observations
Telehealth care (added to clinic-based care)	
Patient completed intake visit with MTM pharmacist	% of enrolled patients with pharmacist follow-up within 6 weeks
Systematic home BP telemonitoring, data transmitted	Patient survey, equipment orders, EHR flow sheet data
Systematic home-based care by telephone/secure email	Number of pharmacist phone/email follow-up visits
Action taken for uncontrolled home BP	% of encounters with elevated home BP with antihypertensive medication class added

Abbreviations: blood pressure (BP), systolic blood pressure (SBP), medical assistant (MA), primary care physician (PCP), electronic health record (EHR), Medication Therapy Management (MTM).

Table 2
Definition and source data for aim 1 outcomes.

Variable	Description	Data source	Timing
Aim 1 primary outcome			
Systolic BP	Change in systolic BP	EHR vital signs	Trajectory over 12 and 24 mo.
Aim 1 secondary outcomes			
Side effects	New survey items	Patient survey	Baseline, 6, 12, 24 mo.
Patient care experience/ satisfaction	BP care rating, PACIC items [61]	Patient survey	Baseline, 6, 12, 24 mo.
Self-monitoring/ confidence in self-care	e-BP questionnaire items [52]	Patient survey	Baseline, 6, 12, 24 mo.
Aim 1 other outcomes			
Diastolic BP	Change in diastolic BP	EHR vital signs	Trajectory over 12 and 24 mo.
Antihypertensive drugs	Number of antihypertensive drug classes	EHR Medication	Status over 24 mo.
Lipid levels	Total, HDL and LDL cholesterol	EHR lab	Trajectory over 12 and 24 mo.
Statin use	Current use of statins	EHR Medication	Status over 24 mo.
Smoking	Current cigarette smoking	EHR	Status over 24 mo.
10-year CV risk (age 40–85)	ACC/AHA pooled risk equation [63]	EHR vital signs, lab, diagnoses	Trajectory over 12 and 24 mo.
30-year CV risk (age 18–39)	Framingham model [64]	EHR vital signs, lab, diagnoses	Trajectory over 12 and 24 mo.
Laboratory abnormalities	Potassium, sodium, creatinine	EHR lab	Trajectory over 12 and 24 mo.
Hypotension, dizziness, fainting	ICD-10 codes I95.x, R42, R55	EHR encounters, diagnoses	Any post-baseline occurrence.

Abbreviations: blood pressure (BP), electronic blood pressure (e-BP), electronic health record (EHR), Patient Assessment of Care for Chronic Conditions (PACIC), cardiovascular (CV), high-density lipoprotein (HDL), low-density lipoprotein (LDL), American College of Cardiology/American Heart Association (ACC/AHA), International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10).

by a similar process to the referral work queue used in best practice clinics, except that scheduling outreach was done by an MTM program coordinator rather than a clinic assistant.

Patients referred to an MTM pharmacist in telehealth clinics attended an initial one-hour face-to-face visit. During this initial visit, pharmacists conducted a full medication review and followed the standard hypertension protocol under their collaborative practice agreement, which includes medication adherence assessment, titration of anti-hypertensive medication, and lifestyle and nutrition counseling. Pharmacists also offered the option of home BP telemonitoring. For those electing to participate, pharmacists measured the patient's arm to select the appropriately sized cuff, instructed patients on proper technique for home BP measurement, reviewed home BP goals (< 135/85 mmHg, or 5 mmHg lower than clinic goal) and provided patients with a packet of information about monitoring BP at home and expectations while working with the MTM pharmacist. Written materials were available in English, Spanish, Somali, Hmong, and Vietnamese. Patients were asked to check their BP at least 6 times weekly (eg, 3 days each week, morning and evening), with duplicate measurements each time if possible. Phone follow-up with the pharmacist was scheduled for 2–3 weeks after the initial visit, and an electronic order for the home BP device was transmitted from the EHR to the telemonitoring vendor, AMC Health (New York, NY).

Patients received the home BP telemonitoring kit at their home within 3–4 business days. The kit contained a BP monitor with upper arm cuff, a cellular modem, and an instructional packet. Patients with arm sizes ≤17.7″ in circumference received an A&D model UA-767 *Plus* BT-Ci telemonitor, and those with arm sizes > 17.7″ in circumference received a Welch Allyn 1500 Series (901042). Patients were contacted by AMC Health customer service to ensure the monitor was properly set up and the modem was transmitting data.

The BP devices transmitted data to the modem via Bluetooth, which then sent the data to the vendor's cloud storage via cellular network. Data were then securely passed into the EHR (Epicare, Epic, Verona, WI) from the vendor's cloud through an HL7 interface within minutes, where they were filed into a dedicated remote monitoring vital signs flowsheet that could be viewed by any clinician. The MTM pharmacist also received a summary of each patient's flowsheet BPs every 7–14 days, and special alerts if a BP was extremely high (SBP ≥ 190, DBP ≥ 120) or low (SBP < 80), or if no BP values were transmitted for 2 weeks.

Following the initial visit, the MTM pharmacist communicated with the patient primarily by telephone every 2–4 weeks, adjusting medication, encouraging adherence, and advising lifestyle changes. Pharmacists used an interactive web-based data visualization tool that summarized the patient's home BP data from a select time period to guide treatment decisions per standard protocol. Other CV risk factors including smoking, hyperlipidemia, hyperglycemia in diabetic patients, and use of aspirin were addressed as needed using evidence-based protocols. A Program Navigator supported patient adherence to home monitoring and phone visit attendance through phone calls and letters. MTM pharmacists documented all patient encounters in the EHR and sent encounter notes electronically to the PCP. Because MTM pharmacists were co-located in clinics with PCPs, informal in-person communication and consultation also occurred.

Patients were engaged in telemonitoring until BP was controlled or until the pharmacist and patient agreed that telehealth care was unlikely to result in further BP lowering. BP control was defined as three or more consecutive visits at least two weeks apart with ≥75% of home BP measurements below 135/85 mmHg. Patients were discharged from telehealth if they were persistently non-adherent with home monitoring or phone visits or became unreachable. Based on home BP trajectories in our previous study, telehealth monitoring duration was expected to last an average of 4 months, with flexibility as needed [39]. When telemonitoring was discontinued, patients returned the telemonitoring device to the vendor via pre-paid shipping and were sent an equivalent non-transmitting device to keep in order to continue monitoring their BP at home (A&D model 767 or 787, depending on arm circumference). At the conclusion of home telemonitoring, MTM pharmacists provided a warm hand-off to the PCP by sending an EHR message summarizing medication changes and BP results achieved during the intervention.

