Pragmatic Trial Comparing Telehealth Care and Optimized Clinic-Based Care for Uncontrolled High Blood Pressure
Short Title: Hyperlink 3 (15-103)
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STUDY PROTOCOL

Supplemental appendices compiled in separate document, saved here: x Protocol - appendix attachments\2017.11 Hyperlink 3 Protocol Appendices.pdf

1. Background and Significance

1.A. Background

1.A.1. Impact of the condition on the health of individuals and populations. Abnormally high blood pressure (hypertension) is the most common chronic condition for which patients see primary care physicians, affecting 80 million (about one in three) U.S. adults, and is a major risk factor for heart attacks, stroke, heart failure, and kidney failure.[1] The estimated direct and indirect cost of high blood pressure (BP) in 2011 in the U.S. was $46.4 billion. Compared with other modifiable cardiovascular (CV) risk factors, poorly controlled hypertension is the leading cause of death among women and the second leading cause of death among men after smoking.[2] About half of patients with hypertension in the U.S. do not have their BP controlled to recommended levels, and control rates are even lower in racial/ethnic minority and low socioeconomic status populations.[3-6] Attaining BP control to recommended levels has been shown to lower the risk of future CV events (heart attacks and strokes), the most common global cause of death and disability.[1]

1.A.2. Previous research and gaps in evidence addressed by the proposed trial. National data from 2003-2012 has shown some improvement in the control of hypertension to just over 50%,[3-6] well below the goals set by Healthy People 2020 (61.2% by 2020), the Million Hearts Initiative (65% by 2017), and the American Medical Group Association Measure Up/Pressure Down campaign (80% by 2016).[7-9] Although access to health care remains a barrier to attaining control, recent evidence suggests that 89% of people with uncontrolled hypertension have a regular source of health care, and 85% had insurance.[3] Although high BP usually doesn't have symptoms, more than 80% of people with hypertension are aware they have it, and men, women, and Hispanic and black Americans all had awareness levels above 80%.[5] Similarly, most patients with hypertension are being treated with medication (76%). There is currently little difference in treatment rates by race/ethnicity, although more women (81%) than men (71%) are treated. Patients with hypertension visit a physician, on average, 4 or more times a 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 and combinations of drugs, even when BP is elevated at several clinic visits, a complex phenomenon dubbed "clinical inertia."[11] Patients also contribute by resisting advice to change their lifestyle, start medication, or take their medication as prescribed. Sometimes this resistance is related to stressful lives, side effects, medication costs, or not being convinced that their BP is a problem.[12-14]

Thus, while improving access to care, awareness of hypertension and initiation of treatment for hypertension are important, addressing these factors in isolation is likely to result only in small improvements in hypertension control. Rather, the best current opportunities to improve BP control center on the way clinicians and patients interact in the health care setting. Research over the last several decades has shown that the most potent interventions are those that reorganize 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.[15-18] 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 mm Hg, and the absolute proportion of patients achieving BP control improved by 20%.[15] The largest BP effects were seen in studies in which the care manager was able to recommend treatment changes without further direct action by the physician. A recently updated meta-analysis including 31 additional studies confirmed these findings, albeit with somewhat smaller BP reductions (5/2 mm Hg, proportion achieving BP control improved by 12%).[19] However, several of the studies included in the meta-analysis also suggested that team-based care for hypertension may simultaneously reduce cholesterol levels and improve blood sugar control in adults with diabetes, thus reducing long-term CV risk even further than would be achieved based on BP reductions alone. 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. [20] Based on this strong evidence, the Community Preventive Services Task Force recommended team-based care to improve BP control.[21] A key research gap identified in this systematic review was the need for more evidence on scalability of team-based care in large and diverse populations, multiple sites, and multiyear evaluations. In addition, few studies have measured patient-reported outcomes of team-based care, and the results of such measurements have been inconsistent.[19]

Self-measured home BP monitoring has been identified as a useful, cost-saving adjunct to team-based care for hypertension in comprehensive evidence reviews.[15,16,22-26] A recent systematic review concluded that home BP monitoring alone results in small BP reductions at 6 months compared with usual care (a difference of -3 mm Hg for systolic BP [SBP, the top number] and -2 mm Hg for diastolic BP [DBP, the bottom number]). In contrast, improved BP outcomes were greater in high-quality studies that combined home BP monitoring with additional support interventions for as long as 12 months (SBP reductions of -3.4 to -8.9 mm Hg, DBP reductions of -1.9 to -4.4 mm Hg).[27] Additional support was defined as patient education, counseling, or telemedicine support. An individual patient data meta-analysis conducted by members of this research team reached similar conclusions.[28] The biggest research gaps identified were the need to determine the long-term effects of home BP monitoring beyond 12 months and in key subgroups that are more likely to have difficulty with BP control (eg, older persons, those with more severe hypertension, those with CV disease, diabetes, or kidney disease).

Both patients and health care organizations are increasingly interested in alternatives to traditional clinic visits. Home BP monitoring is an essential ingredient for such alternatives for hypertension care. Our previous work on the Hyperlink study (R01 HL090965) used telemonitoring and telephone for communication between patients and pharmacists based in primary care clinics. Patients with uncontrolled hypertension in the intervention group safely achieved double the rate of sustained BP control compared with patients who continued to receive routine primary care.[29] Previous research in other care settings has shown similar improvement in BP control without the need for clinic visits.[30-33] However, some group practices have achieved very high rates of BP control using quality-improvement methods without routine use of home BP monitoring, telehealth, or expanded care teams.[34,35] Thus, it is unclear whether these improve care for uncontrolled hypertension compared with clinic-based care that is organized according to current best practices.

National strategic planning groups for comparative effectiveness studies have identified the research gaps noted above as high priority topics. The Institute of Medicine has called for studies comparing the effectiveness of various strategies aimed at integrating pharmacists into primary care (eg, pharmacist-provided medication management to improve condition-specific outcomes).[36] The Agency for Healthcare Research and Quality has cited self-measured BP as a topic needing future research, specifically calling for longer-term randomized controlled trials to examine clinical outcomes, identify subgroups likely to benefit, and clarify what types of additional support are most effective.[37]

This pragmatic trial is aimed at improving hypertension care in a large health system and will address these research gaps by: **1)** Comparing two different organizational models for team-based care, one that incorporates current best practices but relies primarily on the physician-medical assistant dyad and face-to-face visits (clinic-based care) and one that extends team-based care outside the confines of the clinic by adding telehealth care coordinated by a pharmacist (telehealth care). **2)** Incorporating self-measured home BP telemonitoring as a systematic part of the telehealth care intervention in a long-term evaluation that is large enough to determine its effects in key subgroups. **3)** Measuring patient-centered outcomes as well as traditional clinical outcomes (eg, BP, other CV risk factors). **4)** Measuring and evaluating the implementation of a pragmatic, large-scale, long-term program of clinic-based care and telehealth care for patients with uncontrolled hypertension in the primary care setting using electronic data sources.

1.B. Significance

1.B.1. Potential for the study to improve health care and outcomes. This study will compare the clinical effectiveness and effects on patient-reported outcomes of two different models of team-based care for uncontrolled hypertension and study how the interventions are implemented in the real-world setting of a large health system. A large body of evidence from both observational and interventional studies has shown that even small reductions in BP result in substantial reductions in rates of heart disease and stroke. The estimated effect of lowering BP by 5 mm Hg diastolic reduces the relative risk of stroke by 34% and heart disease by 21%[38] and stroke deaths by 40% and vascular disease deaths by 30%.[39] Even SBP and DBP reductions as small as 2-3 mm Hg are predicted to reduce stroke by 10%-28% and heart disease by 5%-9%.[39-42]

Numerous stakeholders have endorsed the need to improve hypertension care in the primary care setting, where most patients receive care. "Controlling high blood pressure" is a key national quality measure in the Healthcare Effectiveness Data and Information Set (HEDIS). This measure is publicly reported in Minnesota for all medical groups and published on the Minnesota Community Measurement Web site.[35] Practice-based quality measures generally show higher levels of BP control than national levels because they include only diagnosed patients receiving care in the previous 2 years. These are useful for assessing important variations in practice. For example, in the state of Minnesota for 2015 dates of service, the average publicly reported rate of meeting recommended goals for hypertension control by all reporting medical groups is 77%, but individual medical groups range from 37% to 91%. HealthPartners clinics fell in the average range, at 75%, and also show substantial between-clinic variation. There is an 8% gap in BP control rates between white and black patients (unpublished data). The primary care, nursing, and pharmacy departments, each represented in this project as stakeholders, convened a working group to redesign primary care systems to improve hypertension control and make care more consistent. Our group faced uncertainty about the best methods to improve BP outcomes in clinical practice, a dilemma likely shared by many others.

1.B.2. Evidence for efficacy or effectiveness of the interventions being compared

1.B.2.1. Best practice clinic-based care. The clinic-based care approach we adapted for this project is based on elements from several programs that have been shown to be effective in other settings, albeit based mostly on observational evidence. Kaiser Permanente's hypertension program 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, 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.[34,43,44] This program was associated with improvement in hypertension control, according to the HEDIS measurement, 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. There was much 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.

Other groups have put forth similar recommendations for reorganizing clinic-based hypertension care: the American Medical Association's STEPSforward program for clinical practice redesign,[45] the American Medical Group Association's Measure Up/Pressure Down campaign,[46] and the Million Hearts program for controlling hypertension.[47] 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. Registries are also considered an important component to track patients over time and between visits. Consistency with guidelines from

other national organizations suggests that these constitute current best practices for clinic-based care.[48-50] However, most of the individual elements of the recommendations are based on expert opinion, and even the well-publicized Kaiser model results are based on observational studies. 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.

1.B.2.2. Telehealth Care. We and others have found nurse- or pharmacist-led telehealth care with home BP monitoring to be a particularly effective intervention for lowering BP in patients with uncontrolled hypertension.[51] A recent study among U.S. veterans compared a telemonitoring intervention with various types of nurse management to usual care.[31] The largest effect was observed for combined behavioral and medication management in patients with uncontrolled BP (SBP was 15 mm Hg lower at 12 months and 8 mm Hg lower at 18 months than control). In 387 urban African-Americans with uncontrolled BP randomly assigned to community nurse-managed telemonitoring or usual care, intervention group patients had a 5 mm Hg greater reduction in SBP at 12 months.[52] A trial conducted in UK primary care practices included automated text messages or email as part of a home BP telemonitoring intervention.[53] BP was 4/2 mm Hg lower in the intervention patients than in the usual care patients after 6 months. In another recent study conducted in a managed care setting, patients randomly assigned to home BP telemonitoring combined with pharmacist-led care had greater reductions in SBP (-21 mm Hg) than usual care (-8 mm Hg) over a 6-month intervention period.[30]

Two randomized trials conducted by members of this research team also strongly support combining telehealth care with home BP self-monitoring and management support by pharmacists. Margolis, et al conducted a cluster-randomized trial at HealthPartners comparing pharmacist-led care management plus home BP telemonitoring with usual primary care in 450 patients with uncontrolled hypertension.[29] Unlike many previous studies, there were few exclusion criteria, and patients with a broad range of comorbidities and hypertension severity were enrolled. The intervention patients had an 11/6 mm Hg greater drop in BP than the usual care patients at 6 months (P<0.001), and a much higher proportion had controlled BP (72% vs. 45%, P<0.001). The improved BP results were sustained with less intensive pharmacist contact at 12 months and 18 months (6 months after the intervention ended). A trial by Green, et al in a managed care setting used secure email messaging to send home BP data to pharmacists for 12 months.[33] The intervention group had lower BP (14/7 mm Hg vs. 5/4 mm Hg, P<0.001) and better BP control (56% vs. 31%, P<0.001) than usual care.

The effect of telehealth care on patient-centered outcomes is much less well-studied than BP outcomes. A qualitative analysis of the UK trial of telemonitoring with automated patient decision support found that intervention patients and clinicians felt more confident in treatment decisions based on home BP. Before the intervention, they were hesitant to increase medication based on BP measurements taken on a single day in the clinic.[54] Conversely, they perceived that multiple telemonitoring measurements were more accurate, were difficult to ignore, and led to action. In the previous study at HealthPartners, the intervention was associated with significant improvements in patient satisfaction with 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 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.[55]

Members of the investigator team for this proposal have conducted a meta-analysis and computer-model simulation to predict outcomes of team-based care for hypertension in large populations. This suggests sizable potential for benefit of interventions for uncontrolled hypertension that include a pharmacist or nurse who can adjust medications, provide education and counseling on adherence and lifestyle, and support self-management. Based on data from 30 studies, these interventions led to, on average, a reduction of SBP of about 8 mm Hg, reductions in LDL-cholesterol ("bad" cholesterol) by about 12 mg/dL, and increases in HDL-cholesterol ("good" cholesterol) by about 1 mg/dL.[20] The analysis

showed that, over 10 years, widespread adoption of this type of team-based care would reduce the number of persons with uncontrolled hypertension by 4.7 million (about 13%) and avert 192,000 heart attacks and 204,000 strokes.

