Mass General Brigham

Institutional Review Board
Intervention/Interaction Detailed Protocol

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Project Title:	Leveraging Electronic Health Record (EHR) Tools to Help Reduce Health Disparities for Patients with Uncontrolled Hypertension
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1. Background and Significance

Hypertension is a major public health problem affecting an estimated of 100 million Americans[1] and is projected to cost the healthcare system upwards of $220 billion by 2035.[2] Racial disparities in hypertension control have been recognized for decades.[3] The prevalence of hypertension among black adults is substantially higher than in non-Hispanic white adults.[4] Despite modest improvements in treatment initiation, control rates in black patients continue to lag.[4,5] These disparities are especially problematic because of racial differences in the consequences of disease. For example, a 10-mmHg difference in systolic blood pressure is associated with an 8% increase in stroke risk for whites but a 24% increase for blacks.[6] Rates of hypertension treatment and control are more than 10% lower for Hispanic/Latinos than whites.[7,8] Hispanics/Latinos also experience worse long-term cardiovascular health outcomes, with higher risks of stroke and end-stage renal disease than whites.[5]

There are many contributors for the persistent racial/ethnic differences in hypertension control outcomes. Dr. Khatib, Advocate co-investigator, conducted a widely-cited systematic review of barriers to hypertension control and proposed a conceptual framework.[9] Of these, a lack of treatment intensification, underuse or prescribing of racially-based oral antihypertensives, and suboptimal follow-up care are thought to be central contributors to racial/ethnic disparities.[10-14]

In up to half of treatment episodes, healthcare providers do not intensity antihypertensive treatment when indicated, often referred to as clinician inertia.[15-17] Dr. Khatib's systematic review identifies several contributors including clinicians being inappropriately satisfied with their patient's current level of control, concerns about treatment side effects, and concerns about accuracy of blood pressure readings obtained during office visits. Clinical inertia may pose a greater problem for minorities.[8,18] The 2014 JNC-8 guidelines and the 2018 ACC/AHA antihypertensive guidelines now explicitly recommend specific treatment choices for hypertension based on race/ethnicity.[19,20] Some clinicians remain unaware of the nuances in guidelines, and non-guideline concordant antihypertensive treatment, for black patients in particular, may still contribute to differences in blood pressure control between groups.[21,22]

Effectively managing hypertension also relies on the ability to monitor response to therapy. Despite guideline recommendations for close follow-up when adjusting drug regimens, minority patients are less likely to return to clinical care than white patients.[5,23] Patient self-management, such as blood pressure

monitoring necessary for titration, are also lower among minority patients, in part because of inability to afford in-home blood pressure monitoring cuffs as well as differential recommendations by providers about self-monitoring.[16] Other social determinants of health, such as poor health literacy and limited insurance coverage, are more prevalent among black and Hispanic/Latino patients.[24,25] Referral rates to social work and nephrologists for renal care are also lower, which further increases gaps in health outcomes.[26,27]

Many EHRs systems contain a range of clinical decision support tools such as alerts, reminders, and defaults.[25] The widespread adoption of EHRs presents a scalable opportunity for the implementation of EHR-based interventions.[31] The existing literature supports the potential for health information technology (IT) to improve health care quality.[32-37] In a recent systematic review, 56% of 236 studies found that decision support improved prescribing and preventive care.[38] Of 147 studies that evaluated clinical outcomes, >75% showed that EHR tools improved these outcomes. Despite this encouraging evidence, few studies have evaluated how health IT can be leveraged to reduce disparities,[39] particularly as other research suggests that the adoption of patient-facing tools, such as EHR portals, is up to 50% lower in minority patients.[40,41]

Despite the promise of EHR-based interventions to improve health care quality, to our knowledge, only two trials have specifically sought to prospectively evaluate whether EHR-based interventions can reduce racial/ethnic disparities.[42] One of these demonstrated that EHR-based "report cards" provided to physicians could reduce disparities in diabetes care.[43] The other trial found that guideline-based decision support reduced disparities in hypertension treatment.[42] Other observational studies have also provided supportive evidence.[44-51] Across these studies, performance reports, decision support, and registries appear to be the most successful strategies.[43,44]

Therefore, we propose a pragmatic randomized trial to test the impact of a multicomponent health IT intervention on blood pressure control and racial and ethnic disparities.

2. Specific Aims and Objectives

The overall goal of this project is to improve existing decision support for hypertension control and to reduce disparities in treatment, consistent with professional guidelines and quality metrics. To achieve this, we will **conduct and evaluate a cluster randomized trial to determine whether health IT tools targeted to providers improve blood pressure control for patients with uncontrolled hypertension.**

Our primary hypothesis is that a health IT intervention will improve systolic blood pressure (primary outcome), concordance with hypertension guidelines (secondary outcome), diastolic blood pressure (secondary outcome), treatment intensification (secondary outcome), and post-visit patient-provider follow-up (tertiary outcome) compared with usual care.