Patients had the opportunity to re-engage with the MTM pharmacist any time after completing the home BP intervention. The Program Navigator monitored post-intervention office visit BPs and conducted phone outreach to patients with uncontrolled BP, reinforcing home BP monitoring, medication adherence and helping to schedule follow-up care with the pharmacist or PCP as needed.

2.7. Outcomes and Measurements

2.7.1. Primary aim 1 outcome

The primary outcome was change in SBP after 12 months of follow-up (Table 2). BP values that were routinely collected in clinical encounters were extracted from the EHR to assess study eligibility and change in SBP for 24 months thereafter. Our previous research has shown that using BP recorded in the EHR for clinical care and BP

measured in a research setting resulted in similar intervention effectiveness [40].

2.7.2. Secondary aim 1 outcomes

Secondary outcomes were change in patient-reported outcomes (PROs) between baseline and 6 months, corresponding with the expected length of the telehealth intervention. PRO measures were collected by patient surveys (Table 2), which were available in English, Spanish, Somali, Hmong, and Vietnamese. All enrolled patients were mailed a baseline survey within one week of their index encounter, with telephone follow-up of initial non-responders by trained interviewers. Baseline respondents received follow-up surveys 6, 12 and 24 months after enrollment administered by mail, telephone or electronically according to the patient's preference. The initial baseline survey mailing included a $2 non-contingent cash incentive, and patients also received a $10 gift card for each completed survey [41–43].

The survey was developed using existing questions with known psychometric properties where available. Where not available, questions were written by the project team, reviewed by patient partners for face validity and pilot tested with patients similar to the target population. Survey questions included demographics, rating of general health, rating of BP care over the last 6 months [44], patient experience of hypertension care (modified from Patient Assessment of Chronic Illness Care survey) [45], frequency and sharing of BP measurements outside of clinic [44], confidence in managing blood pressure [44], side effects from medications (developed for this study), and overall burden of blood pressure care (modified from the Treatment Burden Questionnaire) [46].

2.7.3. Aim 1 other outcomes

We also collected clinical information from the EHR on cardiovascular risk factors that may be influenced directly or indirectly by telehealth care or clinic-based care (DBP, antihypertensive medication use, lipid levels, statin use, and smoking.) These data were used to calculate overall cardiovascular risk based on 10-year AHA/ACC pooled risk Eqs. [47] and the Framingham 30-year risk Eq. [48]. The study also monitored laboratory abnormalities that may be affected by hypertension medications (sodium, potassium, creatinine), as well as diagnostic codes for hypotension, dizziness, and fainting (I95.x, R42, R55) that might result from overly aggressive blood pressure lowering.

2.7.4. Aim 2 outcomes

Aim 2 outcomes included barriers and facilitators to intervention uptake and fidelity that help explain primary and secondary intervention effects. We used constructs from the RE-AIM and CFIR frameworks [49–51] to evaluate barriers and facilitators to the adoption, implementation, and maintenance of the intervention, monitor intervention implementation fidelity and adaptations, and interpret reasons for variations in implementation success or failure.

Quantitative indicators of intervention implementation included enrollment and follow-up rates, measures of engagement in telehealth care, and the hypertension care process measures described in Table 1, which were also stratified to the clinic and clinician level. Qualitative data, including semi-structured interviews and focus groups with patients, clinicians, and system leaders, observational field notes, and systematic assessment of stakeholder priorities were used to explore barriers and facilitators to intervention implementation and maintenance throughout the observation period and understand adaptations needed for successful implementation. The RE-AIM measures are listed in Table 3.

2.8. Analysis

2.8.1. Aim 1 analyses

H1.1 will be tested using random coefficients models in which SBP values documented at all qualifying encounters for 24 months post-enrollment are predicted from a random clinic intercept and the fixed effects of clinic-randomized treatment group, time elapsed in years from enrollment to the SBP, the treatment by time interaction, index visit SBP, stratification variables, and characteristics related to SBP that are imbalanced across treatment groups. Enrolled patients are assigned to the treatment group to which their clinic is randomly assigned, regardless of their adherence to any component of the clinic-based care or telehealth care approaches in an intention-to-treat (ITT) analysis. The time parameter estimates the annual rate of change in SBP among clinic-based care patients, while the time by treatment parameter estimates the difference in rate of SBP change among telehealth relative to clinic-based care patients. The H1.1 model will be adapted for H1.2 by replacing the elapsed time parameter with a dummy indicator to denote whether the PRO is an enrollment or 6-month survey response.

We will analyze whether treatment effects differ among patient subgroups defined by enrollment SBP, age, race/ethnicity, socioeconomic status (defined by Medicaid insurance vs. other payor), and comorbidity (diabetes, cardiovascular disease, and number of prescribed medications at enrollment).

2.8.2. Aim 1 power analyses

A power analysis estimated the minimum detectable standardized effect (MDSE) for the time by treatment effect in the H1.1 random coefficients models under a range of assumptions about the number of SBP values from each eligible patient and the intraclass correlation (ICC) in SBP values due to patients' receiving care at the same clinics. We used data from patients (age 18–85, diagnosed with hypertension, current visit BP ≥ 150/95, most recent previous encounter BP ≥ 150/95, ≥ 1 follow-up visit) seen 5/1/2017 through 2/28/2018 in the randomized Hyperlink clinics to inform power analysis assumptions. These patients (N = 4967) had, on average, 3.3 SBP measurements recorded over 10 months (Median = 3, range 1–23), with index M_{SBP} = 159.9, index SD_{SBP} = 16.1, all BP M_{SBP} = 150.7, and all BP SD_{SBP} = 20.4. In a 3-level (BP measure, patient, clinic) variance components model of SBP, the clinic ICC = 0.003 and the patient ICC = 0.28. Power estimates assumed n = 100 eligible patients in each of 20 clinics, 3 SBP per patient over 24 months and a clinic ICC = 0.01–0.03 in a 2-level (BP measure, clinic) variance components model.