1.B.2.3. Need for a study comparing clinic-based and telehealth care models. In summary, we have identified gaps that support the need for a comparative effectiveness trial. **1)** Although clinic-based care has achieved high levels of BP control in some highly integrated, large health systems, few practices have achieved the same outcomes. Rigorous evidence supporting most of the best practices is lacking. **2)** Despite strong evidence from research studies showing that nurse- and pharmacist-led team-based care and telehealth interventions result in large and lasting improvements in BP, it is unclear how successfully these can be implemented at scale in real-world settings without research support. **3)** It is also uncertain whether such resource-intensive care achieves better clinical results, and **4)** it is not known how it affects patient experience compared with traditional clinic-based care if best practices were adopted. The research 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 physician-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). HealthPartners, the setting for the study, already uses some of the components of best practice in its clinic-based care, but further improvement in BP results is needed. HealthPartners is therefore poised to adopt other elements of best practice for clinic-based care (eg, protocols to promote consistent treatment and follow up for elevated BP, a hypertension registry to improve population management), but there are no plans to adopt telehealth care for hypertension widely in clinical practice without the research infrastructure to compare it rigorously with clinic-based care provided by this proposal. The study will support systematic data collection and analysis on implementation and outcomes, but intervention clinical care costs are supported by HealthPartners.

2. Objectives

2.A. 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.

Hypothesis 1.1: Compared with patients in clinics assigned to clinic-based care, patients in clinics assigned to telehealth care will have a 5 mm Hg greater change in systolic blood pressure over 12 months of follow up.

Hypothesis 1.2: Compared with patients in clinics assigned to clinic-based care, patients in clinics assigned to telehealth care will report: a) fewer treatment side effects; b) better ratings of patient experience of hypertension care; and c) higher self-monitoring rates and confidence in self-care.

2.B. Aim 2

Conduct an evaluation of reach, adoption, implementation, and maintenance of the telehealth care and clinic-based care interventions using a mixed-methods approach supported by the RE-AIM framework and the Consolidated Framework for Implementation Research (CFIR)

3. Study Design

The study compares two alternative health care service designs emerging as the dominant choices for clinicians and health systems wanting to redesign and improve hypertension care outcomes. It builds on previous hypertension quality improvement initiatives and the Hyperlink study, which used telemonitoring and telephone communication between patients and clinical pharmacists. The study design incorporates many elements of pragmatic trials: few exclusion

criteria, flexible interventions delivered in routine care, and routine follow up to determine outcomes.[56] It is a cluster-randomized comparative effectiveness trial in 20 primary care clinics (Figure 1). [Note that 21 primary care clinics were eligible to participate (see section 4.B.) and agreed to be randomized. Four of the clinics were co-located in two buildings (two practices in each) and had shared nursing leadership. Each of the co-located clinics were randomized as one unit; therefore there are 19 units of randomization. For simplicity throughout the rest of this protocol we will continue to refer to the study as including 20 primary care clinics.] The clinic-based care approach will use recommended best practices in ~10 clinics and ~1000 patients. It relies primarily on the physician-medical assistant dyad and face-to-face visits. The telehealth care approach adapts and implements a successful research-tested model in ~10 clinics and ~1000 patients. It differs from clinic-based care through the systematic use of home BP telemonitoring and home-based telehealth care coordinated by a pharmacist. Aim 1 compares outcomes that are important to patients and other stakeholders, including BP lowering, treatment side effects, patient experience, and self-care. Aim 2 evaluates the extent and between-clinic variability of the adoption, implementation, maintenance, and reach of the interventions. Data collected for Aim 2 will also be used to monitor and improve fidelity to the interventions. Please see Appendix F for a high level overview of the study design.

To ensure that the study addresses the relevant questions and concerns of patients, caregivers, clinicians, and other healthcare stakeholders, the research team includes two patient investigators, a patient advisory board (PAB), and a stakeholder advisory board. The roles, structure and function of these individuals and groups are described more fully in section 13 (Organization) and Appendix I.

4. Study Population

4.A. Setting

HealthPartners is a nonprofit integrated health system in Minnesota and western Wisconsin serving more than 1.5 million health plan members and more than 1 million patients. It includes a multispecialty group practice of more than 1,700 physicians, seven hospitals, and 47 primary care clinics. HealthPartners accepts all forms of commercial insurance, Medicaid, and Medicare, and the patients are diverse by age, race/ethnicity, and socioeconomic status.

4.B. Recruitment and randomization of clinics

The population of interest is patients with uncontrolled hypertension cared for by HealthPartners primary care providers (PCPs) at 20 representative primary care study clinics. Clinics will be eligible to participate if they have a Medication Therapy Management (MTM) pharmacist onsite at least one half-day per week and use standardized methods to measure BP with validated oscillometric BP monitors. Eligible clinics will be contacted via their leadership and invited to participate if they are willing to be randomly assigned to clinic-based care or telehealth care, participate in training, participate in limited data collection activities, and receive periodic feedback on implementation of the elements of clinic-based care or telehealth care according to their randomized assignment. Eligible clinics will be assigned to strata based on the proportion of hypertensive patients with controlled BP and the number of days per week that a pharmacist is available. Each stratum will include at least 4 clinics. The study statistician will assign a random unique identifier to each eligible clinic and then randomly and equally assign them to clinic-based care or telehealth care within strata.

4.C. Inclusion and exclusion criteria

Patients who meet the study inclusion criteria for uncontrolled hypertension will be identified in real-time at primary care encounters based on EHR data. Patients who meet the study inclusion criteria: 1) are aged 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 PCP in the last 12 months with or without a hypertension diagnosis code; 4) meet high BP study criteria at the current visit in the study primary care clinic where their assigned PCP practices; and 5) met high BP study criteria at their most recent previous qualifying encounter.

According to the nursing protocol for BP measurement, BPs are repeated if the first BP is elevated, defined as an SBP $\geq$ 140 or DBP $\geq$ 90. Study criteria for high BP for patients are defined as SBP $\geq$ 150 or DBP $\geq$ 95 in the first BP and in a repeated BP within an encounter. A qualifying previous encounter is defined as an office visit with a medical assistant (MA), nurse, physician, nurse practitioner, or physician assistant in internal medicine, family medicine, pediatrics, geriatrics, cardiology, endocrinology, or nephrology clinics. Study criteria for high BP are based on estimates of the number of eligible patients and capacity of the study clinics to accommodate additional follow-up referrals. They may be adjusted if warranted by changes in patient volume or clinic capacity.

The study will exclude 1) pregnant patients, since they require specialized obstetric care, 2) patients with end-stage kidney 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 is broadly represented since these criteria eliminate only a small fraction of hypertensive patients. These four groups of patients are also excluded from quality improvement measurements based on HEDIS and from MN Community Measurement publicly reported data.

4.D. Enrollment of patients

For patients who have an elevated BP at a primary care encounter (nurse or provider) but do not yet meet the study's high BP criteria for two consecutive qualifying visits, providers and clinic staff are encouraged to use a standardized hypertension referral order that facilitates scheduling a BP follow up with a provider of their choice (nurse, primary care provider, MTM pharmacist, or specialist).

If the patient meets all study inclusion and exclusion criteria, the patient will be identified automatically upon BP entry through algorithms within a web-service and flagged as "eligible" for Hyperlink. The MA will receive a best practice alert (BPA) that if accepted will open an order for hypertension follow up. The MA will "pend" this order for the provider. Once pended, the order can be removed or signed, but must be addressed by the provider before the encounter can be closed. The follow-up BP order contains defaults to nurse, PCP, or MTM as dictated by appropriate clinic-based care or telehealth care depending on the clinic assignment (see section 5 on Interventions.) The defaults can be modified by the provider prior to signing order using their professional judgement. Once the order is signed and the encounter is closed, the patient is flagged as "enrolled" in the study.

Enrollment will occur in two phases, Vanguard and Main Trial. Vanguard Phase enrollment will begin at the start of Year 2 with 2-4 Vanguard clinics to test procedures and make adjustments so that they are running smoothly. Enrollment of patients will continue until the study sample of 2000 eligible patients has been enrolled in the main trial from the 20 study clinics (Figure 1). In order to avoid very unequal distribution of cluster sizes, enrollment will continue for each clinic until a cap is met (e.g., 200 in a large clinic) or until a minimum is met (e.g., 40 in a small clinic). An average-sized clinic would need to enroll about 8-10 patients per month (or 2-3 patients per week) over 12 months to achieve our sample size.

Enrollment uses existing clinic resources, but to ensure that the study population represents the diversity of the HealthPartners population with uncontrolled hypertension, additional resources are budgeted for outreach and transportation for low-income and minority patients to attend visits and to promote their equal participation and retention in the study. Given that there are no special study visits to attend and that BP checks, pharmacist consultations, and any equipment will be provided without charge, we do not believe that these costs will be substantial

barriers to participation.

5. Interventions

Both care models we propose to study have been shown to reduce BP substantially. Best practices for clinic-based care are based primarily on expert opinion and observational studies. Telehealth care has generally been studied in relatively small studies and for limited durations. These models were selected because they represent the dominant choices for clinicians and health systems that want to redesign hypertension care, but they have not been directly compared, and there is little information about patient preferences. Thus, our main research question is which approach to treating people with uncontrolled high BP produces the best outcomes. Both are rooted in the Chronic Care Model developed and refined by Wagner and colleagues.[57] This model identifies delivery system design, decision support, information systems, and self-management support as essential elements for improving chronic illness care in health systems. These elements foster productive interactions between informed patients and prepared practice teams. Both models use multiple levels of delivery system design to create positive feedback loops whereby uncontrolled BP is recognized and prompts timely treatment adjustment and BP re-measurement until BP control is attained.

5.A. Best Practice Clinic-Based care

The components of best practice clinic-based care are based on a review of the literature and current guidelines (section 1.B.2.1.). They were further discussed in a HealthPartners working group to improve hypertension care that includes nurses, pharmacists, physicians, administrators, and researchers. The best practices are achievable by motivated primary care practices of all sizes using readily available EHR technology. Similar models are being promoted and disseminated by the professional organizations that are stakeholders in this project.

As operationalized for this project the best practices fall into two categories: a) infrastructure and policies that promote high quality care, and b) hypertension care processes that promote recognition, timely treatment adjustment, and follow-up of uncontrolled BP until control is attained.

5.A.1. Current infrastructure and policies

1. Accurate BP measurement is promoted by the consistent use of validated oscillometric BP monitors (Omron HEM 907XL) according to a standard nursing protocol. The protocol includes proper cuff size, proper positioning of the patient, and requires a repeat BP measurement after 5 minutes of rest when the initial BP is elevated. Both automated EHR alert and physical reminders are used to prompt repeat BP measurement at the same visit when the initial BP is elevated. (See Appendix A for Nursing BP Measurement Protocol)
2. Patients have access to no-cost blood pressure recheck visits with an MA and consultations with a clinical pharmacist trained in medication therapy management (MTM) to follow up on uncontrolled BP at clinic encounters. MTM pharmacist consultations are face-to-face visits in the patient's primary care clinic and generally do not include ongoing follow up. Patients may self-refer or can be referred by a PCP, MA, or RN.
3. A hypertension registry is used to enumerate the patient population with hypertension (controlled and uncontrolled). The registry is used to identify and contact patients who need follow-up for uncontrolled hypertension. (See Appendix D for Hypertension Registry Standard Operating Procedure, Appendix E for Hypertension Registry Technical Specifications
4. PCPs use an evidence-based hypertension treatment algorithm that promotes low-cost generic medication and single-pill combination therapy, when possible. If BP is uncontrolled at an MA visit, the MA may consult a registered nurse (RN) or MTM pharmacist. RNs and pharmacists have separate protocols to adjust hypertension

treatment. If the RN or pharmacist is unavailable at the time of the MA visit, the patient may be contacted by telephone and/or scheduled for a return visit to the PCP. (See Appendix B for MTM Hypertension Protocol, Appendix C for ICSI Guidelines for Hypertension Management)

5. PCP and clinic performance on BP control is measured with monthly feedback. Clinic managers have access to monthly reports and routinely download and distribute them to PCPs. BP control is a high priority performance measure, with open comparison within and between clinics.
6. Home BP monitoring may be encouraged by individual clinicians, but is not supported by infrastructure or policies.