The objectives and endpoints are summarize below:

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To determine whether multicomponent EHR-based health IT tools designed using behavioral	Change in systolic blood pressure from identification to 12-month follow-up, using values in the EHR	These outcomes are rapidly measurable using EHR data and will provide evidence of blood pressure control.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
principles targeted at providers improve blood pressure control for patients with uncontrolled hypertension as compared with usual care (no intervention).		
Secondary		
To determine whether multicomponent EHR-based health IT tools designed using behavioral principles targeted at providers improve concordance with hypertension guidelines, diastolic blood pressure control, and treatment intensification compared with usual care.	Percentage of patients with well-controlled blood pressure (<140/88mmHg) at 24 months follow-up, using values in the EHR. Percentage of patients with intensification of medication in the 24-month follow-up period, defined by addition of therapy or increasing dose. Percentage of patients with guideline-concordant medications ordered in the follow-up period. Change in the gap in systolic blood pressure between Black and Hispanic/Latino patients and non-Hispanic patients from identification to 12-month follow-up Change in diastolic blood pressure from identification to 12-month follow-up	These outcomes capture the extent to which there is an improvement in concordance with hypertension guidelines, diastolic blood pressure control, and treatment intensification during the follow-up period.
Exploratory		
To better understand patient and provider's perspective on hypertension management through the AAH healthcare system	Analysis of de-identified qualitative interviews including patients and providers from AAH primary care sites	These outcomes will inform the research methods and health IT tool design for the pragmatic cluster randomized trial.
To determine whether multicomponent EHR-based health IT tools designed using behavioral principles targeted at providers improve post-visit patient-provider follow-up compared with usual care.	Clinical encounters, using number of office visits, telephone calls and patient portal interactions between AAH primary care providers and patients during the 24-month follow-up period	These outcomes measure the post-visit patient-provider follow-up during the follow-up period.
To assess the implementation of the intervention in practices	Adoption of the EHR interventions and integration of the intervention into clinics	These outcomes will be used to evaluate aspects of the implementation of the intervention and will provide valuable information regardless of the clinical results of the trial.

3. General Description of Study Design

3.1 Study site

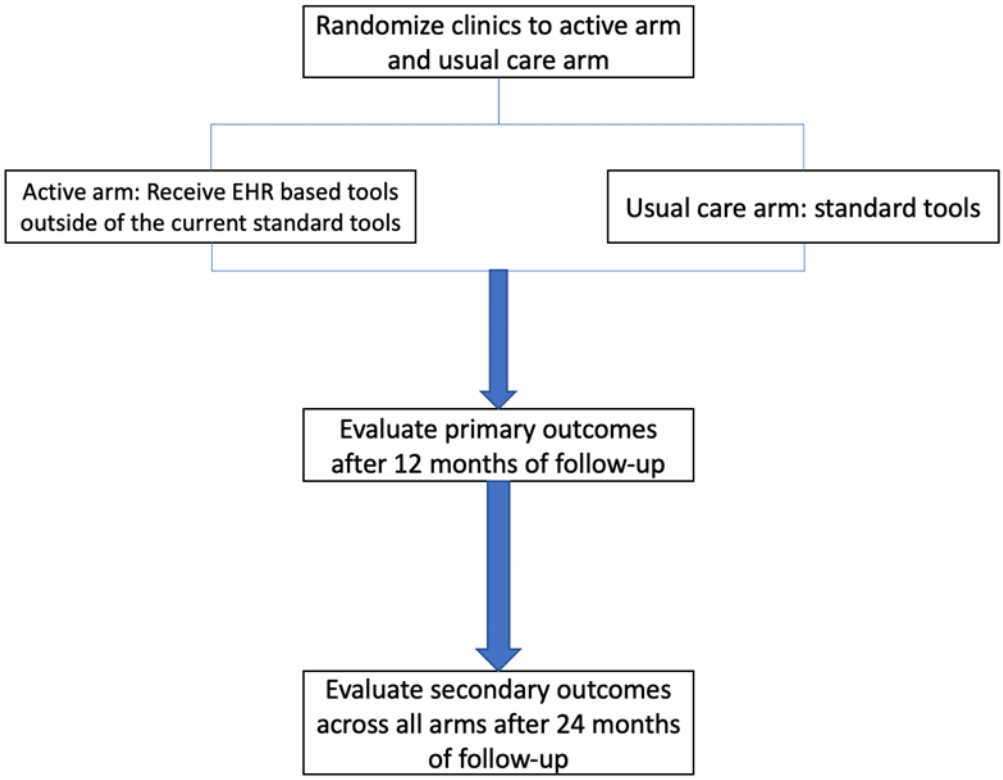
The study will be conducted in outpatient primary care practices of Advocate Aurora Health (AAH), a large integrated delivery network in Wisconsin and Illinois. AAH has a fully functional EHR, Epic, that supports computerized ordering of medication.

3.2 Overall design

In the first Phase (Aim 1), we will analyze 30 de-identified qualitative interview transcripts that were conducted with 15 patients and 15 providers (14 primary care physicians and 1 medical assistant) from two AAH primary care clinics to understand perspectives on hypertension management and identify opportunities to improve EHR tools for providers. The interviews were previously conducted between October 2020 and March 2021 under the oversight and approval of the Advocate Aurora Health IRB. In brief, treating physicians provided approval for potential patient participants to be contacted. Eligibility criteria for the interviews included a diagnosis of hypertension and seeking care at one of the two pilot practices. After approval, patients were conducted for their willingness to be interviewed and consent was obtained using a fact sheet. Providers were eligible for the interviews based on their practicing as clinicians in the pilot practices. Each interview was conducted using an approved semi-structured interview guide and were audio-recorded and subsequently transcribed. Participants were offered compensation for their time. All data were previously de-identified. We are seeking approval by the MGB IRB for the analysis of the de-identified data collected during these interviews.