Under these assumptions, the MDSE for the time by treatment parameter in the H1.1 analysis, assuming 80% power and α_2 = 0.05, ranges from MDSE < −0.124 when the clinic ICC = 0.01 to MDSE < -0.174 when the clinic ICC = 0.03. These MDSE correspond to annual reductions in SBP that are between 20.4*0.124 = 2.53 mmHg and 20.4*0.174 = 3.55 mmHg greater among patients in telehealth relative to clinic-based care clinics. Based on our previous research and systematic reviews, we believe a 5 mmHg greater reduction in SBP will be achieved in eligible patients in telehealth care compared with clinic-based care [21,29,52]. A difference of 5 mmHg is a clinically important reduction in BP that substantially lowers the risk of stroke and heart disease, and even smaller reductions of 2 or 3 mmHg have clinically important effects [53–57].

Patient-reported outcomes (PROs) will be analyzed using the H1.2 model. We estimated survey response rates of 60% at baseline (N = 1200) and 75% at 6 months among baseline responders to estimate the 6 month sample size of N = 900, spread evenly across clinics. Relative to the biologically based SBP, we anticipate higher clinic-based intraclass correlations for PROs (ICC = 0.02–0.03). The MDSE comparing 6-month PROs among telehealth relative to clinic-based care patients are MDSE > 0.239 when ICC = 0.03 and MDSE ≥0.270 when ICC = 0.02. For PROs, a between-groups difference of Cohen's d = 0.20–0.30 is small, consistent with the goal of detecting meaningful differences in patient-reported side effects, care experiences, and self-management.

Table 3
Aim 2 Re-aim measures.

Measure	Description
Reach	1) Proportion of eligible patients who a) have signed hypertension referral order (enrolled) b) have some hypertension follow-up within 6 weeks, c) follow up with MA in clinic-based care group, d) follow-up with pharmacist in telehealth care group, and e) initiate home BP telemonitoring (telehealth only) 2) Proportions of 1a-1e by key subgroups (systolic BP, age, race/ethnicity, payor, co-morbidity at baseline)
Effectiveness	1) Outcomes listed in Table 2 2) Outcomes by key subgroups (systolic BP, age, race/ethnicity, payor, co-morbidity at baseline)
Adoption	1) Proportion of eligible patients enrolled by clinic and PCPs 2) Characteristics of high and low enrolling clinics and PCPs
Implementation (Fidelity)	1) Items listed in Table 1 at 12 months post-implementation overall, across clinics and in subgroups 2) Adaptations made to interventions during first year
Maintenance	1) Items listed in Table 1 at 24–36 months post-implementation overall, across clinics and in key subgroups (systolic BP, age, race/ethnicity, payor, co-morbidity at baseline) 2) Adaptations made to interventions after first year 3) Plans for sustaining interventions and/or spreading to other clinics

Abbreviations: blood pressure (BP), medical assistant (MA), primary care physician (PCP).

2.8.3. Aim 1 per-protocol analysis

Given the pragmatic, unblinded, and cluster-randomized study design, there is potential in this study for otherwise-eligible patients to not be enrolled and for enrolled patients to subsequently seek or receive treatment modalities (including no treatment) that are not consistent with their assigned protocol (Table 1). Furthermore, we would like to know what the impact of actual receipt of the intended intervention by the individual, as opposed to clinic-level assignment, has on study outcomes. A per-protocol analysis, which evaluates the average effect of the interventions as though everyone followed the trial protocol, is planned to complement the ITT primary analysis [58,59]. The ITT approach in this study may be subject to bias due to 1) differential likelihood of enrollment based on PCP knowledge of treatment assignment, and/or 2) differential self-selection of patients following through with the assigned treatment intervention. Because these processes operate post-randomization, the randomization scheme cannot ensure confounder balance by enrollment or treatment status, and the study population can be considered as analogous to an observational cohort. To account for these sources of potential bias, we will use inverse probability weighting to estimate the per-protocol effect of the telehealth intervention on blood pressure outcomes [60,61].

Inverse probability weighting can be used to estimate unbiased measures of effect where selection bias or confounding is present, under specific assumptions [62,63]. To estimate the per-protocol effect of the telehealth intervention on BP outcomes, we will use a two-stage modeling process. In the first stage, we will construct logistic regression models for 1) enrollment, and 2) patient adherence to the assigned treatment. Candidate variables for inclusion in these models are specified in the protocol a priori and in Table 1. Specifically, in best practice clinics, patients will be considered adherent to protocol if they follow up with a medical assistant within 6 weeks post-index for a BP recheck as advised. In telehealth clinics, patients will be considered adherent to protocol if they: 1) follow up and complete an intake visit with an MTM pharmacist within 6 weeks, 2) submit home BP measures, and 3) complete follow-up visits (telephone/e-mail) with an MTM pharmacist. Successful adherence to group-specific protocol will be identifiable from study data. Absence of documentation of these requisite follow-up components will be considered nonadherence to protocol.

From these candidate variables, models will be optimized using Lasso selection based on the Bayesian Information Criterion. Individual probabilities of enrollment/adherence can then be calculated based on each patient's vector of covariate values. Stabilized inverse probability weights will then be calculated, combined (enrollment IPW * adherence IPW), and diagnostically evaluated as previously described [63,64]. We will implement bias analyses as well as upper/lower bounds for the per-protocol effect, which will provide a range of plausible values under various sets of realistic assumptions to complement the per-protocol effect estimate [65,66].

2.8.4. Aim 2 analysis

Two analysis processes will support our implementation evaluation aim, both of which utilize RE-AIM metrics for reach, adoption, implementation, and maintenance and accompanying explanatory qualitative data (Table 3).

Reach is defined as the proportion and representativeness of eligible patients who are enrolled, complete recommended follow-up care with PCP (clinic-based care) or MTM pharmacist (telehealth), and engage in home BP telemonitoring (telehealth). Adoption is the representativeness of the clinics that are willing to offer the program. Implementation and Maintenance are defined by clinics' fidelity to the elements of each clinic's assigned care approach. Key fidelity measures include best practice hypertension care processes (e.g. BP accuracy, repeat elevated BPs, recognition of uncontrolled BP, and acting on uncontrolled BP) and telehealth care elements (e.g. quantification of home BP telemonitoring engagement and use of evidence-based treatment regimens). We collected qualitative data to provide insights and explanations about the variation in these measures across clinics and over time.