All of the above infrastructure and policy elements are currently in place in all HealthPartners primary care clinics. Elements 1, 3, 4, and 6 may vary in implementation between and within clinics and will therefore be measured for implementation fidelity as described in section 7.D and Table 2.

5.A.2. Hypertension care processes

The study will create and enhance automated EHR tools to promote the following iterative process:

1. Recognition of uncontrolled BP and high BP study criteria at primary care encounters
2. Therapeutic action to address uncontrolled BP at primary care encounters (may include medication adjustment, addressing non-adherence, and counseling on lifestyle changes)
3. Follow-up visits to re-assess uncontrolled BP within 2-4 weeks. Follow-up visits may be scheduled with a PCP, MA, or MTM pharmacist.

Blood pressure in the ambulatory primary care setting at HealthPartners is measured by the MA during the rooming process for a clinic appointment, or at the time of a nurse blood pressure check using an electronic, automated monitor. If an initial BP $\geq$ 140/90 is entered into the EHR vital signs field it will trigger an automated BPA pop up to remind the MA to repeat the BP if the initial BP is elevated after 5 minutes of rest. If the study inclusion/exclusion criteria are met on the repeat BP, a new BPA appears on the computer screen prompting the MA to open and pend an order for hypertension follow up. The default follow-up interval is 2 weeks unless the BP is $\geq$ 180/110 in which case the default follow up interval is set to 1 week. The type of provider for the follow up visits defaults to nurse, PCP, or MTM depending on the clinic randomization. All defaults can be changed by the MA or at provider discretion if desired by clicking a different options within the order, but the patient is enrolled by any signed order.

Implementation and fidelity to hypertension care processes will be measured as described in Section 7.D and Table 2 using EHR vital sign, diagnosis, current medications, medication order, and encounter data stored and linked to individual study patient IDs and encounters. The study will foster reliable processes in all study clinics through training, measurement, and feedback to improve the consistency with which the hypertension follow up orders are pended, signed, scheduled, and completed.

5.B. Telehealth care

The design of the telehealth care intervention is based on our experience and the literature reviewed in section 1.B.2.1. The Chronic Care Model domain that differs most from clinic-based care is the strong self-management support built into the telehealth care intervention. Recent systematic reviews found that home BP monitoring alone resulted in small and non-sustained BP reduction, while adding support resulted in larger BP reduction that was sustained for at least 12 months.[58] Therefore, there is ample evidence from efficacy trials that the combination of home BP monitoring and telephone or online follow up is synergistic. The combination creates a powerful feedback loop that permits sequential trials of treatment changes and rapid assessment of their effect on BP, side effects, and other outcomes. It is critical to have a dedicated health care provider to receive, interpret, and act on the home BP monitoring data in collaboration

with patients. Our analyses of Hyperlink and e-BP have shown that the strongest predictors of BP lowering in these trials were the intensity of home BP monitoring, communication between patients and pharmacists, and medication treatment intensification.[59]

In our previous research on telehealth care for uncontrolled high BP, we conducted focus groups with patients and pharmacists in the study. Several key themes emerged that suggested ways to improve the intervention to better meet patients' needs. Focus group patients told us that trust in the relationship is important to them, whether working with a PCP or an MTM pharmacist. Patients reported having more trust in pharmacists if they understood their qualification to treat high blood pressure. They were dissatisfied when they perceived poor communication between the pharmacist and their PCP. Second, patients have highly personal needs when it comes to initiating medication or finding the best medication. They value clinicians who listen and engage instead of just "pushing pills", an attribute that was also strongly endorsed by the pharmacists. Patients have varying goals related to medication; many want to avoid or discontinue medications, if possible, in favor of lifestyle interventions. Side effects of medications are a major concern. Therefore, patients want a flexible approach rather than a one-size-fits-all model for treating hypertension, and this in turn supports acceptance, adherence, and satisfaction with treatment. Finally, patients benefited from both seeing their BP data (reinforcement) and having a trusted provider see their data (accountability). These led to long-term adoption of regular self-monitoring and specific strategies to keep their BP under control; therefore, patients strongly preferred to keep the BP monitor after they stop regularly working with the pharmacist.

Suggestions from the focus groups and analyses of study data were used to modify our previous telehealth care intervention[29] in the following ways. **1**) The qualifications of pharmacists to treat hypertension and the collaborative nature of their work with the patient's PCP will be emphasized. **2**) In order to remove barriers for team care, home BP data will be transmitted and stored in the HealthPartners Epic EHR, rather than in a password-protected third-party Web site. Home BP data will be maintained in a flowsheet that is separate from BP measured during clinic visits. **3**) Trajectories of BP during the Hyperlink study showed maximum BP lowering after an average of about 3 months, with little additional BP lowering during the remainder of the 6 months of intensive intervention and 6 additional months of maintenance. Therefore, rather than having a fixed duration, the telehealth care intervention will be flexible and tailored to individual patients' needs. **4**) Patients will have several options for transmitting home BP data (further details below). In any case, patients will be given their own BP monitor for long-term use.

Telehealth care clinics will offer best-practice clinic-based care, but eligible patients in these clinics will be referred for telehealth care with systematic home BP telemonitoring and BP management through the MTM pharmacist. Referrals will take place using the same hypertension follow up orders used for clinic-based care, but the default will be MTM pharmacist follow-up. There is currently a high rate of appointment completion following referral to MTM pharmacists. As in the clinic-based care group, the study will foster reliable processes to improve the consistency with which the order set is used and uncontrolled BP is re-assessed by an MTM pharmacist within 4 weeks. Following an initial face-to-face intake visit, the MTM pharmacist and patient will communicate by telephone or secure e-mail (according to patient preference) at regular intervals, adjusting medication using established care protocols and collaborative practice agreements until BP control has been achieved. Pharmacists will also support lifestyle changes and adherence to treatment. Other CV risk factors including smoking, hyperlipidemia, hyperglycemia in diabetic patients, and use of aspirin will be addressed as needed using evidence-based protocols, since this is the customary practice of MTM pharmacists at HealthPartners.

5.B.1. Intake visit with MTM pharmacist

1. The pharmacist in telehealth care clinics will receive an EHR alert that the patient is a Hyperlink-3 study patient. The pharmacist follows standard MTM procedures for assessment of new patient including measurement of BP and determination of correct BP cuff size.
2. The pharmacist emphasizes that the PCP has referred the patient and that they will be collaborating on the patient's care, explains the pharmacist's training and qualifications to treat hypertension, determines if patient is willing to use home BP monitoring equipment and communicate by phone or email, and complete appropriate documentation in EHR.
3. The pharmacist determines with the patient the most appropriate method for home monitoring and instructs the patient on proper use of equipment, positioning, and BP cuff size.
4. The patient is advised to check blood pressure 6 times weekly (eg, 3 days each week, morning and evening), with duplicate measurements each time if possible.
5. Pharmacists instructs patient on individualized BP level indicating control (5 mm Hg lower than clinic goal for SBP and <85 mm Hg for DBP goal) and goal to have 75% of home BP readings below that level.
6. Pharmacist orders BP monitoring equipment and obtains consent for data sharing if needed.
7. MTM pharmacist follows a slightly modified version of the current HealthPartners MTM hypertension management protocol regarding lifestyle counseling, medication initiation, titration, labs, and follow up plan. (Appendix B for MTM Hypertension Protocol)

5.B.2. Follow-up visits with MTM pharmacist

Follow-up visits will typically be done by phone or secure e-mail on the HealthPartners EHR portal. In some cases in-person visits may be preferable due to patient communication needs (eg, patient is severely hearing impaired, requires interpreter). Visits will be documented in the EHR using a visit template and routed to the PCP. The first 3 follow-up visits will be at 2 week intervals, then may be spaced at longer intervals every 2-4 weeks for up to 6 months as decided by the pharmacist and patient. Based on our experience, we anticipate that most patients will only need telehealth care management for 3 or 4 months.

1. Pharmacist reviews lifestyle, medication adherence, and BP readings with patient.
2. Pharmacist adjusts medications as needed based on aim to have $\geq$ 75% of BP readings at controlled level. If this is not the case, discuss options with patients with emphasis on the most effective action that is clinically appropriate (add new medication, increase medication dose, improve adherence, intensify lifestyle management). The superior effectiveness of adding a new low-dose medication makes this the preferred option in many circumstances.
3. Subsequent follow up visits by phone every 2-4 weeks.
4. When $\geq$ 75% of BP readings are controlled at 3 consecutive follow-up visits, begin transition back to clinic-based care with PCP visit to document clinic BP.
5. If BP is not controlled in 3 months, schedule follow-up appointment with PCP to determine next steps.

5.B.3. Communication with primary care team and transition from telehealth care:

Clear communication among team members will take place by formal and informal discussions and shared notes in the EHR. When patients attain stable BP control in 3 consecutive telehealth visits, they will transition to routine clinic-based care and will be given a high-quality non-data transmitting home BP monitor if they do not already have one. The entire episode of telehealth care will be summarized in the EHR using a standard note template. Patients may re-enter the telehealth care intervention if clinic BP reverts to uncontrolled levels or if they detect recurrence of uncontrolled home BP by continued self-monitoring.

5.B.4. Home BP monitoring options:

A note on cost: Patients will not be billed in any way for their MTM visit or for blood pressure monitoring equipment. HealthPartners does not charge patients for MTM visits. Blood pressure monitoring equipment will be provided free of cost to the patient using study resources. Given that we are testing a program that we hope will be adopted by HealthPartners if it improves hypertension outcomes, we must pay attention to keeping equipment costs as low as feasible.

1. Non-transmitting BP monitor (LifeSource 767) with manual data entry into MyChart: This is the lowest cost option for the study budget, but it requires that patients are willing and able to manually enter BP into the EHR portal (MyChart) for viewing by the MTM pharmacist. This option also requires internet and computer access.
2. Bluetooth BP monitor (Lifesource 767pbt-ci) with automated data upload to MyChart via AMC Health: This option is the most expensive for the study budget due to a monthly fee, but it will work well for patients who do not have access to the internet at home or who are unwilling or unable to accurately manually enter home BP data. Telemonitoring equipment will be supplied by the vendor AMC Health.
3. Bluetooth BP monitor (models to be determined) with automated data upload via smartphone app: This option has the potential to be as inexpensive for the study budget as Option 1 and as simple as Option 2. However, it requires the patient to have a smartphone with the correct app. We do not currently have capability or permission to use this option at HealthPartners, but will be working intensively to make it available during the study.

Implementation and fidelity to hypertension telehealth care processes will be measured as described in Section 7.D and Table 2 using EHR vital sign, diagnosis, current medications, medication order, and encounter data stored and linked to individual study patient IDs and encounters.

6. Training

All 20 clinics will receive hands-on, in-person intervention training for their staff, conducted by a physician investigator, a project manager or coordinator, and the clinic's Care Delivery Supervisor. Training will be conducted in June and July of 2017, prior to the official start of the study interventions.

All clinics will receive training on:

- The hypertension management workflow, including best practice alerts and referral orders for hypertension care
- Communication with patients about hypertension care referrals
- Follow-up with patients regarding unscheduled or missed referral visits
- Omron BP machine best-practice use, re-emphasize need for second BP when elevated

Telehealth clinics will receive training on:

- Details of telemonitoring program for discussion with patients
- Operation of telemonitoring equipment and technical support options
- Use of patient-entered vitals flowsheet (in EMR)

We will include all primary care team members in these initial trainings, including PCPs, RNs, MA/LPNs, and MTMs. We will keep a roster of all staff in these positions at each clinic, and monitor attendance at trainings. The best training format will be determined by the clinic Care Delivery Supervisor. We will record a webinar presentation of our basic training to supplement the in-person/hands-on training, for review by staff who couldn't attend or for use as a reference. After each in-person training we will collect evaluation feedback to determine whether the training is meeting the needs of each clinic.

Care Delivery Supervisors will be provided with a simple 1-2 page "guide" for the hypertension care interventions, so they may continue to support their staff in reinforcing best practices.

Need for follow-up trainings will be determined at the conclusion of the initial in-person training.