In the second Phase, we will conduct a 2-arm pragmatic cluster randomized clinical trial to evaluate whether a multicomponent health IT intervention improves blood pressure control and reduces racial/ethnic disparities. Participating clinics will be randomly assigned to one of 2 arms: (a) Arm 1: multicomponent, intervention and (b) Arm 2: usual care (i.e. no intervention). Providers and in each arm will receive the same intervention for up to 24 months after randomization, which will allow us to determine the relative effectiveness of each approach as well as their long-term impact on clinical outcomes. Primary care providers in the intervention clinics will receive electronic decision support tools to guide their care of eligible patients. Providers in usual care clinics will receive usual care at AAH. Patients will not receive any intervention or outreach independent of their provider or care team. We will use EHR data to implement the EHR tools, identify study subjects, track study progress, and evaluate the effect of the interventions.

3.3 Study schema



4. Subject Selection

4.1 Inclusion Criteria

The trial will include provider subjects with eligible patients. Specific decision support at the point of care will also appear for patients whose latest outpatient/ambulatory blood pressures are elevated (i.e., SBP≥140 or DBP≥90). There is no upper limit for SBP or DBP, as this cutpoint is driven by HEDIS criteria and would otherwise exclude patients who may be in greatest need of care. Limited inclusion criteria will be applied to maximize generalizability in accordance with pragmatic trial principles outlined by PRECIS-2 (PRagmatic Explanatory Continuum Indicator Summary). The patient population will only be included for the purpose of providers receiving decision support and for the purpose of analyzing the effect of the intervention. The study criteria are defined below.

Provider-subjects will receive EHR interventions if they are primary care providers (internal medicine, family medicine, geriatrics) employed by AAH at one of the 24 participating clinics cluster randomized to the intervention.

EHR patient data will be collected retrospectively for analysis and used for the EHR tools for providers based on the following criteria:

1. Medical Group Medical Home Population: 1 visit with PCP in past 2 years (rolling 24 months) and Patient has a medical group PCP as their EPIC General PCP
2. Current age 18-85 years

3. Hypertension diagnosis on EPIC Problem list OR at least 2 visits (office/telehealth/telephonic) with an encounter diagnosis of HTN on different dates, with at least one during the last 24 months (rolling dates)
4. Latest outpatient/ambulatory (exclude urgent care) SBP ≥140 or DBP ≥90 (12 months rolling) (lowest measure if more than one taken at the same time) (no upper limit)

4.2 Exclusion Criteria

Providers and patients not meeting the inclusion criteria above will not be included in the analysis of the trial. No other exclusion criteria will be used.

4.3 Recruitment and Retention

4.3.1 Inclusivity of study subjects

The primary study population for receiving any of the EHR-based interventions will be primary care providers at one of the 24 clinics. Providers will receive EHR-based decision support tools for the care of their eligible patients. Eligible patients are those based on HEDIS quality improvement criteria used at AAH and will include those 18-85 years of age, having had 1 visit with their primary care provider in the last 2 years and are diagnosed with hypertension. Specific decision support at the point of care will also appear for patients whose latest outpatient/ambulatory blood pressures are elevated (i.e., SBP≥140 or DBP≥90). The patient population will only be included for the purpose of providers receiving decision support and for the purpose of analyzing the effect of the intervention.

Pilot data indicate that participants will cover a broad range of participants by gender and race/ethnicity. Of these, 39.8% are White, 37.4% are Black or African American, 7.3% are Hispanic, 5.0% are Asian/Pacific Islander, 9.7% are other races or unknown. Further, given the minimal risk nature of the study, participants will not receive incentives, remuneration, or be required to provide informed consent.

5. Subject Enrollment

5.1 Waiver of informed consent

We are seeking a waiver of informed consent and HIPAA authorization for all data collected in this study, including the previously conducted deidentified patient interview transcripts. The goal of this project is to improve decision support to increase guideline concordant care for patients with poorly controlled hypertension. First, the nature of this intervention involves testing EHR decision support directly for providers (using information already available to them and a similar infrastructure they use in the course of regular clinical care). Second, the ability to understand the true effect of the intervention as it is delivered in the real world would be difficult to ascertain if true informed consent was sought. Third, obtaining informed consent would predictably reduce the number of patients participating in the study, especially those from unrepresented populations, and therefore undermine the generalizability of the study results, a foundational aspect of pragmatic clinical trial principles. Fourth, providers will retain all oversight of their patients' care and will be able to make therapeutic choices based using their professional judgement. Fourth, this approach has also been approved by Advocate clinical leadership and their IRB. We also request a HIPAA waiver of patient authorization to access EHR data (retrospectively) necessary for outcome evaluation, as doing so would be impractical and infeasible to conduct the study.

An organization-wide announcement will be circulated across participating AAH clinics to inform providers of the launch of an intervention leveraging clinical decision support tools to support improved prescribing for adults. Providers randomized to the intervention group will also receive basic quality improvement training on the EHR decision support tools, as is currently done at AAH in usual care.

5.2 Randomization and blinding

Clinics will be randomized to treatment arms in equal proportions. We will use clinic-based cluster randomization to minimize the possibility of contamination in study interventions between practices and clinic staff. For the randomization, we will use covariate constrained randomization in R software based on clinic characteristics to reduce potential imbalances between the clinics assigned to the treatment arms. The clinics/providers will not be blinded to which arm they were assigned to, as blinding in the context of an intervention that is intended to motivate action will be infeasible. Physicians randomized to usual care will not have any way of accessing the EHR interventions. Patients of physicians in the usual care arm will have access to the patient portal but will not be receiving any assistance from medical assistants or any of the after-visit activities. Moreover, only primary care physicians will be included (specialists will not receive any enhanced clinical decision support or report cards), and feasibility data suggest that there is minimal crossover of patients with other primary care physicians given the nature hypertension management at Advocate. Therefore, any risk of contamination within practices is low, and any contamination that does exist would bias the trial results towards the null.