First, we will compare the RE-AIM constructs between care models using rapid analyses over the intervention period. This “Learning Evaluation” approach includes gathering data describing changes and how they are implemented, collecting relevant process and outcome data, assessing multi-level contextual factors affecting implementation, supporting clinics in using the data to make improvements, and developing sustainable measurement strategies [67]. We will provide real-time feedback of these data to clinic leaders to promote intervention fidelity. Then, we will develop qualitative research questions in order to identify and remediate implementation barriers and to understand patterns. Semi-structured interviews and focus groups will be collected from various stakeholders to explore these questions, with the primary aim of reducing those barriers. We will examine all measures for evidence of disparities between patient subgroups and prioritize exploring any observed disparities to ensure equitable access to the intervention across patients. Findings from each qualitative data collection event will be summarized briefly and used by the study team to make operational changes to the intervention design or support clinics in adapting their intervention delivery as needed. Observational [68,69] field notes and chart review data will be utilized similarly. All rapid data analysis and subsequent conclusions and decisions will be carefully documented. Over time, the quantitative reports and qualitative data summaries will present a historical record of aggregate, clinic and clinician-level data, key events and adaptations, and assessments of

implementation success [70,71].

Second, we will complete a summary assessment of barriers and facilitators to intervention implementation utilizing a more standard mixed-methods content analysis. We will utilize the 24 months of quantitative data reports and accompanying qualitative data to describe barriers and facilitators to intervention uptake and fidelity by RE-AIM measures listed in Table 3. We will conduct a group process to draft and apply a codebook for each qualitative dataset. Two coders will code qualitative data using NVivo. Inter-coder agreement will be assessed throughout this process with an 80% benchmark for agreement. We will identify and describe themes and patterns related to the quantitative RE-AIM measures at three levels: overall, by clinic, and by individual clinician. A complete codebook and audit trail will be maintained to map decision points in the analysis, and stakeholder feedback about findings will be collected to validate and refine our conclusions. This multi-level analysis will begin as the study progresses into later phases of implementation.

2.9. Ethical oversight

The HealthPartners Institutional Review Board (IRB) reviewed the study protocol (IRB Project number 15–103) and approved a partial waiver of informed consent for enrolling patients in the study because: 1) the interventions did not pose additional safety risks compared to routine care for hypertension, and 2) the study could not have been practicably carried out had written informed consent been required. However, given that following enrollment we attempted to contact all study patients to complete the baseline survey, the IRB required that the cover letter in our initial mailing include language outlining the elements of informed consent. The letter informed patients that returning the survey implied their consent to use both their relevant EHR data and their survey data in the study. For patients who were contacted by telephone, the interviewer script included similar language.

3. Discussion

Despite the public health importance of improving hypertension control, progress at the U.S. population level has been disappointingly slow [6,7]. Research over the last several decades has shown that reorganizing clinical practice to empower non-physician practitioners and patients to work together to encourage self-management, adjust antihypertensive therapy, and conduct follow up in a team-based approach to hypertension care is a potent strategy to improve hypertension control [15–21]. A modeling study found that nationwide adoption of team-based care for uncontrolled hypertension could reduce uncontrolled hypertension by 13% and prevent 638,000 CV events over 10 years [19]. Still, critical gaps remain in understanding how to implement team-based care interventions in diverse primary care settings.

The current pragmatic trial compares the effectiveness of two different models of team-based care for uncontrolled hypertension. The best practice clinic-based care approach we adapted at HealthPartners and used as one comparator for this project is based on elements from several hypertension clinical care programs that have been shown to be effective in other settings, albeit based mostly on observational evidence. One such program at Kaiser Permanente was gradually implemented over more than a decade in northern and southern California and includes the following key elements: use of evidence-based guidelines; a comprehensive hypertension registry to track patients over time and between visits; regular measurement and feedback on performance metrics; medical assistant visits for BP measurement; and promotion of a simple treatment algorithm based on single-pill combination pharmacotherapy [32,33,72]. This program was associated with improvement in hypertension control from 44% in 2001 to 80% in 2009 in northern California and from 54% in 2004 to 86% in 2012 in southern California. Racial, ethnic, and language disparities in BP control were reduced as well. There was less concomitant improvement in hypertension control in California at non-Kaiser practices (63.4% to 69.4%) and nationally (55.5% to 64.1%) during the same period. Adoption of the Kaiser model in safety net clinics was associated with improved BP control in all racial and ethnic groups [73].

Other groups have put forth additional detailed process recommendations for reorganizing clinic-based hypertension care: the American Medical Association's Target: BP program for clinical practice redesign [74], the American Medical Group Association's Measure Up/Pressure Down campaign [75], and the Million Hearts program for controlling hypertension [36]. Key elements include: 1) promotion of accurate BP measurement; 2) repeat measurement when BP is elevated; 3) addressing elevated BP at every visit; 4) use of an evidence-based standardized protocol, including low-cost medications and single-pill combination therapy, when possible; 5) reassessing the patient every 2 to 4 weeks until BP is controlled; and 6) partnering with patients and families to improve self-monitoring, adherence, and lifestyle changes. However, most of the individual elements of the recommendations are based on expert opinion, and even the well-publicized Kaiser studies use observational time series designs. Therefore, the evidence for best-practice clinic-based care would be strengthened greatly by comparing it to another care model using a rigorous research design.