The following training materials will be developed by the study team with input from stakeholders by May 2017:

1. Detailed outline of training objectives
2. Scripts for patient communication about interventions (central outreach, nursing, physicians, pharmacists)
3. After Visit Summary content with patient instructions
4. Frequently Asked Questions for both interventions
5. Guide for Care Delivery Supervisors
6. Instructions for set-up and use of Telemonitoring Equipment (Telehealth Clinics only)

Further training will be provided during in-person visits from the study staff to clinics throughout the intervention period. At least 10 clinics will receive a quarterly in-person visit by a study coordinator and all clinics receive in-person visits for continued training and evaluation every six months. The content and objectives of these in-person visits is to be determined.

7. Outcomes

The study outcomes have been selected based on input directly elicited from patients and other stakeholders participating in this project. The Aim 1 outcomes address the relative effectiveness of clinic-based care and telehealth care in improving key clinical and patient-reported outcomes (Table 1). The Aim 2 outcomes are directed toward evaluating intervention implementation fidelity (Table 2) and other RE-AIM measures (Table 3). No additional research visits will take place to gather outcomes data.

7.A. Primary Aim 1 outcome

The primary outcome is change in SBP after 12 months of follow-up (H1.1). SBP values that are routinely collected in primary care will be extracted from the vital signs field in the EHR at the two qualifying encounters and at all subsequent qualifying encounters over the next 24 months for all enrolled patients.

7.B. Secondary Aim 1 outcomes

Aim 1 patient-reported secondary outcome measures are treatment side effects; experiences and satisfaction with hypertension care; home BP self-monitoring; and confidence in self-care. These outcome data will be collected using patient surveys. These patient-reported secondary outcome measures were selected based on 1) patient ratings of importance, 2) evidence that previous similar telehealth interventions led to improvements, 3) importance of the measure as a potential mediator of intervention effect, and 4) the measure cannot be obtained from the EHR, claims or any other routinely collected patient data. All enrolled patients will be mailed a baseline survey that includes primary patient-reported outcome measures within one week of their qualifying encounter, with telephone follow-up of non-responders. They will also be asked to complete follow-up surveys 6, 12 and 24 months later that will be administered by mail, telephone or electronically according to the patient's preference. The secondary Aim 1 analyses will focus on patient reports in the baseline and 6 month surveys. A draft of the patient survey is included in Appendix H.

Patients' reports of BP treatment-related side effects will be assessed using the Treatment Satisfaction Questionnaire for Medication (TSQM) and a side effect symptom checklist modeled after the PERSYVE questionnaire.[58] The TSQM global satisfaction and effectiveness, side effects, and convenience subscales demonstrate adequate internal consistency

(Cronbach α = .86-.90) and positive correlation with self-reported health. Among patients with hypertension, all three subscales were correlated with global medication satisfaction.[59]

Patient Assessment of Chronic Illness Care (PACIC). The PACIC [60] will quantify patient experience of hypertension care, including self-management support, along dimensions in the Chronic Care Model. The overall PACIC scale has demonstrated excellent internal consistency (Cronbach α = .93; subscale α=.77-.90) and adequate test-retest reliability over 3 months (overall .58; subscales .47-.68). It has been shown to be highly responsive to a telehealth intervention for hypertension.

Satisfaction with health care provider communication will be measured with the 6 items from the Clinic & Group Consumer Assessment of Healthcare Providers and Systems (CG-CAHPS). The CG-CAHPS survey is a product of the Agency for Healthcare Research and Quality's CAHPS program, which is a public-private initiative to develop and maintain standardized surveys of patients' experiences with ambulatory and facility-level care. The scale has good internal consistency (Cronbach α = .89), is highly correlated with overall physician ratings, and the scale items have been shown to be responsive to a previous telehealth care intervention.[61] In addition, this subset of items is currently in use to assess patient satisfaction with care at HealthPartners clinics and other medical groups nationally as part of the NRC Picker 'Connect Experience' survey. BP self-monitoring rates and confidence in self-care will be measured by items used in previous research[29,55] that have been shown to be responsive to intervention.

7.C. Aim 1 other outcomes

Other clinical outcomes include cardiovascular risk factors other than systolic BP (DBP, lipid levels, statin use, antihypertensive medication use, smoking, and overall cardiovascular risk based on 10-year AHA/ACC pooled risk equations [62] and the Framingham 30-year risk equation [63] that may be influenced directly or indirectly by telehealth care relative to clinic-based care. The study will also monitor laboratory abnormalities in electrolytes and kidney function that may be affected by hypertension medications, as well as low blood pressure (hypotension) and fainting that might result from overly aggressive blood pressure lowering. All secondary clinical outcome values and dates are routinely documented in the EHR as they are measured at clinic encounters or are returned as laboratory values.

The patient survey will also include some items and scales that do not meet the criteria for secondary outcomes but have been identified by patients or investigators as potentially important, as well as all responses from the 12 and 24 month surveys.

7.D. Aim 2 outcomes

The Aim 2 analyses are directed toward evaluating intervention uptake and providing timely feedback to clinic and care teams to improve fidelity to both interventions. We will rely on two well-accepted frameworks, the RE-AIM framework[64] and the Consolidated Framework for Implementation Research (CFIR)[65] to identify barriers and facilitators to adoption, implementation, and maintenance; monitor intervention implementation progress and adaptations; and interpret reasons for variations in implementation success or failure. The reach, adoption, implementation and maintenance of both interventions will be evaluated using the definitions of each measure found in Tables 2 and 3.

8. Measurements

8.A. EHR for clinical measures

The primary outcome, SBP, and other clinical outcomes will be extracted from data documented in the electronic health record (EHR). An EHR tool that operates in HealthPartners primary care clinics is automatically triggered when vital sign

data are saved to the EHR. The tool searches the EHR to gather the most recent vital signs (e.g., SBP, DBP) and laboratory values (e.g., total cholesterol, LDL, potassium, sodium, creatinine), current medications (e.g., antihypertensive medications, statins), lifestyle data (e.g., smoking status, BMI), safety events (hypotension, fainting), and socio-demographic information (e.g., age, ethnicity, race). These data elements are used to calculate total cardiovascular risk (e.g., 10 year Hard CV risk via the ACC/AHA risk model; 30 year lifetime risk via the Framingham model) and to alert the provider to abnormalities (e.g., potassium, sodium, creatinine values that are out of range). The EHR tool documents the information that was aggregated for each triggering event, including the dates that were associated with each data element (e.g., date of cholesterol test). The tool also assigns a random unique identifier to each patient so that data elements stored in the EHR as part of routine care may be readily extracted and re-assembled to describe within-person changes in clinical outcomes over time.

8.B. Patient Survey for patient-reported outcomes

All study-enrolled patients (n=2000) will be invited to complete a series of surveys that will be the source of the patient-reported primary outcomes (i.e., treatment side effects, experiences and satisfaction with hypertension care, self-management support, confidence in self-care). Appendix H Figure 1 describes the process for collecting survey data from patients The EHR tool will identify patients at the visit when they are enrolled in the study and transmit their contact information to the HealthPartners Survey Research Center (SRC). The SRC will mail a letter to request their participation in a series of surveys, a paper questionnaire and a $2 non-contingent incentive, a practice known to increase response rates and reduce the likelihood of non-response error.[66,67] The SRC's professional phone interviewers will call patients who do not return the paper survey to attempt to complete a survey via phone within 2 weeks of enrollment.[68] At the end of the survey, respondents will be asked what mode they prefer for follow-up surveys 6, 12 and 24 months later. First contact for follow-up surveys will be made via the respondent's preferred mode. Non-respondents to the enrollment survey will not receive further surveys. All four surveys (enrollment, 6, 12, and 24 months) will include the patient reported outcome measures. The secondary analyses (H1.2) will make use of data collected from the enrollment and 6m surveys while other outcome analyses will make use of data collected at all four time points. Patients who complete enrollment, 6, 12, and 24 month surveys will be mailed a $10 gift card. Patients who are on the HealthPartners Institute Exclusion List will not receive a survey.

9. Evaluation Reporting

Clinic managers and primary care physician chiefs will be provided with a monthly summary of measures pertaining to their blood pressure care and the study interventions. The reports will include measures found in Tables 2 and 3, and will be linked to clinics' blood pressure control performance measures provided by HealthPartners. At 12 and 24 months, a more extensive report will be populated that will include a summary of field observations, focus group and interview data, and other data supporting recommendations for the clinics.

Field observations will be made by study staff visiting clinics in-person and speaking with clinic managers and staff as feasible and observing the rooming process. The study team will meet to discuss observations and other sources of data prior to compiling monthly reports or making recommendations. Reports will be available and shared online, and viewable across clinics.

10. Analysis

10.A Aim 1 Primary and Secondary Analyses

The Aim 1 hypotheses pertain to the effectiveness of telehealth care, predicting that, relative to clinic-based care, it will improve SBP by a practically meaningful 5 mm Hg after 12 months of follow up (H1.1) and patient-reported outcomes (PRO) after 6 months of follow up (H1.2). H1.1 will be tested using random coefficients models in which post-enrollment SBP values will be predicted from clinic-randomized treatment group (Telehealth), time elapsed from enrollment to the SBP (YEARS), and the treatment by time interaction. The most basic form of the H1.1 model will be:

$$SBP_{ij} = \gamma_{00} + \gamma_{10}\,Telehealth_i + \gamma_{01}YEARS_j + \gamma_{11}\,Telehealth_i*YEARS_j + [u_{i0} + e_{ij}],$$

where EHR-derived SBP values documented at all qualifying encounters for 24 months will vary randomly across randomized clinics (u_{i0}) and time (e_{ij}). Enrolled patients will be 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. YEARS will be scaled so that 0 represents the date of the primary care encounter at which the patient was enrolled in the study and 1 represents 365 days later. Parameter γ_{01} will therefore estimate the annual rate of change in SBP among clinic-based care patients, and parameter γ_{11} will estimate 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 YEARS component of γ_{01} and γ_{11} with a dummy indicator (6M) for whether the PRO is an enrollment or 6-month survey response.

SBP and PRO are expected to be approximately normally distributed, although the suitability of alternate error distributions and link functions will be assessed if their distributions depart from expectations. Should we observe an imbalance between study groups in the characteristics of randomized clinics, particularly in factors that moderate the fidelity with which the care models may be implemented, we may include clinic-level variables (e.g., % patients >65) as covariates or treatment modifiers, as appropriate.

SBP values are expected to decline over time among clinic-based care patients so that $\gamma_{01}<0$. H1.1 will be most strongly supported if $\gamma_{11} \leq -5.0$ and $P<.05$, so that the estimated rate at which SBP values improved over 12 months was at least 5 mm Hg greater among telehealth patients relative to clinic-based patients. PROs are expected to be similar at baseline but months to have improved among telehealth patients by 6 months so that $\gamma_1 >0$ and $P<.05$.

10.A.1. Aim 1 Other Analyses

We plan to explore whether treatment effects differ among patient groups defined by age, race/ethnicity, socioeconomic status, and comorbidity. While we anticipate that on average across all patient groups telehealth care will reduce SBP by 5 mm Hg more than clinic-based care, we will separately quantify the treatment effect for all H1 outcomes among targeted patient subgroups. The H1 analytic models can be easily adapted to include parameters for patient covariates as well as interactions of patient covariates with time or time by treatment.

The H1 analytic models can be readily adapted for secondary and sensitivity analyses. As presented, H1.1 assumes a linear rate of change in SBP over time. The model can be readily adapted to assess the immediate effectiveness of telehealth during the first 6 months following eligibility separately from the 6- to 12- and 12- to 24-month periods, when short-term improvements in SBP or PROs may be differentially maintained over a longer time frame. Similarly, parameters γ_{01} and γ_{11} can be allowed to vary randomly so that the rate of SBP change is different for each of the 20 randomized clinics. We could then assess, for example, whether clinic-specific rates of change are related to clinic characteristics or the fidelity with which the care model was implemented.

10.A.2. Per Protocol Analysis Plan

Given the pragmatic, unblinded, 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 treatment interventions (including no treatment) outside of their assigned protocol. Furthermore, we would like to know what the impact of actual receipt of the intervention (as opposed to clinic-level assignment) has on study outcomes. Therefore it will be desirable to conduct a per-protocol analysis (average effect of telehealth vs. best practice, had everyone followed the trial protocol) to complement the intention to treat (ITT) results of the primary analysis.[69,70] Preliminary data suggests that the ITT approach in this study may be subject to bias due to 1) differential likelihood of enrollment based on provider 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.