6. STUDY PROCEDURES

6.1 Study sites

The study will be conducted in outpatient primary care practices of Advocate Health, a large integrated delivery network in Wisconsin and Illinois. Advocate has a fully functional EHR, Epic, that supports computerized ordering of medications.

Based on input from AAH clinical leadership, the following 24 clinics will be randomized to one of two study arms (intervention or control).

Clinic
Advocate Medical Group Beverly 9831 S Western
Advocate Medical Group Olympia Fields 4001 Vollmer
Advocate Medical Group Chicago 1357 W 103rd
Advocate Medical Group South Holland 100 W 162nd
Advocate Medical Group Sykes 2535 S Martin Luther King
Advocate Medical Group Des Plaines 77 Rand Rd
Advocate Medical Group Park Ridge 1775 Ballard
Advocate Medical Group Chicago 6434 W North
Advocate Medical Group Chicago 4025 N Western
Advocate Medical Group Orland Park 9550 167th
Advocate Medical Group Glenview 1412 Waukegan
Advocate Medical Group Palos Hills 7620 W 111th
Advocate Medical Group Morton Grove 6131 Dempster
Advocate Medical Group Lincolnwood 6540 N Lincoln
Advocate Medical Group Elgin 1710 Randall
Advocate Medical Group Chicago 4211 N Cicero

Advocate Medical Group South Elgin 2000 McDonald
Advocate Medical Group Chicago 3134 Clark
Advocate Medical Group Frankfort 21160 Lagrange
Advocate Medical Group Hazel Crest 3330 W 177th
Advocate Medical Group Libertyville 825 S Milwaukee
Advocate Medical Group Oak Lawn 4220 W 95th
Advocate Medical Group Chicago 2301 93rd
Advocate Medical Group Oak Lawn 9555 S 52nd

6.2 Study interventions

Clinics randomized to the control arm will not receive any additional EHR-based tools outside of the current standard tools offered to Advocate providers and patients. The intervention arm will receive EHR-based tools that will be delivered at several time points during a patient's care episode.

6.2.1 Provider Training

Prior to study implementation, providers randomized to the intervention arm will receive a brief quality improvement training on how to use the new EHR-based tools. Providers will not be required to use these tools for the purpose of this study but will be offered these training opportunities to ensure they can properly utilize them if they choose to do so, as is standard AAH practice for implementing new EHR tools.

6.2.2 Pre-visit interventions

Providers in the intervention arm will receive an EHR-embedded dashboard which will highlight racial/ethnic differences in rates of achieving blood pressure control within their patient panel. Using EHR data, we will identify eligible patients: (1) Medical Group Medical Home Population: 1 visit with PCP in past 2 years (rolling 24 months) and Patient has a medical group PCP as their EPIC General PCP, (2) current age 18-85 years, (3) hypertension diagnosis on EPIC Problem list OR at least 2 visits (office/telehealth/telephonic) with an encounter diagnosis of HTN on different dates, with any during the last 24 months (rolling dates) performing provider, and (4) latest outpatient/ambulatory (exclude urgent care) SBP ≥140 or DBP ≥90 (12 months rolling) (lowest measure if more than one taken at the same time).

Among these eligible patients, patients included in the primary analysis will be those that had an in-person visit at one of the trial clinics. This is because the primary decision support aimed at providers is based on office visits. Patients are first identified as eligible for this analysis based on the first time that they had a visit at one of trial clinics. The dashboard will also provide individual-level information for patients with poorly-controlled blood pressure including (a) most recent blood pressure values, (b) current therapies (based on the medication list), (c) next scheduled appointment, and (d) social determinant needs. Patients in the intervention arm will receive outreach via MyChart, a component of the patient portal, to answer questions regarding their social determinants of health (SDoH).

6.2.3 During visit interventions

Providers will receive clinical decision support within relevant patients' charts that highlight the patient's under-treated blood pressure and its consequences and potential impacts of social needs (i.e., social determinants of health collected during clinical care). This clinical decision support will appear during chart opening when a patient with blood pressure above goal presents in the clinic. The clinical decision support will include enhanced presentation of content, highlighting risks of undertreatment and providing guideline-concordant treatment intensification options. To facilitate the intensification of

treatment (when appropriate), the clinical decision support will also contain an embedded order set (i.e., a SmartSet) to prompt physicians to change or intensify medication based on practice guidelines. Templated SmartText will also be embedded into the Notes section of the EHR to improve charting for hypertension patients. When providers sign off on patient notes, they may be prompted with requirements and recommendations for action items.

Patients who did not complete the SDoH screening pre-visit will be provided with a "SDoH Patient Handout" prior to collection of social determinants of health data during clinical care to introduce them to the type questions that will be asked and why their providers are collecting this information. This handout is currently used as part of clinical care at AAH.

Providers will have the opportunity to provide patient education materials (i.e., information to appear in the after-visit summary), which can be automatically ordered within the clinical decision support and are already available at Advocate. These will provide pre-templated instructions about treatment, current blood pressure values, and self-monitoring recommendations, such as using or buying blood pressure cuff, that are easily understood by all patient populations including those with low health literacy.