The telehealth care approach takes advantage of increasing interest by patients and health care organizations in alternatives to traditional clinic visits. Recent changes in technology, reimbursement for telehealth, and quality measures allowing for remote monitoring have also reduced some barriers to this model of care. Furthermore, there is strong evidence for its effectiveness from randomized clinical trials in varied populations. Three randomized trials conducted in integrated health systems, including the site of the current trial, support combining electronic transmission of home BP monitoring data and care management by pharmacists [29,44,76]. These trials each found roughly a 10 mmHg lower systolic BP and 20–30% greater proportion achieving controlled BP in the intervention groups compared with patients receiving usual care over follow-up periods of 6 to 12 months. A trial among U.S. veterans compared a telemonitoring intervention with various types of nurse management to usual care [77]. The largest effect was observed for combined behavioral and medication management in patients with uncontrolled BP (15 mmHg lower systolic BP at 12 months than usual care). In urban African-Americans with uncontrolled BP randomly assigned to community nurse-managed telemonitoring or usual care, intervention group patients had a 5 mmHg lower systolic BP at 12 months [78]. Two randomized trials conducted in UK primary care practices included a home BP telemonitoring intervention and structured communication between patients and primary care practitioners [79,80]. In both trials systolic BP was 4–5 mmHg lower in the intervention patients than in the usual care patients after 6 to 12 months. Several review articles discuss the effectiveness of telemonitoring for hypertension [81,82].

The effect of telehealth care on patient-centered outcomes is less well-studied than its effect on BP outcomes. In the previous study at our institution, the intervention was associated with significant improvements in patient satisfaction with some aspects of their care (clinicians listening carefully, explaining things clearly, and respecting what the patients said) [29]. Patients also reported feeling more able to communicate with their health care team, to incorporate home BP monitoring into their routine, and to keep their BP under control. In the e-BP study by Green, patients who worked with pharmacists reported strong and consistent improvements in the way their care reflected principles outlined for high-quality chronic illness care [83].

Qualitative analysis of the UK trials of telemonitoring with automated patient decision support found that intervention patients and clinicians felt more confident in treatment decisions based on home BP [84]. They perceived that multiple telemonitoring measurements were more accurate than office measurements, and they were less hesitant to increase BP medication than based on BP measurements taken on a single day in the clinic. Patients felt that telemonitoring was

convenient, that it helped them feel empowered and "looked after", and they valued the timely communication with their health care provider [85].The current study's focus on patient-reported outcomes and robust patient/stakeholder engagement strategy will shed further light on critical issues of importance to patients and health systems [86].

Three core organizing principles informed some of the choices in this trial's design. First, there is increasing interest in the concept of "learning health systems." These were defined more than a decade ago as health care organizations in which "knowledge-generation is so embedded in the core of the practice of medicine that it is a natural outgrowth and product of the health care delivery process and leads to continual improvement in care." [87] Second, the trial is designed as hybrid type 2 effectiveness-implementation study that blends clinical effectiveness and implementation research aims [88]. Third, we incorporated "pragmatic" design principles that would provide a more realistic test of these approaches to care [89–91]. Key features of pragmatic trials are 1) broad eligibility with minimal exclusions, 2) recruitment through usual appointments at a diverse range of clinic,3) conducting the trial in a setting similar to where the results will be applied, 4) a flexible intervention meant to be applied in a typical clinical environment, 5) a usual care comparison, 6) unobtrusive measurement of adherence to the intervention, 7) minimal formal research follow up, 8) a clinically meaningful primary outcome, and 9) an intention-to-treat analysis. All of these features are intended to increase usefulness of the trial results to the intended users and speed uptake into clinical practice. Pragmatic trials may also lower research costs by using existing health system infrastructure and information systems to streamline recruitment, intervention, data collection, and endpoint ascertainment.

The pragmatic design of the current study differs in key ways from the previous proof-of-concept efficacy study we conducted [29]. The eligibility criteria are in some ways even broader to mimic the patients who are included in the National Committee for Quality Assurance hypertension quality measure [92]. However, the requirement for higher levels of BP was chosen for the practical reason to reduce the extremely large number of patients with BP $\geq$140/90 mmHg on two consecutive primary care visits. Our automated enrollment methods were designed to identify and recruit a high proportion of the eligible population without the need for research personnel. Using the $\geq$140/90 mmHg cut point would have identified far more patients than the required sample size and would have overwhelmed the capacity of our system to provide additional MTM pharmacist and BP check appointments to eligible patients. We acknowledge that the higher level of qualifying BP may be accompanied by more treatment resistance and a greater degree of co-morbidity. Another consequence of the automated recruitment with no requirement for research clinic visits is that the study population may be substantially less motivated to participate in the study interventions. On the other hand, the study sample and results are likely to be more generalizable to routine practice in caring for patients with persistently uncontrolled severe hypertension.

4. Conclusions

This study will directly compare long-term outcomes of two different organizational models for team-based care, one that incorporates current best practices but relies primarily on the clinician-medical assistant dyad and face-to-face visits (clinic-based care), and one that extends care outside the confines of the clinic using telehealth care, systematic home BP telemonitoring, and care coordination by a pharmacist or nurse practitioner (telehealth care). The comparators represent two alternative health care service designs emerging as the dominant choices for clinicians and health systems for primary care practice redesign to improve hypertension care outcomes. This pragmatic trial will inform health systems about the strengths and limitations of implementing home BP telemonitoring with pharmacist management for uncontrolled hypertension in the primary care setting.

Funding and clinical trial registration

The study was funded by a contract with the Patient Centered Outcomes Research Institute (PCORI/IHS-1507-31146) and is registered at clinicaltrials.gov (NCT02996565).