Directed acyclic graphs (DAGs) have been used to depict causal relationships and illustrate potential sources of bias in epidemiologic studies.[71] Briefly, DAGs consist of nodes (e.g., treatment, outcome, other variables) presented in temporal sequence and connected by arrows, which indicate potential causal pathways. If there is no arrow connecting two nodes, it can be assumed that no causal relationship exists. Where 'backdoor' paths can be identified, estimation of causal effects may be biased[4].[72] For this study a DAG might be drawn as depicted in Figure 1, where:

- ***Z*** is randomized treatment assignment;
- ***S=1*** represents selection (enrollment) into the study;
- ***A*** is actual treatment receipt (patient adherence to assigned intervention);
- ***Y*** represents BP-related study outcomes;
- ***L*** is a vector of observed patient prognostic factors (e.g., age, comorbidities);
- ***U*** represents a vector of (possibly unmeasured) patient characteristics predictive of adherence to the assigned intervention protocol.

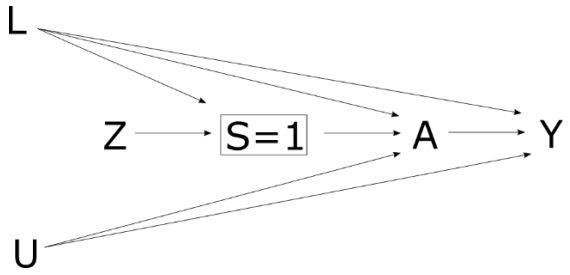

Figure 1. Directed acyclic graph representing the primary study aims.

For the per-protocol analysis, we are interested in estimating the effect of ***A*** on ***Y*** (as opposed to the ITT effect of randomized assignment ***Z*** on ***Y***). The DAG above shows multiple backdoor paths from ***A*** to ***Y***: 1) through ***L***, 2) through conditioning on the collider ***S*** and then through ***L***, and 3) through ***U***. 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.[72,73]

Inverse probability weighting can be used to estimate unbiased measures of effect where selection bias or confounding is present, under specific assumptions.[74,75] 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 will be specified *a priori*; 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.[75,76]

Based on contextual knowledge and preliminary summaries of the study population, we anticipate that the variables listed in Table 1 (in addition to clinic assignment of telehealth vs. best practice) may be associated with enrollment and/or treatment adherence. All will be considered for model inclusion. Patient-reported outcome measures (PROMs) will be available only for patients who are enrolled (and complete a survey), thus, these will be considered for the patient adherence model, but not the model for enrollment.

Table 1. Candidate Covariates for Inverse Probability Weight Models for Enrollment and Adherence

Demographics	**Comorbidities**	**Labs / Vital Signs**	**Other**	**Survey PROMs**
▪ Age ▪ Gender ▪ Insurance Status ▪ Race/Ethnicity ▪ SES ▪ Primary Language	▪ Comorbidity Index (e.g., Charlson, Elixhauser) ▪ CVD/CHD ▪ CV Risk Score ▪ Smoking	▪ Baseline BP ▪ BMI ▪ eGFR ▪ Creatinine	▪ BP Meds ▪ Med Count ▪ Utilization ▪ Clinical characteristics (e.g., % BP control) ▪ Provider characteristics (e.g., Specialty) ▪ Calendar time	▪ Self-Rated Health ▪ Prior BP Monitoring ▪ Education ▪ Employment ▪ Life Satisfaction ▪ Self-Efficacy

In the second stage of analysis we will apply the weights to generalized linear regression models to estimate the effect of per-protocol treatment on study outcomes. This model will be restricted to study patients who followed their assigned protocol (MTM visit if intervention, no MTM visit if best practice). By weighting individuals by their inverse probability of enrollment/adherence, we essentially create a pseudo-population for analysis, in which factors that were unbalanced in those who were enrolled/adherent vs. those who were not are no longer unbalanced. The effect estimate from this weighted model then represents the unbiased effect of actual, per-protocol treatment on BP outcomes.

The validity of inverse probability weighting depends on the assumptions of consistency, positivity, correct model specification, and exchangeability.[74,75,77] *Consistency* (the outcome observed for a given patient is consistent with their true outcome given their actual treatment status) is generally assumed to hold in this context.[76] The *positivity* assumption requires a non-zero probability of receiving every level of exposure (telehealth, best practice) for every combination of covariate histories, which can be evaluated empirically.[76] If we detect violations (or near-violations) of positivity, we will report these in tabular form, attempt to diagnose these as deterministic (a group of patients who would never be treated) or stochastic (random zeroes due to insufficient sample size), and implement one or more of the following approaches: 1) restrict the study population to patients with some likelihood of receiving telehealth;[77,78] 2) re-specify the models and/or confounding variables, and/or truncate weights, in an effort to achieve acceptable balance

in bias due to nonpositivity vs. confounding;[76,78] 3) modify the definition of treatment;[78] and/or 4) use alternative estimation methods which are less sensitive to nonpositivity (e.g., g-computation, g-estimation of structural nested models, targeted maximum likelihood estimation).[79-82] The potential for *model misspecification* to bias results can be mitigated by conducting a series of sensitivity analyses similar to those demonstrated in Cole and Hernan,[76] with the objective of optimizing the bias-variance tradeoff.

Exchangeability refers to the assumption that comparison groups (telehealth vs. best practice) are 'exchangeable' with respect to distributions of risk factors for outcomes (BP), possibly conditional on measured covariates.[76] This assumption is more generally recognized as 'no unmeasured confounding,' which applies to most epidemiologic studies. Although this assumption is untestable, we believe it will be reasonably defensible for several reasons. First, the model for enrollment is likely to be largely dependent on clinic-level treatment assignment and patient clinical characteristics, which would have been available to the provider, and will be available for analysis. Second, although the model for treatment adherence is more likely to be driven by factors that are not routinely captured in clinical data, we will have several relevant patient-reported survey measures (see Table 1) available for study participants. Third, 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.[83,84]

10.A.3. Power for Aim 1 Analyses

A power analysis estimated the minimum detectable standardized effect (MDSE) for γ_{11} in the H1.1 model 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 M=3.3 SBP over 10 months (Median=3, range 1-23), index M_{SBP}=159.9, index SD_{SBP}=16.1, all BP M_{SBP}=150.7, all BP SD_{SBP}=20.4, and a 3-level variance components model of SBP estimated ICC_{clin}=.003 and ICC_{pt}=.28. For power estimates, conservatively assumed n=100 eligible patients in each of 20 clinics, 3 SBP per patient over 24 months and ICC_{clin}=.01-.03 in a 2-level variance components model.

Under these assumptions, the H1.1 analysis is powered (80%, α_2=.05) to detect γ_{11}<-.124 (when ICC_{clin} = .01) and γ_{11}<-.174 (when ICC_{clin}=.03) so that an annual reduction in SBP that is 20.4*(.124-.174)=2.53-3.55 mm Hg greater among patients in telehealth relative to clinic-based care clinics will be statistically detectable. Based on our previous research and systematic reviews, we believe a 5 mm Hg greater reduction in SBP will be achieved in eligible patients in telehealth care compared with clinic-based care.[19,29,85] We assert that 5 mm Hg 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 mm Hg have clinically important effects.[38-42] The analysis should be sufficiently powered to observe clinically meaningful between-group differences in SBP reduction.

Patient-reported outcomes from the eligibility and 6 month surveys, corresponding to the beginning and end of intensive intervention, will be analyzed using the H1.2 model . We conservatively estimate 60% and 75% eligibility and 6 months response rates. Relative to the biologically based SBP, we anticipate higher clinic-based variance components for PROs (eg, ICC_{clin}=0.02-.03) for PROs. The MDSE comparing 6-month PROs among telehealth relative to clinic-based care patients are γ_{11}=.239-.270. We expect to be able to detect 6-month differences of about 4.5 to 6 points (scale range = 0-100) on the TQSM (subscale SDs=18.7-22.6) and about 0.25 points (scale range = 1-5; SD=1.0) on the PACIC. For self-reported outcomes, a between-groups difference of Cohen's d = .20-.30 is small, consistent with the goal of detecting meaningful differences in patient-reported side effects, care experiences, and self-management.

10.A.4 Missing data

Rich pre-enrollment EHR data will enable a detailed assessment of the demographic and clinical characteristics of patients who engage in each component of the clinic-based and telehealth care approaches. While the specific reasons for engagement, or lack of engagement, are not captured, it will be possible to quantify the likelihood of engagement for well-defined segments of the eligible population. Among enrolled patients, the absence of documentation of a care process or vital sign in the EHR should not be interpreted as a missing value, but rather as indicative of a care process or test not having been performed within the health system. Truly missing observations (e.g., SBP measured, value not available) will be extremely rare, undetectable, and assumed to be missing at random (MAR). EHR derived data fields will be treated as complete for these reasons.

The HealthPartners Survey Research Center will employ state-of-the-art methods to minimize unit and item nonresponse for patient-reported outcomes. The disposition of each contact attempt to complete a survey will be documented by the Survey Research Center. For mailings and email, this includes undeliverable addresses and active refusals or volunteered ineligibility due to language that are returned via these modes. For telephone surveys, these dispositions include noncontact, refusal, ineligibility, and bad telephone number. For item nonresponse, we expect less than 5% missing data on any single item. We will use a fully conditional specification approach to build a multiply imputed H1.2 dataset that assumes unobserved values resulting from item-non-response are MAR. The imputation model will include all predictors from the H1.2 analytic model as well as EHR-derived auxiliary predictors that may be correlated with PROs to improve imputation precision.

The H1.1 and H1.2 analytic models rely on maximum likelihood approaches to estimate all parameters. These models are sufficiently flexible to accommodate unbalanced data (e.g., outcomes per patient, patients per clinic) and rely on covariance structures for model estimation so that all available data from the intent-to-treat sample contribute to parameter estimation. Mixed models are predicated on a MAR assumption which is all but certain to be met in the case of H1.1, and possibly met in the imputed H1.2 dataset.

Non-random processes such as dislike, subpar implementation, or feelings of pressure to report favorably on a care approach model may result in missing PROs, and may differentially operate across study groups. We will thoroughly examine all available EHR and survey data fields for relationships with the likelihood of missingness and values of available data. These data fields will be included in a series of multiple imputation models that add sensitivity parameters that quantify increasingly severe departures from randomness to the imputed values. We will quantify the impact of these hypothetical departures on the conclusions drawn from the MNAR imputed datasets and assess the plausibility of MNAR processes that would undermine conclusions drawn from assumed-MAR data.[86]

10.B. Aim 2 Analysis Plan.

We will compare adoption, implementation, maintenance, and reach over time and between care models using both quantitative and qualitative data collected throughout the intervention period. A “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 sites in using the data to make improvements, and developing sustainable measurement strategies.[87] Under the guidance of Dr. Crabtree, our study will collect data relevant to each component of a Learning Evaluation, and we will use a mixed-methods presentation of our data to provide real-time monitoring and feedback to stakeholders to support intervention fidelity and a summary assessment of how fully each care model was implemented.[88,89] The modality to achieve a systematic and responsive evaluation will be “joint reports” organized by components of the RE-AIM framework (adoption, implementation, maintenance and reach), produced and distributed monthly over 24 months.[90,91] Summary level data describing care

processes, care outcomes, changes, and contextual factors will be presented in aggregate and by study site. The integrated reports will include interpretation and recommendations from our team to each clinic to support development of a successful care model, and will be disseminated to stakeholders in webinars and written form. Stakeholder feedback will be collected and interpretations adjusted accordingly. Over time, these reports will present a historical record of summary-level data, key events and adaptations, recommendations, and assessments of success to describe the implementation process and provide sites with a methodological framework to continue improvement in BP care in the future.

Adoption will be described by clinic characteristics (e.g. geographic region, size, patient mix, pre-implementation performance metrics), field observation notes (clinic site visits, meeting minutes, and notes on organizational context) and interviews with clinicians and clinic leaders about barriers to adoption and willingness to be randomized.

Implementation and Maintenance will be described by metrics representing elements of the care approach to which clinics have been assigned. Implementation fidelity is expected to be similar for some (eg, BP accuracy, free BP checks, repeat elevated BP, re-assessed elevated BP, registry use) while others may be more frequent in one group (clinic-based or telehealth). Field observation notes (site visits, chart audits), interviews with clinicians, and patient focus groups will provide insights into differences in the metrics, but also perspectives at the clinic and organizational level about the implementation and maintenance process itself (eg, barriers or disagreement with the care process, factors promoting success, adaptations to clinicians protocols, and description of the care patients report receiving). We will produce key aggregate summaries of these data at 12 months (Implementation) and 24 months (Maintenance), along with statistical comparison between groups with 95% CIs.