6.2.4 Post-visit interventions
We will streamline patient-subjects' access to the online patient portal by including information about the patient portal in the patients' after-visit summary and enabling providers to order nurse blood pressure check visits. Advocate has 24/7 online appointment scheduling capabilities that can be leveraged.

6.3 Schedule of visits

There are no study-specific visits in this trial. We have outlined the time points in which data are collected below for implementation and evaluation of the interventions.

Data collection	**Pre-randomization**	**Follow-up**
EHR review for provider eligibility	X	
Provider characteristics (Demographics)	X	
Systolic blood pressure	X	X
Antihypertensive dosage	X	X
Resource use - Clinical encounters, using number of office visits, telephone calls and patient portal interactions	X	X

6.3.1 Implementation evaluation

As part of an implementation evaluation, several assessments will be conducted with the Advocate Aurora Health clinic personnel at the clinics which were randomized to the intervention arm.

1. Provider Interviews
   We will conduct recorded phone or virtual interviews with consenting Advocate primary care providers who were randomized to the intervention arm to explore: (1) barriers to hypertension management, (2) experience with the study-specific EHR tools, and (3) opinions of sustainability of the intervention. Providers will be invited to participate via email (see attachment).

Prior to the interviews, providers will be asked to provide verbal informed consent for participation (see Fact Sheet attachment). Participants will not be forced to participate and may withdraw their consent to participate at any time. Participants will be informed that participation in voluntary and that the interviews are part of a research study.

Each interview will be conducted by an Advocate investigator and a BWH investigator. A semi-structured interview guide will be utilized (see attachment). Following provider interviews, the recordings will be transcribed. The transcriptions will be used to help evaluate the implementation of the intervention. We plan to interview approximately 15-20 providers.

2. Clinic manager survey followed by discussion at clinic manager meeting
   Clinic managers at each of the clinics assigned to the intervention arm will receive an email from Advocate leadership asking them to respond via email to a questionnaire (see attachment) regarding their experience implementing the study tools into the clinic workflow. They will also be invited to attend a regularly-scheduled clinic manager meeting that they currently already have scheduled as part of regular clinical care and management to provide additional feedback.

   The responses to the clinic manager survey and discussion will be obtained by Advocate research staff, who will provide summary of these outcomes to the broader study team. No identifying information will be shared with Brigham and Women's Hospital study staff.

6.4 Data sources and collection

6.4.1 Sources of research material, data that will be recorded, when data will be collected
Data regarding patients' medical history, disease control, medication use and health care utilization will be obtained from AAH EHR data or pharmacy dispensing data for analysis of the trial. De-identified transcripts of recordings from patient and provider interviews will also be used for qualitative analysis for Aim 1 (interviews previously conducted under the IRB approval of Advocate Aurora Health).

The Advocate data warehouses reside in an Oracle 9i environment and consists of the Clarity and Payer databases. The Clarity database is a relational database that contains clinical and financial information from the Epic Suite of products; including the electronic medical record system (EpicCare), the appointment scheduling system (Cadence), the patient accounting system (Resolute), the patient web portal and the master patient index (Identity). The various tables within the Clarity database are refreshed on a daily, weekly or monthly basis.

These data are listed in the Attachments.

6.4.2 Linkages to subjects, access to subject identities
Individually identifiable data are maintained for patient care purposes within the Advocate Network and is needed to identify patients and to monitor care recommendations by providers. Without this linkage, we could not fulfill the study's objectives. To protect the confidentiality of these data, only the provider group's data analyst and project manager will have access to personal identifiers while linking the data and constructing study variables for the trial. After linkage is completed and study variables are created, all identifiable information will be deleted from the study database. All data transfers between the organizations will be accomplished using secure file transfer protocols. Only HIPAA-limited data will be

shared with the study team based at Brigham and Women's Hospital, who are all properly trained in research management and approved by the IRB. All personally identifiable health information will be kept under lock and key. The only HIPAA identifiers that will be received by the study team at Brigham and Women's hospital are dates, which are necessary for the evaluation of study outcomes (e.g., change in systolic blood pressure between certain dates.)

6.5 Study endpoints

The trial will be completed 24 months after trial launch. At the end of the study period, data will be extracted retrospectively from electronic health records; the primary analysis will be on patients who visited one of the 24 clinics during the study period and who meet the inclusion criteria.

Primary:

- Change is systolic blood pressure from patient identification (i.e., the most recent encounter that identified the patient as eligible) through 12-month follow-up, using values recorded in the EHR

Secondary:

- Percentage of patients with well-controlled blood pressure (<140/88mmHg) or <130/80 mmHg for those with comorbid conditions defined by clinical guidelines at 12 months follow-up, using values in the EHR
- Percentage of patients with intensification of medication in the 12-month follow-up period, defined by addition of therapy or increasing dose
- Percentage of patients with guideline-concordant medications ordered in the 12-month follow-up period
- Change in the gap in systolic blood pressure between each of Black and Hispanic/Latino patients and non-Hispanic White patients from the last encounter before identification through 12 months after, using values in the EHR
- Change in diastolic blood pressure from the encounter before identification through 12 months after, using values recorded in the EHR

Exploratory:

- Frequency of viewing the dashboard, SmartSet order set, documentation choices, and acknowledgement reasons
- Intervention fidelity: BPAs (alerts) firing as intended

Clinical encounters, using number of office visits, telephone calls and patient portal interactions between AAH primary care providers and patients during the 12-month follow-up period. These outcomes will also be measured in the remainder of the follow-up period until the end of administrative censoring at the end of the 2-year trial.