References

[1] P. Rui, T. Okeyode, National Ambulatory Medical Care Survey: 2015 State and National Summary Tables, https://www.cdc.gov/nchs/data/ahcd/namcs_summary/2015_namcs_web_tables.pdf, (2015) Accessed Jul 18, 2019.
[2] D. Mozaffarian, E.J. Benjamin, A.S. Go, et al., Heart disease and stroke statistics–2015 update: a report from the American Heart Association, Circulation 131 (4) (2015) e29–322.
[3] P.K. Whelton, R.M. Carey, W.S. Aronow, et al., ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, Hypertension 71 (6) (2018) 1269–1324.
[4] G. Danaei, E.L. Ding, D. Mozaffarian, et al., The preventable causes of death in the United States: comparative risk assessment of dietary, lifestyle, and metabolic risk factors, PLoS Med. 6 (4) (2009) e1000058.
[5] Q. Yang, M.E. Cogswell, W.D. Flanders, et al., Trends in cardiovascular health metrics and associations with all-cause and CVD mortality among US adults, JAMA 307 (12) (2012) 1273–1283.
[6] S.S. Yoon, M.D. Carroll, C.D. Fryar, Hypertension prevalence and control among adults: United States, 2011–2014, NCHS Data Brief 220 (2015) 1–8.
[7] C.D. Fryar, Y. Ostchega, C.M. Hales, G. Zhang, D. Kruszon-Moran, Hypertension prevalence and control among adults: United States, 2015–2016, NCHS Data Brief 289 (2017) 1–8.
[8] A.L. Valderrama, C. Gillespie, S.C. King, M.G. George, Y. Hong, E. Gregg, Vital signs: awareness and treatment of uncontrolled hypertension among adults–United States, 2003-2010, MMWR Morb. Mortal. Wkly Rep. 61 (2012) 703–709.
[9] J. Fang, Q. Yang, C. Ayala, F. Loustalot, Disparities in access to care among US adults with self-reported hypertension, Am. J. Hypertens. 27 (11) (2014) 1377–1386.
[10] C.J. Hsiao, D.K. Cherry, P.C. Beatty, E.A. Rechtsteiner, National Ambulatory Medical Care Survey: 2007 summary, Natl. Health Stat. Report 27 (2010) 1–32.
[11] P.J. O'Connor, Overcome clinical inertia to control systolic blood pressure, Arch. Intern. Med. 163 (22) (2003) 2677–2678.
[12] G.E. Wetzels, P. Nelemans, J.S. Schouten, M.H. Prins, Facts and fiction of poor compliance as a cause of inadequate blood pressure control: a systematic review, J. Hypertens. 22 (10) (2004) 1849–1855.
[13] A.J. Rose, D.R. Berlowitz, M.B. Orner, N.R. Kressin, Understanding uncontrolled hypertension: is it the patient or the provider? J. Clin. Hypertens. 9 (12) (2007) 937–943.
[14] D.J. Hyman, V.N. Pavlik, Characteristics of patients with uncontrolled hypertension in the United States, N. Engl. J. Med. 345 (7) (2001) 479–486.
[15] J.M. Walsh, K.M. McDonald, K.G. Shojania, et al., Quality improvement strategies for hypertension management: a systematic review, Med. Care 44 (7) (2006) 646–657.
[16] L.G. Glynn, A.W. Murphy, S.M. Smith, K. Schroeder, T. Fahey, Interventions used to improve control of blood pressure in patients with hypertension, Cochrane Database Syst. Rev. 3 (2010) CD005182.
[17] B.L. Carter, M. Rogers, J. Daly, S. Zheng, P.A. James, The potency of team-based care interventions for hypertension: a meta-analysis, Arch. Intern. Med. 169 (19) (2009) 1748–1755.
[18] B.L. Carter, H.B. Bosworth, B.B. Green, The hypertension team: the role of the pharmacist, nurse, and teamwork in hypertension therapy, J. Clin. Hypertens. 14 (1) (2012) 51–65.
[19] S.P. Dehmer, M.M. Baker-Goering, M.V. Maciosek, et al., Modeled health and economic impact of team-based care for hypertension, Am. J. Prev. Med. 50 (5 Suppl 1) (2016) S34–s44.
[20] Community Preventive Services Task Force, Team-based care to improve blood pressure control: recommendation of the Community Preventive Services Task Force, Am. J. Prev. Med. 47 (1) (2014) 100–102.
[21] K.K. Proia, A.B. Thota, G.J. Njie, et al., Team-based care and improved blood pressure control: a community guide systematic review, Am. J. Prev. Med. 47 (1) (2014) 86–99.
[22] F.P. Cappuccio, S.M. Kerry, L. Forbes, A. Donald, Blood pressure control by home monitoring: meta-analysis of randomised trials, BMJ 329 (7458) (2004) 145.
[23] E.P. Bray, R. Holder, J. Mant, R.J. McManus, Does self-monitoring reduce blood pressure? Meta-analysis with meta-regression of randomized controlled trials, Ann. Med. 42 (5) (2010) 371–386.
[24] R. Agarwal, J.E. Bills, T.J. Hecht, R.P. Light, Role of home blood pressure monitoring in overcoming therapeutic inertia and improving hypertension control: a systematic review and meta-analysis, Hypertension 57 (1) (2011) 29–38.
[25] A. Arrieta, J.R. Woods, N. Qiao, S.J. Jay, Cost-benefit analysis of home blood pressure monitoring in hypertension diagnosis and treatment: an insurer perspective, Hypertension 64 (4) (2014) 891–896.
[26] B.R. Fletcher, J. Hartmann-Boyce, L. Hinton, R.J. McManus, The effect of self-monitoring of blood pressure on medication adherence and lifestyle factors: a systematic review and meta-analysis, Am. J. Hypertens. 28 (10) (2015) 1209–1221.