Reach will be quantified as the proportion and 95% CI of eligible patients who pass through each step of engagement in their clinic's care approach: attend BP check, have uncontrolled BP, follow up with PCP (clinic based) or pharmacist/NP (telehealth). We expect similar proportions of patients in each care approach to meet these criteria both monthly and in aggregate over 24 months. We will examine eligible patient characteristics for evidence of disparities in Reach, and field observations, interviews, and patient focus groups will be examined for barriers to engagement, reasons for any disparity in engagement, and potential solutions.

By the end of the study period, we will have accrued 24 months of integrated data reports that we will use to construct recommendations to clinics to continue improvement in BP care. Our final report will include data stratified and summarized on several dimensions describing key events over the course of implementation: context (time and setting), approach to care models by clinics and clinicians, patient experiences, barriers, objections, and factors promoting success. These data will be used to compare how fully each care model was implemented and to recommend strategies for clinics to monitor their own progress in improving BP care in the future using standardized reports.

10.C. Reporting Plan (IR-6).

Reports of the trial design and outcomes will include sufficient information to allow assessments of the study's internal and external validity. The external validity can be assessed in part by conformity to PRECIS2 criteria, including broad eligibility criteria, a real-world health care system setting, enrollment and flexible interventions carried out by clinical staff, and follow up conducted without additional research visits.[56] Reports of the trial outcome will conform to the CONSORT guidelines, including the extensions for patient-reported outcomes and cluster-randomized trials.[92-94]

11. Data Management

The overwhelming majority of data used to assess implementation and test the Aim 1 and 2 hypotheses are derived from electronic sources whose primary function is to deliver and document care delivered in a health care setting. Clinic staff update missing or invalid values as needed at each clinic encounter. Fields used to characterize patients included in the preliminary analyses were virtually 100% populated, with race being the most frequently missing (4%).

EHR-based data are identified by encounter- and patient-specific (ie, medical record number, MRN) identifiers that link information across tables. The study programmer will maintain a crosswalk that associates each MRN with a HIPAA-compliant random identifier that uniquely identifies patients in the analytic datasets and survey sampling frames.

12. Key Milestones and Timeline

Below are dates for key study activities. See Appendices J, K and L for full timeline, enrollment timeline, and milestones as reported to PCORI.

12.A. Study Start-up

- Jan 1, 2017: Protocol and research application completed, submitted to IRB
- March 1, 2017: IRB approved study protocol
- Jan-Feb 2017: AMC vendor testing and Epic vitals flowsheet development
- May 2017: Pilot test patient survey

12.B. Enrollment and Interventions

- May-July 2017: Recruitment and training of clinics (site visits to n=20 clinics)
- July 2017: First clinics “go live” with interventions as randomized for Vanguard Phase
- November 2017: Main Trial enrollment begins
- March 1, 2019: Patient enrollment complete
- March 1, 2021: Final Patient Surveys collected (24-months)
- “Implementation Phase” of Interventions (0-12 months): August 2017-July 2018
- “Maintenance Phase” of Interventions (12-24 months): August 2018-July 2019
- Evaluation Reports to clinics: Monthly, September 2017-August 2019

12.C. Key reporting milestones

- Reporting Periods for Interim reports to PCORI: January 1 and July 1 annually, 2017-2021
- DSMB Meetings: Twice annually, August and February 2017-2021
- Patient Advisory and Stakeholder Advisory Board Meetings: Once/quarter, April, July, October and January 2017-2021.

12.D. Publication and Dissemination

See below section 16 for details on milestones related to publication and dissemination.

13. Organization

This study represents a unique collaboration between research organizations, care systems, patient co-investigators and advisors, and other interested stakeholders. The study teams are organized to draw on strengths of all collaborators. Collaborators include:

- HealthPartners Institute
- HealthPartners Medical Group, Health Plan, and Pharmacy Departments
- Patient Investigators
- Patient Advisors (from HealthPartners and nationally via Health eHeart Alliance)
- University of California San Francisco and Health eHeart Alliance
- Researchers from Group Health Institute, Robert Wood Johnson Medical School, University of Mississippi Medical Center
- Professional representatives from American Society of Hypertension, AMC Health, American Medical Association, American Heart Association

Team members and stakeholders will be arranged around a core team with smaller topic sub-groups that will shift according to the study's needs, and additionally a Patient Advisory Board and Stakeholder Advisory Board that will each have some cross-over with the study team. See Appendix I for an org chart of the study team. Scopes of work are described below.

13A. Steering Committee/Core Team.

The Steering Committee will consist of the Principal Investigator, co-investigators, representatives from each subcommittees, and project managers. This group will lead the direction of the study and have leaders of each of the below workgroups represented in most research team meetings. Core team meetings occur weekly.

13.A.1. Clinic Operations workgroup. The Clinic Operations Team will co-develop the intervention workflows for patients with hypertension and develop an implementation plan for the two interventions. This team will also review clinic performance over time and offer recommendations to the research team about how to best support intervention success in the clinics.

13.A.2 Technology and Informatics workgroup. This team will identify device vendors and develop infrastructure for BP telemonitoring and home BP monitoring data transfer into Epic. This team will also design electronic tools to track patient data and ensure consistent intervention processes. The team will work closely with HP to test and gain approval for use of systems and tools developed for the study.

13.A.3. Measurement and analysis workgroup. The Measurement and Analysis Team will develop and refine measures to successfully carry out Aims 1 and 2. Measures will include EHR and claims electronic data, patient-reported data collected by surveys, and qualitative data collected by focus groups and field observations. This team will also be responsible for developing monitoring reports to clinical partners to support intervention fidelity and assess intervention implementation using the RE-AIM model.

13.A.4. Engagement workgroup. The Engagement Team will work to determine the best ways to engage patients and other stakeholders including those on the Patient and Stakeholder Advisory Boards and other stakeholders in order to ensure full implementation of the interventions and clear dissemination of results.

13.B. Patient Advisory Board

The PAB consists of two patient investigators and 6-9 patient advisors from HealthPartners and Health eHeart Alliance (administered at University of California at San Francisco). The Health eHeart Alliance will facilitate the convening of the study PAB and ongoing meetings. Over the course of the project, the PAB will advise the research team about the patient perspective on all aspects of the study including: implementation, communication strategies and reporting of results.

Specific key goals for the PAB include: advising on patient reported outcomes, vetting and testing the patient survey, advising on communication with patients about the interventions, reviewing interim results and identifying opportunities for maximizing the interventions' "reach" and success in engaging a wide diversity of patients. The PAB will advise the study team on disseminating results to a wide variety of organizations and stakeholders, especially patients.

Meetings will take place by teleconference at quarterly intervals following a series of introductory teleconferences. There will also be one in-person meeting before the interventions begin for the PAB to give concentrated input on the study intervention design. PAB members will be compensated at a rate of $50/hour for each hour of meeting time. Payments will be disbursed twice per year from Health eHeart.

13.C. Stakeholder Advisory Board

The SAB will consist of representatives from the organizations listed above. These advisors will be consulted in smaller sub-groups for specific feedback on study design, study progress, and dissemination throughout the life of the project. We want to ensure our study remains responsive to the needs and priorities of these stakeholders, so the research remains practical and relevant when study funds no longer support this work.

Specifically we aim to gather formal input from:

- Clinical stakeholders (physicians, nurses, clinic administration)
- Health plan stakeholders (supplying telemonitoring equipment)
- IS&T stakeholders(supporting Epic and other technical needs for the project)
- External stakeholders (our vendors, professional organizations like American Heart Association, etc)

We will meet with each of these groups of stakeholders on an ongoing basis, and compile twice annual reports to PCORI about stakeholder input and response to our project. Groups of stakeholders will be brought together for joint discussions as needed to gather the type of input that would benefit from diverse viewpoints. Stakeholder Advisors are not compensated for their participation in these meetings, as they are primarily professional colleagues.

14. Human Subjects Protection

14.A. Protected Health Information and sources of data

All necessary data to determine study eligibility, conduct the study interventions, and test the study hypotheses among n=2000 enrolled patients are derived from (a) the EHR, (b) health plan pharmacy claims, and (c) surveys of eligible patients in both study arms. Limited EHR data will include demographics, vital signs, orders, diagnoses, encounters, and laboratory data for specified periods.

Among a smaller group of consenting participants, we will collect focus group data on their experiences receiving BP care. Additional qualitative data will be collected using field observations in clinics, short surveys and interviews with

pharmacists and physicians. These data will be used to assess the impact of study interventions on outcomes. A detailed description of the inclusion and exclusion criteria for study subjects can be found in section 4.c. We anticipate accessing up to 5000 patient records to achieve n=2000 enrolled patients.

14.B. Potential risks to subjects

Potential risks to subjects relate to the treatment of hypertension and consist principally of adverse events related to medications, which can potentially be severe or even fatal. However, all treatment in the study in both intervention groups is evidence-based and limited to FDA-approved treatment. Although patients in the telehealth group may be treated with greater numbers and higher doses of antihypertensive therapy, previous telehealth trials with pharmacist or nurse management have not reported greater adverse events in the telehealth group. In the previous telehealth trial conducted by this research team there were several more episodes of hypotension in the telehealth group than in the usual care group, although this difference was not statistically significant. All such episodes occurred in patients with diabetes or kidney disease who had a lower BP treatment goal (<130/80 mm Hg) than is the goal in this study (<140/90 mm Hg). Therefore, the risks of participating in the study are considered minimal and no greater than those incurred through routine treatment of hypertension. We have described below the methods used to minimize this risk.

Additional risks to patients are also minimal and include principally the risk of violation of confidentiality. Measures to minimize these risks are also discussed below.

Study participants may choose alternative treatments and procedures with their treating clinician. Participants in the telehealth group are free to decline telemonitoring or any component of the telehealth care intervention.

14.C. Adequacy of Protection Against Risks

14.C.1. Protection of Informed Consent

14.C.1.a EHR and claims data collection

We have been granted a partial waiver of documentation of informed consent from the HealthPartners Institutional Review Board (IRB) for the collection of electronic health record and claims data following reasons:

1. The clinic-based care model is considered a standard of care and has not been shown to have any risks greater than routine care for hypertension;
2. The telehealth care intervention has been studied in multiple settings and has not been shown to have any risks greater than routine care for hypertension using current guidelines for BP control;
3. The enrollment of patients by clinic staff in the routine care setting would make it impractical to obtain informed consent; and
4. We will not require special research visits to collect data from participants and will use health data that is routinely recorded in the EHR.

This means that patients will receive care at their clinic according to their clinic's randomization status and will not be aware of any relationship between research and their clinic care for their blood pressure at the time of their clinic visit.

These conditions apply for patients until they are contacted and respond to our mailed survey. Once a patient responds to the survey, the 3rd criteria above no longer applies. Therefore we have included a question at the end of the survey to request consent to use medical record data. See Appendix H.

14.C.1.b Patient Surveys

Participants will consent to the surveys through an affirmation demonstrated by the survey completion. The first (enrollment) participant survey will be mailed to an individual patient within 1 week of the clinic visit that qualified them to be enrolled in this study (see section on surveys). That initial survey mailing will include a cover letter explaining the purpose of the survey and why that patient is receiving it. It will include all the elements of consent that would normally be included in a consent form, and an explanation that returning or completing this survey includes the patient's agreement that their responses and EHR data related to hypertension can be used for research purposes. Patients who are identified and enrolled by Wizard but who are on the HPI Exclusion List will not be sent a survey. (See Appendix H for draft survey instrument and other patient materials).

14.C.1.c. Patient focus groups and HealthPartners employee interviews

Focus group participants will be recruited from among patients completing surveys. They will undergo a documented consent process prior to participating in any focus group. During the recruitment process for participation in focus groups they will be told the basic elements of consent (e.g. time required, privacy risks, audio recording and transcription, de-identification, incentive, etc). Upon arriving to the focus group, the patient will be given time to review the entire consent form and will have an opportunity to sit privately with a research coordinator to ask any questions. Only participants who agree and consent to participate will be included in the group. Anyone who chooses to decline will be offered an incentive for their time for attending.

HealthPartners employees who may be interviewed for evaluation purposes will not be asked to sign a formal consent because their interviews will be considered part of a continuing process improvement effort in partnership with the system stakeholders invested in this project. However, these employees will be assured of their privacy and will only be interviewed upon their personal agreement.