7. Risks and Discomforts

We believe that the risks to participation for both physicians and patients are no more than minimal for several reasons. First, the interventions aim to emphasize guideline-recommended treatments for patients with persistently elevated blood pressure. Second, all treatment decisions will ultimately be made by licensed primary care physicians. Finally, the intervention is physician-focused and delivered through interventions that use information already available to physicians that is also guideline concordant and intended to reduce disparities in care. We believe there is no more than minimal risk

involved to the physician subjects, as the physicians will simply be given tools to alter their behaviors towards guideline recommended care. All medical decisions are ultimately made by the physician. This trial will not interfere with the ordinary workings of the primary care practices.

There is a small risk associated with altering hypertension medication prescribing, including hypotension, bradycardia, allergic reactions, and other adverse effects. However, in prior trials that increase intensification of blood pressure regimens, the risks have been similar in intervention and control arms. We believe the potential risks of treatment intensification as part of this trial are the same, or less than what is encountered during routine, guideline-concordant hypertension care, given the focus on patients with persistently elevated blood pressure. Final prescribing decisions will always be at the discretion of the patient's PCP.

Another potential small risk to patients will be privacy of health information. We will minimize the risk to privacy by taking appropriate steps to limit access to data to study investigators. Clinical data on the care for patients will be retrieved from the electronic medical records.

8. Benefits

This study is designed to improve electronic health record prescribing tools for providers caring for adult patients with uncontrolled hypertension. Potential benefits for participants in this study include improved decision support tools and guideline-concordant prescribing. Thus, the research could have both immediate benefits for physicians by increasing hypertension awareness and treatment knowledge, as well as for their patients who might benefit from improved blood pressure control. We will also evaluate implementation of the interventions to allow for future scalability.

Additionally, the subjects and society may benefit in the future from accumulated knowledge that originates from this research. We will also produce several EHR tool deliverables for this work for the public, researchers, and policymakers, which will be shared as generalized knowledge.

9. Statistical Analysis

9.1. Statistical hypothesis

We hypothesize that the intervention will lower mean systolic blood pressure to a larger degree than usual care. The null hypothesis will be no difference between patients identified as eligible in the intervention arm and usual care. All analyses will use intention-to-treat principles.

9.2. Sample size determination

We powered the study to detect a 5.0 mmHg mean change in SBP between the intervention arm and control arm from randomization through 12 months, assuming a standard deviation (SD) of 13.5, an alpha threshold of 0.05, and an intra-cluster correlation (ICC) of 0.1. With these assumptions, we estimated that at least 24 eligible primary care clinics including 537 providers and 49395 patients that were identified as eligible for inclusion in the analysis will provide >80% power to detect differences in our primary outcome. The 5.0 mmHg mean change was chosen as this is considered to a clinically meaningful change in SBP and was observed in prior systematic reviews of interventions in hypertension. This estimate also accounts for regression to the mean and includes SDs that were derived from our prior work and Advocate feasibility data.

9.3. Analyses of endpoints

Descriptive statistics will be calculated for all variables and presented overall and by group using mean + SD for continuous variables, as well as counts or percentages for categorical variables. Comparisons will be made between groups for all outcomes using absolute standardized differences. The unit of analysis is at the patient-level.

For the primary outcome, we will use generalized estimating equations (GEE) to adjust for the cluster design with an identify link function and normally-distributed errors. If >10% of data is missing, we will use multiple imputation for our study outcomes, as we have done in prior research. We will test the robustness of this approach with sensitivity analyses that use alternative methods of handling missing data. For baseline characteristics between arms with a standardized difference >0.1, we will repeat our analyses after adjusting for these covariates. We will also conduct analyses by racial/ethnic subgroup. In secondary analyses, we will also use longitudinal modeling to account for multiple SBP values over follow-up.

For secondary outcomes, we hypothesize that the intervention will lead to more patients with well-controlled blood pressures, higher rates of treatment intensification and guideline concordance. The null hypotheses will be no difference between the intervention arm and usual care. For these outcomes, we will use GEE with an identify link and normally-distributed errors for continuous variables and with a log-link function and Poisson-distributed errors for categorical variables. For outcomes that are non-normal, we will use GEE with a log-link function and Poisson-distributed errors, as in our prior work. For all primary and secondary outcomes, the study analysts and investigators will be blinded to treatment allocation until after the analyses are complete. We will also evaluate other implementation outcomes, including clinical outcomes past the initial 12 month follow-up, until 24 months (i.e., the end of the trial), to explore durability of treatment effects.

De-identified qualitative interview transcripts (interviews previously conducted under the IRB approval of Advocate Aurora Health) will be analyzed using immersion-crystallization methods using Dedoose qualitative software (SocioCultural Research Consultants, LLC). In this approach, we immerse ourselves in the collected data and then articulate the salient themes during the crystallization process. We will continue this approach of cycles of concentrated textual review until all data are examined, and meaningful patterns emerge from the data. Collected data will be used to describe and understand both patient and providers perspectives on hypertension management.

Because this is a randomized trial, our primary analyses are planned as unadjusted; however, if there are strong patient-level predictors of the outcomes not balanced by stratified randomization, we will adjust for these in the primary analyses.