[27] K. Uhlig, K. Patel, S. Ip, G.D. Kitsios, E.M. Balk, Self-measured blood pressure monitoring in the management of hypertension: a systematic review and meta-analysis, Ann. Intern. Med. 159 (3) (2013) 185–194.
[28] K.L. Tucker, J.P. Sheppard, R. Stevens, et al., Self-monitoring of blood pressure in hypertension: a systematic review and individual patient data meta-analysis, PLoS Med. 14 (9) (2017) e1002389.
[29] K.L. Margolis, S.E. Asche, A.R. Bergdall, et al., Effect of home blood pressure telemonitoring and pharmacist management on blood pressure control: a cluster randomized clinical trial, JAMA. 310 (1) (2013) 46–56.
[30] CMM in Primary Care Research Team, The Patient Care Process for Delivering Comprehensive Medication Management (CMM): Optimizing Medication Use in Patient-Centered, Team-Based Care Settings. July, http://www.accp.com/cmm_care_process, (2018).
[31] G.W. Imbens, Experimental design for unit and cluster randomized trials, Prepared for the International Initiative for Impact Evaluation, 2011 http://cyrussamii.com/wp-content/uploads/2011/06/Imbens_June_8_paper.pdf Accessed Jul 18, 2019.
[32] K.M. Shaw, J. Handler, H.K. Wall, M.H. Kanter, Improving blood pressure control in a large multiethnic California population through changes in health care delivery, 2004-2012, Prev. Chronic Dis. 11 (2014) E191.
[33] R.D. Feldman, G.Y. Zou, M.K. Vandervoort, C.J. Wong, S.A. Nelson, B.G. Feagan, A simplified approach to the treatment of uncomplicated hypertension: a cluster randomized, controlled trial, Hypertension 53 (4) (2009) 646–653.
[34] Measure, Act and Partner (M.A.P.) to help Patients Control Blood Pressure and Ultimately Prevent Heart Disease, https://www.stepsforward.org/modules/hypertension-blood-pressure-control, (2015).
[35] American Medical Group Association Foundation, Measure Up Pressure Down, http://www.measureuppressuredown.com/.
[36] Centers for Disease Control and Prevention, Protocol for Controlling Hypertension in Adults, https://millionhearts.hhs.gov/files/Hypertension-Protocol.pdf, (2013).
[37] M.A. El Assaad, J.A. Topouchian, B.M. Darne, R.G. Asmar, Validation of the Omron HEM-907 device for blood pressure measurement, Blood Press Monit. 7 (4) (2002) 237–241.
[38] K.L. Margolis, T.J. Kerby, S.E. Asche, et al., Design and rationale for home blood pressure telemonitoring and case management to control hypertension (HyperLink): a cluster randomized trial, Contemp. Clin. Trials. 33 (4) (2012) 794–803.
[39] M. Beran, S.E. Asche, A.R. Bergdall, et al., Key components of success in a randomized trial of blood pressure telemonitoring with medication therapy management pharmacists, J. Am. Pharm. Assoc. (2003). 58 (6) (2018) 614–621.
[40] K.L. Margolis, S.E. Asche, S.P. Dehmer, et al., Long-term outcomes of the effects of home blood pressure telemonitoring and pharmacist management on blood pressure among adults with uncontrolled hypertension: follow-up of a cluster randomized clinical trial, JAMA Netw. Open 1 (5) (2018) e181617.
[41] J.Y. Ziegenfuss, J. Tillema, K. Dean, T. Kottke, Cost and quality trade-offs in a well-being survey of HealthPartners patient members, American Association for Public Opinion Research 70th Annual Conference 2015; Hollywood, FL, 2019.
[42] P. Edwards, I. Roberts, M. Clarke, et al., Methods to increase response rates to postal questionnaires, Cochrane Database Syst. Rev. 2 (2007) MR000008.
[43] D.A. Dillman, J.D. Smyth, L.M. Christian, Internet, Mail and Mixed-Mode Surveys, the Tailored Design Method, (2014).
[44] B.B. Green, A.J. Cook, J.D. Ralston, et al., Effectiveness of home blood pressure monitoring, web communication, and pharmacist care on hypertension control: a randomized controlled trial, JAMA 299 (24) (2008) 2857–2867.
[45] R.E. Glasgow, E.H. Wagner, J. Schaefer, L.D. Mahoney, R.J. Reid, S.M. Greene, Development and validation of the Patient Assessment of Chronic Illness Care (PACIC), Med. Care 43 (5) (2005) 436–444.
[46] V.T. Tran, M. Harrington, V.M. Montori, C. Barnes, P. Wicks, P. Ravaud, Adaptation and validation of the Treatment Burden Questionnaire (TBQ) in English using an internet platform, BMC Med. 12 (2014) 109.
[47] D.C. Goff Jr., D.M. Lloyd-Jones, G. Bennett, et al., 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, Circulation 129 (25 Suppl 2) (2014) S49–S73.
[48] D.M. Lloyd-Jones, E.P. Leip, M.G. Larson, et al., Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age, Circulation. 113 (6) (2006) 791–798.
[49] R.E. Glasgow, T.M. Vogt, S.M. Boles, Evaluating the public health impact of health promotion interventions: the RE-AIM framework, Am. J. Public Health 89 (9) (1999) 1322–1327.
[50] M.A. Kirk, C. Kelley, N. Yankey, S.A. Birken, B. Abadie, L. Damschroder, A systematic review of the use of the Consolidated Framework for Implementation Research, Implement. Sci. 11 (2016) 72.
[51] L.J. Damschroder, D.C. Aron, R.E. Keith, S.R. Kirsh, J.A. Alexander, J.C. Lowery, Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science, Implement. Sci. 4 (2009) 50.
[52] V. Santschi, A. Chiolero, A.L. Colosimo, et al., Improving blood pressure control through pharmacist interventions: a meta-analysis of randomized controlled trials, J. Am. Heart Assoc. 3 (2) (2014) e000718.
[53] M. Law, N. Wald, J. Morris, Lowering blood pressure to prevent myocardial infarction and stroke: a new preventive strategy, Health Technol. Assess. 7 (31) (2003) 1–94.
[54] S. Lewington, R. Clarke, N. Qizilbash, R. Peto, R. Collins, 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 360 (9349) (2002) 1903–1913.
[55] R. Stamler, Implications of the INTERSALT study, Hypertension 17 (1 Suppl) (1991) I16–I20.
[56] N.R. Cook, J. Cohen, P.R. Hebert, J.O. Taylor, C.H. Hennekens, Implications of small reductions in diastolic blood pressure for primary prevention, Arch. Intern. Med. 155 (7) (1995) 701–709.
[57] J. Sundstrom, H. Arima, R. Jackson, et al., Effects of blood pressure reduction in mild hypertension: a systematic review and meta-analysis, Ann. Intern. Med. 162 (3) (2015) 184–191.
[58] M.A. Hernan, S. Hernandez-Diaz, Beyond the intention-to-treat in comparative effectiveness research, Clin. Trials 9 (1) (2012) 48–55.