14.C.1.d. HIPAA protections

In addition to the internal HP Institute policies, HIPAA itself makes specific provision for waiver of authorization to use PHI for research recruitment purposes under some specific conditions, all of which this study meets: "For research uses and disclosures of personal health identifiers (PHI), an IRB or privacy board may approve a waiver or an alteration of the authorization requirement in whole or in part. A complete waiver occurs when the IRB or privacy board determines that no authorization is required for a covered entity to use and disclose PHI for a particular research project. A partial waiver of authorization occurs when an IRB or privacy board determines that a covered entity does not need authorization for all PHI uses and disclosures for research purposes, such as disclosing PHI for research recruitment purposes. An IRB or privacy board may also approve a request that removes some PHI, but not all, or alters the requirements for an authorization (an alteration)." See: http://privacyruleandresearch.nih.gov/pr_08.asp#8

14.C.2. Protection of safe medical treatment

All hypertension care provided in the study follows evidence-based guidelines and HealthPartners policies and procedures for high-quality care. All staff affected by the study will receive appropriate training, either through HealthPartners or by the study team (see section 6). MTM Pharmacists in the telehealth clinics will use an established protocol for managing hypertension and other CV risk factors, in accordance with long-standing HealthPartners policy

and their collaborative practice or supervisory agreements with clinic physicians (see appendices A-C for evidence-based treatment guidelines)

The study will monitor for adverse effects of study interventions by extracting EHR laboratory data on potassium, sodium, and kidney function, and diagnoses for hypotension and fainting (see section 15 about data safety and monitoring)

14.C.3. Protection of confidentiality and data security

In compliance with HIPAA regulations, no personally identifiable health information (PHI) will be shared outside of the affiliated covered entities (ACE) without obtaining a data use agreement or business associates agreement. HealthPartners Institute and HealthPartners are each one component of a larger organization defined as an ACE under HIPAA regulations. This allows researchers at the Institute to use HealthPartners medical records data for purposes such as those in this study in compliance with HIPAA regulations (i.e., following the concept of "minimally necessary" use of PHI).

The study team has extensive experience in health services research and clinical research with human subjects, with procedures to safeguard privacy and personal information. All study records are protected by:

- Locked storing all paper records in a secure location
- Use of untraceable study ID numbers instead of names wherever possible, and
- Password protection as well as firewalls,
- Strong user login authentication on all electronic devices, and
- Physical security for all electronic devices containing personal information.

Data will be retained in secure storage following the completion of the study in accordance with Minnesota and federal law. We guard against the potential for breach of subject confidentiality through a multi-layered system of data protection policies, processes, staff training, software safeguards and physical security measures for both paper and electronic data involved in research.

The following measures will be taken to protect subjects from the risk of breach of confidentiality:

- All data collected in the study will be identified by using a previously assigned arbitrary and unique subject identification number to each participant.
- A file containing a link between the study ID and individually identifying information will be maintained at by a programmer who is member of the study team through the conclusion of the study.
- A cross-walk table linking the study ID to a patient identity will be destroyed within 6 months after the linked databases needed to test study hypotheses are completed.
- All electronic study data will be maintained in a computerized database residing on a username- and password-protected file-server to which only the researchers involved in the study will have access.
- All study-related paper documents containing individually identifiable information will be maintained in locked file cabinets.

For protection of confidentiality of focus group participants, we will ask participants to maintain the privacy of other participants by not sharing others' information outside of the group as a requirement of participation. However, we will also clearly explain in the informed consent the risk of loss of privacy should other participants disregard the instruction

not to share personal information outside of the group. Any focus group participant can choose to use a pseudonym during the focus group, if he or she desires, for this reason.

To protect the confidentiality of any HealthPartners employees participating in an interview, we will not allow anyone outside of the research team to know the identity of those interviewed. All of the protection to electronic data sources, described above, also apply to the audio recordings and transcripts.

14.D. Potential Benefits of the Proposed Research to Human Subjects and Others

Patients in the study will have no defined personal benefit from participating in this project. Compensation for the time to complete surveys and focus groups will be minimal but appropriate according to effort involved with participation. All patients receiving a survey following enrollment will receive a small $2 incentive with their mailed baseline survey to increase initial response rates. Patients completing a survey by either mail, phone, or online will receive a $10 gift card for their time for each survey completed. Focus group participants will be offered compensation of a $40 gift card for their time plus a meal.

To bolster access of the interventions, some patients may receive transportation assistance to attend a BP check visit to become eligible for the study. Although some patients may receive better management of hypertension as a result of the study interventions, no claim of clinical benefit to an individual patient can or will be made.

14.E. Importance of Knowledge to be Gained

If this study reveals that telehealth care does not result in improved outcomes, practices and care systems can concentrate on optimal implementation of clinic-based care. If telehealth care results in measurably improved outcomes, the study results should lead to greater diffusion of similar care models. The long-term goal of improved hypertension control is to prevent CV and kidney disease, and uncontrolled hypertension is one of the largest contributors to these conditions.

14.F. Inclusion and accessibility

By its nature, telehealth stands to serve the purpose of increasing access of care to patients who may have difficulty attending clinic visits or adhering to treatment protocols. Therefore we aim to ensure inclusion and accessibility of our interventions. This falls under the “reach” measures we describe in Tables 2 and 3.

14.F.1 Women. The eligible study population of patients with uncontrolled hypertension is roughly 50% female; therefore, we expect that at least 50% of the study population will be female as described in the enrollment table.

14.F.2 Children. People ages 18-20 will be included and eligible if they are under the care of a non-pediatric primary care physician. We do not plan to exclude children under the age of 21 if they are receiving adult care, which is standard practice at HealthPartners.

14.F.3 Ethnic and/or racial minorities. The eligible patient population includes about 25% self-identifying people of ethnic/racial minorities. We have allocated additional recruitment resources to increase accessibility of research to this group and enroll at least 25% ethnic/racial minority patients. We plan to bolster minority inclusion in a number of ways. First, we will regularly assess the degree of minority inclusion in our enrolled population. The process measures described in section XYZ can be viewed by patient demographic, so where we locate disparities in participation we can support clinics in addressing it. For example, by targeting outreach from the hypertension registry to minority patients, ensuring follow-up with minority patients who have not attended their intended follow-up visits, and talking specifically

with clinics that serve majority patients of ethnic/racial minority about the barriers they are facing in supporting patients' success with BP care. We will provide transportation support as needed, and we will also consult with our Patient Advisory Board about meeting the needs of patients of ethnic/racial minority backgrounds.

14.F.4 Non-English speaking patients. We will also regularly assess access by primary language. We will not be limiting enrollment and survey participation to only English-speaking patients. All HealthPartners clinics have interpreter services available for in-person clinic visits. Because much of the telehealth intervention is telephone-based, we will encourage use of a Language Line or support non-English speaking patients to attend MTM visits in person with support for transportation costs from the study. Telemonitoring instructions, other intervention materials, and written surveys will be available in English and Spanish. Phone surveys conducted in Spanish will be conducted by bilingual interviewers. We will examine feasibility of material translation into other common languages like Somali and Hmong based on the clinics' populations likely to be enrolled.

14.F.5 Physical Disability. We will support inclusion of patients with physical disability, like vision and hearing impairment or disability that limits mobility, by ensuring these patients receive proper follow up and resources necessary to communicate with their care team and participate in telehealth. We have monetary resources to support the participation of these patients as needed.

15. Data and Safety Monitoring Plan – Approved by DSMB April 17, 2017

Plan for monitoring study conduct and safety

1. Clinic recruitment, randomization and characteristics of clinics

1.1 Clinic recruitment. Clinics will be eligible to participate if they have a Medication Therapy Management (MTM) pharmacist onsite at least one half-day per week and use standardized methods to measure BP with validated oscillometric BP monitors. Eligible clinics will be contacted via their leadership and invited to participate if they are willing to be randomly assigned to clinic-based care or telehealth care, participate in training, participate in limited data collection activities, and receive periodic feedback on implementation of the elements of clinic-based care or telehealth care according to their randomized assignment.

Twenty eligible clinics will be identified for randomization into clinic-based or telehealth care. Four clinics will function as vanguard clinics. Study algorithms will be implemented in the electronic health record systems of these four clinics prior to August 1, 2017. Vanguard clinic staff will have two months to observe how the algorithms modify work flow and offer suggestions for improvement. The study team will incorporate changes as needed based on user feedback prior to implementing the algorithms in the remaining 16 clinics by November, 2017.

1.2 Cluster randomization. Given the relatively limited number of randomization units, we wish to ensure that clinics are not imbalanced across treatment groups on factors related to the primary outcome, the ability to implement the intervention or potential treatment modifiers. Stratifying on clinic BP control should ensure that the treatment groups are similar with respect to the primary outcome (SBP) at the time the intervention is implemented. Clinic BP control is likely related to the how effectively clinical practices that support provision of recommended care are currently implemented, so that balance on clinic BP control may also balance factors related to the likelihood that the interventions will be implemented successfully. Clinic BP control is correlated with the proportion of clinic patients who are members of racial or ethnic minority groups, and with the proportion who have comorbid conditions that complicate hypertension treatment, so that balance on clinic BP control may also balance these potential treatment modifiers. An added practical consideration to incorporate into the randomization scheme is that the vanguard clinics must be split evenly between clinic-based care and telehealth care.

We plan to stratify the clinics first into the 4 vanguard and 16 main study clinics. Participants enrolled in the early Vanguard Phase of the study will not be included in the main trial results. Among the main study clinics we will create 2-4 more small strata of at least 4 clinics each based on the proportion of clinic patients on the hypertension registry whose SBP and DBP meet clinical recommendations for control in the month prior to randomization. The study statistician will assign the clinics within each stratum equally to clinic-based care or telehealth care based on values of randomly generated numbers. The main study clinics in clinic-based care and telehealth care (8 each) should be balanced on clinic BP control. However, the simple randomization of the 4 vanguard clinics may perturb the balance in clinic BP control that could otherwise be attained through stratified randomization of all 20 clinics. We acknowledge that some of the precision gained through stratified randomization may be lost but assert that the opportunity to fine tune the algorithms, work flow or user interface will strengthen the intervention sufficiently to counteract this loss.

1.3 Characteristics of randomized clinics. Administrative and hypertension registry data will characterize each randomized clinic (e.g., MTM days per week, urban setting,) as well as clinic providers (e.g., n of internal medicine, family practice, advance practice; percent female or ethnic / racial minority) and patients (e.g., SBP, DBP, age, gender, ethnic composition and privately insured among all patients and those in hypertension registry). These data will be captured to represent the characteristics of clinics in the month just prior to randomization.

2. Patient enrollment/accrual

2.1 Patient enrollment status. The population of interest is patients meeting high BP study criteria cared for by HealthPartners PCPs at 20 representative primary care study clinics. Very few exclusion criteria are in place to maximize the likelihood that study findings are applicable to the population of interest.

We will monitor the characteristics of three patient groups for departures of the study sample from the population of interest. “Registry eligible” patients are adult patients with a hypertension diagnosis and elevated blood pressure at the time they sought care in a HealthPartners primary care clinic. “Hyperlink eligible” patients are the subset of registry eligible patients who also meet study eligibility criteria. A key tool that the study uses to track enrollment and initiate the study interventions is a modified version of an existing “hypertension follow-up order”. This order will be automatically generated and populated with default values appropriate to each treatment group for Hyperlink eligible patients. Accordingly, the “Hyperlink enrolled” patients are the subset of Hyperlink eligible patients whose provider signed a condition-appropriate hypertension follow-up order initiated by the study. The follow-up order only needs to be signed by the provider, not necessarily completed by the patient, to be Hyperlink enrolled.

We will rely on Clarity data to identify and characterize patients from all randomized clinics who fall into each of these three categories. The Hyperlink algorithms gather Clarity data to calculate and store the fields needed to identify registry eligible and Hyperlink eligible patients. Some of these fields will be joined with data from a separate Clarity extract to identify Hyperlink enrolled patients and characterize patients in all three categories.

2.2 Patient enrollment. Hyperlink patient enrollment will begin in the vanguard clinics in August, 2017, and in all 20 clinics for main trial beginning in November, 2017. The study timeline accommodates an 18 month enrollment period so that the last Hyperlink patient would enroll in March, 2019. The total targeted main trial enrollment across the 20 clinics is N=2000.

We will monitor monthly and cumulative enrollment and calculate the proportion of patients who progress from registry eligible to Hyperlink eligible to Hyperlink enrolled, study-wide and by treatment group and clinic. We do not plan to institute clinic-specific enrollment targets but we will need a sufficient number of patients from the smaller clinics to enroll and contribute data to the primary analysis (n≈50 patients). Similarly, we will need to enroll a sufficient number of patients who are members of racial or ethnic minority groups to support the planned secondary analyses that estimate treatment heterogeneity. We will consider supplemental recruitment methods should the enrollment rate among patients at smaller clinics or among members of racial or ethnic minority groups lag the study-wide enrollment rate.