10. Monitoring and Quality Assurance

10.1 Oversight

General oversight of this project will be performed by the principal investigators (Drs. Choudhry and Lauffenburger) and will occur throughout the study period. Study staff will be trained in appropriate study protocols and procedures and will assist in ensuring the study adheres to the IRB-approved protocol.

10.2 Monitoring Plan

We plan to use a centralized Institutional Review Board (IRB) and a Data Safety Monitoring Board (DSMB) for all aspects of this research. Drs. Choudhry and Lauffenburger are the project PIs at MGB. Advocate Aurora Health (AAH) will cede review to MGB Institutional Review Board, and the MGB IRB will serve as the centralized IRB of record for this trial.

We will establish an independent data and safety monitoring board (DSMB). A DSMB is a requirement for all NIH funded Phase III trials. The DSMB will act in an advisory capacity to the NIH to monitor participant safety and evaluate the progress of the study, review procedures and management of the study. The DSMB reports will be shared with the project and local site PIs within 72 hours of their completion. The DSMB will consist of individuals with experience in quality of care, patient safety, and statistics. The DSMB will meet regularly, either in person, by teleconference call, or via email at the discretion of the DSMB chair, to review data related to the study protocols and ensure protection of patient confidentiality and safety, as well as to monitor the quality of the data collected via the study protocols. Compliance of regulatory documents and study data accuracy and completeness will be maintained through an internal study team quality assurance process.

This trial will be registered with clinicaltrials.gov.

10.3 Adverse events and unanticipated problems

The PIs and study team will meet on a regular basis throughout the study period and will be in direct contact with AAH clinical leadership involved in the project to obtain ongoing feedback.

De-identified study data will be accessible at all times for the MGH PIs and coinvestigators to review, if applicable. We will also ensure that all protocol deviations for the pilot study are reported to the NIH and the IRB according to the applicable regulatory requirements. Compliance of regulatory documents and study data accuracy and completeness will be maintained through an internal study team quality assurance process.

10.3.1 Definition:

Adverse Event (AE): Any untoward or unfavorable medical occurrence in a human study participant, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participants' involvement in the research, whether or not considered related to participation in the research.

- Adverse Events will be classified using the following rating scales:
    - Severity: Mild, Moderate or Severe
        - Mild: Awareness of signs or symptoms but are easily tolerated
        - Moderate: Events introduce a low level of inconvenience or concern but may interfere with daily activities but are usually improved by simple therapeutic measures.
        - Severe: Events interrupt the participants' normal daily activities and generally require systemic drug therapy
    - Expectedness: Unexpected or Expected
        - Unexpected: nature or severity of the event is not consistent with the condition under study
        - Expected: event is known to be associated with the intervention or condition under study.

Serious Adverse Event (SAE): Any adverse event that:

- results in death
- is life threatening, or places the participant at immediate risk of death from the event as it occurred
- requires or prolongs hospitalization
- causes persistent or significant disability or incapacity
- results in congenital anomalies or birth defects
- is another condition which investigators judge to represent significant hazards.

10.3.2 Determination

Given the minimal risk nature of the study which aims to increase guideline concordant care for patients with persistently elevated blood pressures, we do not anticipate any SAEs or AEs. Patients' own primary care physicians will have ultimate decision-making authority for prescribing choices, as they would in routine clinical practice, and we expect any adverse events related to hypertension medication intensification, such as hypotension or bradycardia, to be the same or less as those experienced in routine clinical care, given the focus on patients with uncontrolled hypertension. For example, in the SPRINT[14] trial, which tested intensive BP control among patients age 75 or older, similar rates of serious adverse events occurred in the intensive-treatment group and in the standard-treatment group. In this study, we are using standard blood pressure targets and include a younger patient sample who have persistently elevated blood pressure.

10.3.3 Reporting

As previously described, any adverse events as part of this study are expected to be similar, or lower, than those anticipated in routine hypertension care. The study team will not be providing any direct care to patients and all treatment decisions will ultimately be made by the patients' medical teams at Advocate Aurora Health. Any adverse event will be handled in the course of regular clinical care. Because we are not directly intervening upon patients and will have no patient contact during this study, prospectively tracking adverse events is infeasible. However, physicians will have contact information for our research team to report any concerns, and we will be in regular contact with practice and AAH leadership to monitor for any adverse events that come to attention through any of those channels. Therefore, while we will not be actively monitoring the occurrence of adverse events, which if done would require patient contact and detailed patient-level chart-reviews, we anticipate that the study team will be informed of any AEs or SAEs that do occur. Marlon Everett, MD, cardiologist practicing at AAH, with support by Rasha Khatib, PhD, research manager at AAH, are engaged in support of this project and will help with monitoring of physician feedback that gets routed through traditional departmental channels.

If we become aware of any AEs or SAEs throughout the course of the study, we will collect this information. Any reports of deaths will be submitted to the NIH Program Officer within 24 hours. Any unexpected SAEs will be reported to the NIH PO and the IRB within 48 hours of the study's knowledge of the SAE. All other reported SAEs and AEs received by the study team will be reported to the NIH Program Officer quarterly, unless otherwise requested by the DSMB.