[59] M.A. Hernan, J.M. Robins, Per-protocol analyses of pragmatic trials, N. Engl. J. Med. 377 (14) (2017) 1391–1398.
[60] M.A. Hernan, S. Hernandez-Diaz, J.M. Robins, A structural approach to selection bias, Epidemiology. 15 (5) (2004) 615–625.
[61] S. Toh, M.A. Hernan, Causal inference from longitudinal studies with baseline randomization, Int. J. Biostat. 4 (1) (2008) Article 22.
[62] J.M. Robins, M.A. Hernan, B. Brumback, Marginal structural models and causal inference in epidemiology, Epidemiology 11 (5) (2000) 550–560.
[63] M.A. Hernan, B. Brumback, J.M. Robins, Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men, Epidemiology 11 (5) (2000) 561–570.
[64] S.R. Cole, M.A. Hernan, Constructing inverse probability weights for marginal structural models, Am. J. Epidemiol. 168 (6) (2008) 656–664.
[65] L.A. Barnett, M. Lewis, C.D. Mallen, G. Peat, Applying quantitative bias analysis to estimate the plausible effects of selection bias in a cluster randomised controlled trial: secondary analysis of the Primary care Osteoarthritis Screening Trial (POST), Trials 18 (1) (2017) 585.
[66] S.A. Swanson, O. Holme, M. Loberg, et al., Bounding the per-protocol effect in randomized trials: an application to colorectal cancer screening, Trials 16 (2015) 541.
[67] B.A. Balasubramanian, D.J. Cohen, M.M. Davis, et al., Learning evaluation: blending quality improvement and implementation research methods to study healthcare innovations, Implement. Sci. 10 (2015) 31.
[68] B.F. Crabtree, S.M. Chase, C.G. Wise, et al., Evaluation of patient centered medical home practice transformation initiatives, Med. Care 49 (1) (2011) 10–16.
[69] B.F. Crabtree, P.A. Nutting, W.L. Miller, et al., Primary care practice transformation is hard work: insights from a 15-year developmental program of research, Med. Care 49 (2011) Suppl:S28–35.
[70] M.D. Fetters, L.A. Curry, J.W. Creswell, Achieving integration in mixed methods designs-principles and practices, Health Serv. Res. 48 (6 Pt 2) (2013) 2134–2156.
[71] J.A. Creswell, Concise Introduction to Mixed Methods Research, Sage Publications, 2015.
[72] M.G. Jaffe, G.A. Lee, J.D. Young, S. Sidney, A.S. Go, Improved blood pressure control associated with a large-scale hypertension program, JAMA 310 (7) (2013) 699–705.
[73] V. Fontil, R. Gupta, N. Moise, et al., Adapting and evaluating a health system intervention from Kaiser Permanente to improve hypertension management and control in a large network of safety-net clinics, Circ. Cardiovasc. Qual. Outcomes 11 (7) (2018) e004386.
[74] American Heart Association, American Medical Association. Target: BP, https://targetbp.org/ . Accessed Aug 27 (2019).
[75] American Medical Group Association Foundation, Campaign Planks. Measure up Pressure Down, http://www.measureuppressuredown.com/HCProf/Find/cmpgnPlanks_find.asp, (2015).
[76] D.J. Magid, K.L. Olson, S.J. Billups, N.M. Wagner, E.E. Lyons, B.A. Kroner, A pharmacist-led, American Heart Association Heart360 web-enabled home blood pressure monitoring program, Cardiovasc. Qual. Outcomes 6 (2) (2013) 157–163.
[77] H.B. Bosworth, B.J. Powers, M.K. Olsen, et al., Home blood pressure management and improved blood pressure control: results from a randomized controlled trial, Arch. Intern. Med. 171 (13) (2011) 1173–1180.
[78] N.T. Artinian, J.M. Flack, C.K. Nordstrom, et al., Effects of nurse-managed telemonitoring on blood pressure at 12-month follow-up among urban African Americans, Nurs. Res. 56 (5) (2007) 312–322.
[79] B. McKinstry, J. Hanley, S. Wild, et al., Telemonitoring based service redesign for the management of uncontrolled hypertension: multicentre randomised controlled trial, BMJ. 346 (2013) f3030.
[80] R.J. McManus, J. Mant, M. Franssen, et al., Efficacy of self-monitored blood pressure, with or without telemonitoring, for titration of antihypertensive medication (TASMINH4): an unmasked randomised controlled trial, Lancet 391 (10124) (2018) 949–959.
[81] S. Omboni, T. Gazzola, G. Carabelli, G. Parati, Clinical usefulness and cost effectiveness of home blood pressure telemonitoring: meta-analysis of randomized controlled studies, J. Hypertens. 31 (3) (2013) 455–467 (discussion 467-458).
[82] B. Mc Kinstry, J. Hanley, S. Lewis, Telemonitoring in the management of high blood pressure, Curr. Pharm. Des. 21 (6) (2015) 823–827.
[83] J.D. Ralston, A.J. Cook, M.L. Anderson, et al., Home blood pressure monitoring, secure electronic messaging and medication intensification for improving hypertension control: a mediation analysis, Appl Clin Inform. 5 (1) (2014) 232–248.
[84] M.I. Jones, S.M. Greenfield, E.P. Bray, et al., Patients' experiences of self-monitoring blood pressure and self-titration of medication: the TASMINH2 trial qualitative study, Br. J. Gen. Pract. 62 (595) (2012) e135–e142.
[85] S. Grant, J. Hodgkinson, C. Schwartz, et al., Using mHealth for the management of hypertension in UK primary care: An embedded qualitative study of the TASMINH4 randomised controlled trial, Br. J. Gen. Pract. 2019.
[86] A. Brodt, C.K. Norton, A. Kratchman, So much more than a "pair of brown shoes": triumphs of patient and other stakeholder engagement in patient-centered outcomes research, PXJ 2 (1) (2015) 43–49.
[87] The Learning Healthcare System, Workshop Summary, National Academy of

Sciences, Washington DC, 2007.
[88] G.M. Curran, M. Bauer, B. Mittman, J.M. Pyne, C. Stetler, Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact, Med. Care 50 (3) (2012) 217–226.
[89] S.R. Tunis, D.B. Stryer, C.M. Clancy, Practical clinical trials: increasing the value of clinical research for decision making in clinical and health policy, JAMA. 290 (12) (2003) 1624–1632.
[90] K.E. Thorpe, M. Zwarenstein, A.D. Oxman, et al., A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers, J. Clin. Epidemiol. 62 (5) (2009) 464–475.
[91] K. Loudon, S. Treweek, F. Sullivan, P. Donnan, K.E. Thorpe, M. Zwarenstein, The PRECIS-2 tool: designing trials that are fit for purpose, BMJ 350 (2015) h2147.
[92] National Committee for Quality Assurance, Controlling High Blood Pressure (CBP), https://www.ncqa.org/hedis/measures/controlling-high-blood-pressure/.