2.3 Patient characteristics. Demographic and clinical characteristics of registry eligible, Hyperlink eligible and Hyperlink enrolled, in aggregate and by treatment group, will be presented.

3. Intervention implementation

3.1 Intervention implementation fidelity. Reports that rigorously quantify key measures of intervention fidelity within three subgroups of patients (Registry eligible, Hyperlink eligible, Hyperlink enrolled) will be prepared using routinely collected electronic data captured by the Hyperlink algorithms, through supplemental electronic health record data pulls or via patient surveys. Measures of the extent to which clinic infrastructure and policies are implemented will be calculated using data from relevant subsets of adult patients in all randomized clinics. The reports will be provided to clinic managers and primary care physician chiefs on a monthly or quarterly basis and formatted so that clinic performance relative to goals and to other clinics over time may be easily assessed. Table 2 provides more detail regarding the denominators, numerators and data sources for each measure.

Reports that document the hypertension care processes that are part of the current standard of care for hypertension and common to the interventions delivered in clinic-based care and telehealth care clinics will rely on data from registry eligible, Hyperlink eligible or Hyperlink enrolled patients in all randomized clinics. These reports will also be provided to clinic leaders on a monthly basis and presented so that time trends in clinic performance relative to goals and other clinics are easily assessed. More fine-grained reports that calculate these metrics separately for registry eligible, Hyperlink eligible and Hyperlink enrolled patients, and potentially by provider, will be prepared so that the study team can work with clinic staff to improve performance as needed.

Reports documenting telehealth care intervention delivery will be prepared using data from Hyperlink enrolled patients in the telehealth care clinics. These monthly reports will be provided to clinic staff and provide an opportunity for the study team and clinic staff to collaborate on approaches for improving or maintaining intervention implementation.

DSMB members will be asked to review trends in all three sets of measures to identify potential concerns and make recommendations to the study team if there is potential for significant unequal benefit to patients in one of the treatment arms.

4. Patient outcomes and safety monitoring

4.1 Effectiveness, clinical outcomes. The primary clinical effectiveness analyses will quantify the extent to which there is a larger reduction, or less of an increase, in systolic blood pressure in the 12 months following Hyperlink enrollment among patients in telehealth relative to clinic-based care clinics. Secondary analyses will address whether similar changes are observed in clinical outcomes such as diastolic blood pressure, lipid levels and cardiovascular risk; whether antihypertensive or lipid medications are more aggressively managed among telehealth patients; and whether telehealth patients are less likely to be current smokers. Table 1 summarizes all primary and secondary outcomes. For each clinical outcome, we plan to include all available data in the 24 months following enrollment in the analyses. However, effectiveness will be assessed via a comparison of the rate of change in the first 12 months post-enrollment.

All clinical outcomes data will be documented in the electronic health record or the Hyperlink data repository as observations accrue. Their immediate availability will make it feasible to check assumptions of the clinical effectiveness analyses such as balance on key covariates prior to intervention exposure; the central tendency, variance and distribution of clinical outcomes; the number and timing of observations per person; the viability of assuming a linear rate of change in outcomes, and how non-linear trends might be addressed; and the magnitude of the design effects introduced by cluster randomization and repeated measures within patients. These assumptions can be investigated in aggregate as data accrue, and by treatment group or clinic at the DSMB's request, to inform the conduct of the primary effectiveness analyses.

4.2 Effectiveness, patient outcomes. The effectiveness of the clinic-based care and telehealth care interventions at improving patient reports of side effects, satisfaction with care and confidence in self-care will be assessed by comparing

self-reports of these outcomes from patient surveys. Similar to the clinical effectiveness analyses, patient reported outcomes (PROs) will be collected at enrollment and then 6, 12 and 24 months later but the contrast of interest is the enrollment to 6 month change among telehealth care relative to clinic-based care patients. Missing values resulting from non-consent, non-response, loss to follow-up and item non-response increase the likelihood of misestimating PRO models. The patient survey sampling frame will include a wealth of demographic and clinical information so that we can identify characteristics that are associated with each source of missingness and develop a plan for handling missing data (e.g., multiple imputation).

4.3 Equity of patient benefit. The clinic-based care and telehealth care intervention have both been shown effective in improving hypertension outcomes. The purpose of this work is to estimate their relative effectiveness in improving clinical and patient reported outcomes. It is not expected that either of these approaches will be sufficiently superior to the other to warrant developing stopping rules for clinical benefit. Similarly, the anticipated effect sizes are sufficiently modest and accrue over a time frame such that stopping the trial early for futility would more likely result in a Type II error than offer patients a more beneficial alternative treatment.

4.4 Safety outcomes monitoring. Both interventions have been implemented in primary care settings or systematically studied with no evidence of increased likelihood of risk to patients. It is possible nonetheless that incident diagnoses related to hypertension and antihypertensive medications (e.g., hypotension / fainting, electrolyte disturbances, renal failure) and changes in lab measures indicative of antihypertensive medication (e.g., Na, K, eGFR) may be more evident among patients in one of these two treatment groups, or among patients who are exposed to the intervention as intended. The electronic health record will document each of these safety outcomes as they occur over the course of the study. Because these are more likely to be documented in outpatient than inpatient settings the lag between occurrence and documentation will be minimal.

We will periodically extract data (vitals, diagnosis codes, lab results) from the electronic medical records of Hyperlink enrolled patients to identify the occurrence of each of these safety outcomes in the year prior to and in the time since enrollment. For each outcome and time period, we will calculate the number of events, proportion of patients experiencing the event, rate at which events occur or other metrics in a manner appropriate to their distribution. Outcomes will be compared across treatment groups and time periods with emphasis on whether there are pre- to post-enrollment changes that differ across treatment groups.

4.5 Reporting and analysis plan. DSMB meetings will occur semi-annually through the end of the 24 month observation period of the last enrolled study participant. We propose that summary data described in the Randomization and Enrollment sections of Table 4 be provided to the DSMB for review and discussion in open session at all meetings as data become available. Randomization data are clinic-aggregated measures collected prior to randomization. Presenting this information in open session should not jeopardize the implementation of the interventions or clinical outcome measures. Similarly, Enrollment and Fidelity data will be reviewed by study investigators, and some shared with clinic personnel, on a regular basis. Presenting this information in open session will not divulge outcomes information to the investigators.

The summaries described in the clinical outcomes section primarily make use of post-enrollment patient outcomes. We propose that aggregated summary data, not presented by treatment group or trended across time, be presented in open session. Summaries that disaggregate by treatment group or time remain in closed session until the primary effectiveness analysis comparing trends from enrollment through 6 months is carried out. Similarly, summaries of PROs that provide aggregate information may be presented in open session while those that disaggregate by treatment group or time be presented in closed session until the primary effectiveness analysis comparing change in PROs from baseline to 6 months by treatment group is carried out.

We propose that the rates at which safety outcomes occur be discussed fully in open session. Investigators could meaningfully participate in discussions of how to mitigate differences in risk that may be discovered.

There will be a very limited time frame between the end of the 24 month observation period and the end of the study period. For this reason, we plan to conduct the primary analyses as soon as is feasible without divulging information that could threaten internal validity. The data needed to estimate whether SBP trends in the 12 months following enrollment differ by treatment group should be available in April, 2020. We propose to prepare these data for analysis as soon as they are available so that the planned comparison that estimates the relative effectiveness of these two treatments (not the full H1.1 model) can be carried at that time. We would like to present these results in open session at the Spring or Fall 2020 DSMB meeting. By the time 12 months of clinical outcomes data are available for all enrolled patients, none of the patients will still be participating in any study-related activities. The likelihood that investigator knowledge of these findings could contaminate the care that is delivered to patients or their later clinical outcomes is extremely low. However, any risks outweigh the benefit that could be gained by discussing patterns in SBP in the year post-enrollment among study investigators and with the DSMB, and having time to fully carry out and learn from secondary analyses.

The data needed to carry out the H1.2 analyses comparing change in PROs from baseline to 6 months by treatment group will be available in October, 2019. We propose to prepare these data for analysis in early 2020 and present the results along with the effectiveness comparison in open session at the Spring, 2020 DSMB meeting.

The data needed to carry out the full H1.1 model estimating SBP trends in the 24 months following enrollment will become available in April, 2021, when the 24 month observation period ends. The 24 month survey data will also be available at that time. We plan to carry out the full H1.1 analyses and describe PROs at these later time points in Spring, 2021.

Table 4. Proposal for reports and analyses to share with DSMB in open and closed sessions.		
Randomization		
clinic characteristics	treatment, clinic [a]	open
provider characteristics	treatment, clinic [a]	open
Enrollment		
registry eligible n	cumulative, monthly; aggregate and by treatment, clinic [a]	open
Hyperlink eligible n	cumulative, monthly; aggregate and by treatment, clinic [a]	open
enrolled n	cumulative, monthly; aggregate and by treatment, clinic [a]	open
patient demographics	enrollment status, treatment, clinic [a]	open
clinical measures at enrollment	enrollment status, treatment, clinic [a]	open
Fidelity		
infrastructure and policies	monthly by treatment	open
hypertension care processes	monthly by treatment	open
telehealth care processes	monthly within telehealth	open
Clinical outcomes, post-enrollment		
patient covariates (enrollment)	aggregate, treatment [b]	open
outcome counts	aggregate	open
	treatment	closed
outcome variance	aggregate	open
outcome descriptives	aggregate	open
	treatment by month	closed
Patient reported outcomes, post-enrollment		
outcome counts	aggregate	open

	treatment, missing mechanisms	closed
outcome descriptives	aggregate	open
	treatment by time	closed
Safety outcomes		
diagnoses	aggregate by time, treatment by time, as treated by time [b]	open
lab measures	aggregate by time, treatment by time, as treated by time [b]	open
Primary analyses		
H1.1 12m clinical effectiveness	treatment by time trend interaction enrollment to 12m	open
H1.2 PRO change	treatment by time interaction, B-6m	open
H1.1 effectiveness full model	treatment by time trend interaction enrollment to 24m	open
Aim 2 PRO maintenance	12m, 24m descriptives	open
[a] Clinics will be identified by number rather than name.		
[b] Treatment groups will be identified by random labels rather than "clinic-based" or "telehealth"		

16. Publication and Dissemination

16.A. PCORI Publication Policy

PCORI's policy on research project findings indicates we cannot publish "practice guidelines, coverage recommendations, payment, or policy recommendations" and shall "not include any data which would violate the privacy of research participants or any confidentiality agreements made with respect to the use of data." The following items are outlined in our contract with PCORI.

16.B. Key Journal Publication Milestones.

We will adhere to two key publication milestones outlined in our contract with PCORI:

- **Design/Methods Paper**, published by Nov 1, 2019
- **Primary outcomes paper,** published by Sept 1, 2021

We also intend to publish a paper with the baseline characteristics of the clinics and patients, anticipated to be published by September 2019, about 6 months after enrollment is completed.

Given the scope of the project, we will most likely complete several additional manuscripts. Publication of scientific findings from the study will proceed in a timely fashion once relevant analyses are complete.

16.C. Making Research Findings Publicly Available.

16.D.1. Public Summary of Findings. Besides our primary outcomes paper, we will also produce a summary of research findings for patients, consumers and the general public in order to convey our findings in a

"comprehensible and useful manner to patients and providers in making health care decisions". PCORI will help us develop this summary and ensure it is available in public-access format.

16.D.2. Public access to Journal Articles. An electronic copy of the final peer-reviewed publication of our primary outcomes will be submitted to the National Library of Medicine's PubMed Central to be made available publicly. Costs for this are provided by PCORI.

16.D. In-Person Presentation(s) and Other PCORI-Initiated Events.

We will attend PCORI meetings or other events to present research findings as requested by PCORI. Expenses for these trips will be covered by PCORI.

16.E. Manuscript development and authorship.

The Steering Committee/Core Team will act in the role of a Publication Committee, and will evaluate all proposals for manuscripts not specifically enumerated in 6.B. Recognition through authorship will be distributed among the study investigators so that all study investigators and team members have equitable opportunity to lead and co-author study publications. We will support development of manuscripts by anyone involved with the project as long as the appropriate research team members are involved in the writing and review of the manuscript. The publications arising from the study should avoid overlap and conflicting representation of study findings. Standards for authorship on study publications will adhere to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals of the International Committee of Medical Journal Editors (NEJM 1997;336:309-315) and those established by the destination journals.

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