11. Privacy and Confidentiality

☒ Study procedures will be conducted in a private setting
☒ Only data and/or specimens necessary for the conduct of the study will be collected

- ☒ Data collected (paper and/or electronic) will be maintained in a secure location with appropriate protections such as password protection, encryption, physical security measures (locked files/areas)
- ☐ Specimens collected will be maintained in a secure location with appropriate protections (e.g. locked storage spaces, laboratory areas) **– N/A**
- ☒ Data and specimens will only be shared with individuals who are members of the IRB-approved research team or approved for sharing as described in this IRB protocol
- ☒ Data and/or specimens requiring transportation from one location or electronic space to another will be transported only in a secure manner (e.g. encrypted files, password protection, using chain-of-custody procedures, etc.)
- ☒ All electronic communication with participants will comply with Mass General Brigham secure communication policies
- ☒ Identifiers will be coded or removed as soon as feasible and access to files linking identifiers with coded data or specimens will be limited to the minimal necessary members of the research team required to conduct the research
- ☒ All staff are trained on and will follow the Mass General Brigham policies and procedures for maintaining appropriate confidentiality of research data and specimens
- ☒ The PI will ensure that all staff implement and follow any Research Information Service Office (RISO) requirements for this research
- ☒ Additional privacy and/or confidentiality protections

Advocate investigators will extract data that contains patient health information (PHI) including MRN, first name, last name, date of birth, encounter dates, and Zip Codes. To protect against the risk of inappropriate disclosure of personal health information, only limited data will be shared with study collaborators at Mass General Brigham (MGB) who will oversee and conduct the analysis with insights from the Advocate team. The only PHI that will be shared with the BWH study investigators outside of Advocate are dates (e.g., date of birth, admission/discharge dates, and dates of medication fills), which are necessary to evaluate exposures and outcomes retrospectively. No other study investigators outside of BWH will receive any PHI. Advocate will then disclose HIPAA-limited datasets encrypted by a study key only known to the Advocate investigators to conduct the analyses. These datasets will consist of structured information from the EHR. Sharing this information will be necessary to assess the impact of the interventions.

The electronic data stored at Advocate will be safeguarded by state-of-the-art security protocols. All patient-specific information will be collected by querying Advocate's inpatient and outpatient databases; inpatient data will be necessary to evaluate outcomes such as hospitalizations. Identified patient information will be recorded on a password-protected electronic spreadsheet, with each patient assigned a specific study number. All identifiers (excluding dates) linked to study numbers will be locked and stored separately from the data analysis spreadsheet. The coded spreadsheet will also be stored on a password-protected computer in a locked office with access limited to study investigators only. Only the limited dataset will be utilized for analyses. All identifiers will be destroyed after completion of data analysis. Only study team members will have access to study related documents. All investigators have completed CITI training.

Mass General Brigham (MGB) has computer networks in place that employ up to date virus protection software and enable password-protected access only to study investigators. All data transfers between the organizations will be accomplished using secure file transfer protocols. To ensure the confidentiality

and security of all data, the research team operates a secure, state-of-the-art computing facility housed at MGB Healthcare's data center. The MGB data center is a secure facility that houses both computing environments as well as clinical systems and electronic medical records for several large hospitals in Eastern Massachusetts. Entry into the computer room requires staffed computer room security. The Division's computers are connected to the MGB networking backbone with 10 gigabit-per-second fiber links. Network security is overseen by electronic medical records systems to the research team's data. All data are transmitted to programmers' workstations in an encrypted state. Backups are created using the current Department of Defense standard for data security and are stored in a locked facility. The redundancy, extensive data power, and security of our computer facility confirm our capacity to collect and manage data and ensure confidentiality for all project participants.

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APPENDIX A

Data Monitoring Committee / Data and Safety Monitoring Board Appendix

A Data Monitoring Committee (DMC) or Data and Safety Monitoring Board (DSMB) will be convened for safety monitoring of this research study. The following characteristics describe the DMC/DSMB convened for this study (Check all that apply):

☒ The DMC/DSMB is independent from the study team and study sponsor.

☒ A process has been implemented to ensure absence of conflicts of interest by DMC/DSMB members.

☒ The DMC/DSMB has the authority to intervene on study progress in the event of safety concerns, e.g., to suspend or terminate a study if new safety concerns have been identified or need to be investigated.

☒ Describe number and types of (i.e., qualifications of) members:

Sagar B. Dugani, MD, PhD
Dr. Dugani is an Assistant Professor of Medicine and practicing hospitalist physician at the Mayo Clinic with expertise in the design and evaluation of interventions to promote better quality of care in cardiometabolic disease. His research focuses on disparities in the care of diabetes and heart disease.

Macarius M. Donneyong, PhD, MPH
Dr. Donneyong is an Assistant Professor and epidemiologist at The Ohio State University; he has expertise in hypertension, particularly in the evaluation of disparities in medication use and hypertension outcomes among Black patients and other socioeconomically disadvantaged groups.

Anne Mobley Butler, PhD
Dr. Butler is an Assistant Professor of Medicine at Washington University in St. Louis and epidemiologist with expertise in the study of disease-related burden, prevention, treatment and outcomes in clinical care. Her research focuses on epidemiologic and biostatistical methods; she also has experience in large scale evaluations of disparities.

☒ Describe planned frequency of meetings:
The DSMB will meet twice annually, either in person, by teleconference call, or via email at the discretion of the DSMB chair, to review data related to the study protocols and ensure protection of patient confidentiality and safety, as well as to monitor the quality of the data collected via the study protocols.

☒ DMC/DSMB reports with no findings (i.e., “continue without modifications”) will be submitted to the IRB at the time of Continuing Review.

☒ DMC/DSMB reports with findings/modifications required will be submitted promptly (within 5 business days/7 calendar days of becoming aware) to the IRB as an Other Event.