CLINICAL TRIAL PROTOCOL

Personalizing intervention to reduce clinical inertia in the treatment of hypertension

National Clinical Trial (NCT) Identified Number: NCT04603560

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Summary of Changes from Previous Version

Date of submission	Summary of Revisions Made	Rationale for modification	Approval date
02-09-21	Randomization changed to tertiles of sessions practiced per week	Based on a review of current practice patterns for our providers, stratifying based on number of sessions that a physician practices per week (which is proportional to panel size) is a more practical and predictable measure to use prospectively (since number of sessions per week changes less than visit volumes). Further, tertiles of panel size will be easier to implement with a 3-arm trial than quintiles. The intent of stratification is the same, but our proposed change will be easier to operationalize.	02-18-21
02-09-21	Inclusion/exclusion criteria	To ensure that we enroll only actively-practicing outpatient providers who are able to receive weekly interventions and who care for a sufficient volume of patients, we propose to exclude providers who practice less than one session per week or whose total panel size is less than 100 patients.	02-18-21
02-09-21	Revisions of interventions	We have shortened the text in the two interventions to make it easier and faster for providers to read (social norming, academic e-detailing)	02-18-21
06-02-21	Revision of intervention frequency	We have altered the frequency with which we send out the dashboard component of the social norming intervention from weekly to every 2-4 weeks. This frequency will more accurately reflect the rate of change of the percentage of uncontrolled hypertensive patients among PCPs.	
09-28-21	Revision of inclusion/exclusion criteria Revision of goal blood pressure Addition of subject lines to intervention messages Changed sample size determination calculations Modified study timeline	To ensure we have a large enough pool of participants to draw from, we have altered the study timeline and the eligibility criteria of providers to include those with at least 2 patients meeting the eligibility criteria, instead of the original requirement of at least 10. Additionally, we have modified our blood pressure goal to be <140/90 for all patients to streamline identification of eligible patients. Finally, we have modified our sample size and power calculations to allow us to detect a larger effect size.	

1. Background and Rationale

Hypertension is a large contributing factor to cardiovascular morbidity and mortality among older adults, yet more than half of patients with hypertension have blood pressures above clinical goal.[1] The failure of physicians to initiate or intensify treatment regimens when clinically indicated is often referred to as clinical inertia, and is a well-described phenomenon in the treatment of this condition.[2-5]

Interventions to reduce clinical inertia and improve blood pressure control, including education, reminders, feedback, ambulatory blood pressure monitoring, and pharmacist-driven interventions, have been shown to be effective but only modestly so.[5] One hypothesis for this limited effectiveness is that physicians may have different underlying behavioral factors that contribute to their inertia behavior. A qualitative analysis of cases of clinical inertia in hypertension care identified seven distinct categories of physician justifications for non-intensification.[6]

Behavioral science research suggests that individuals are influenced by factors of which they are not consciously aware. When describing reasons for their own behavior, people generally over-value personal introspection rather than context[7,8] and generate explanations of their behaviors to help resolve cognitive dissonance or the discomfort of an "explanatory vacuum".[9] In the case of inertia, multiple and/or variable underlying behavioral tendencies, such risk aversion, conscientiousness, burnout, or need for closure, are likely more relevant explanations for physician behavior than physician-provided justifications. Thus, rather than relying on justifications, an alternative approach is to measure behavioral factors through surveys and empirically elucidate which physician behavior characteristics are correlated with clinical inertia and with a physician's responsiveness to different interventions intended to address this problem.

Further, physicians are likely influenced by context and may behave differently with different patients. For example, a physician may not intensify treatment with a healthy patient who strongly prefers to try diet/exercise, but that same physician might consider blood pressures values that are just a few points higher than goal to be "close enough" for older patients that have many comorbidities.

Accordingly, we propose to measure physician behavioral factors using survey instruments, test interventions for clinical inertia in hypertension care, and identify characteristics of patients and

physicians that are associated with the likelihood of treatment intensification and their responsiveness to different interventions. This information could then be used to more effectively design and target interventions to those most likely to respond.

2. Study Aims

The main aims are to 1) test two interventions to reduce clinical inertia in hypertension prescribing compared to control and 2) develop a model to predict intervention responsiveness based on physician and patient characteristics.

The objectives and endpoints for this project are summarized below.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Aim 1		
To determine the effectiveness of two interventions to reduce hypertension clinical inertia compared to control	Primary: Intensification of hypertension treatment medications (i.e. dose increase or medication addition) at the time of the patient's visit Secondary: Mean change in systolic blood pressure in each intervention group compared to control over 6 months	These outcomes are directly related to the interventions, are clinically meaningful, and are measurable using routinely collected data in the Electronic Health Record (EHR)
Aim 2		
To identify patient and physician clusters and determine association of those clusters with intervention responsiveness	Characteristics of patient and physician predictors that are associated with 1) clinical inertia in HTN care and 2) intervention responsiveness	A model predicting intervention responsiveness could be used to tailor future interventions specifically to physicians in order to increase intervention effectiveness

3. Study Design

3.1 Study site

Study participants will be recruited from primary care physicians (PCPs) at Massachusetts General Hospital (MGH). MGH is part of Mass General Brigham (MGB), a large integrated delivery network in Boston, MA.

3.2 Overall design

We propose a pragmatic randomized controlled trial to test two interventions targeting clinical inertia in hypertension compared to control, followed by predictive modeling to identify factors that are associated with intervention responsiveness.

For Aim 1, we will use Electronic Health Record (EHR) data to identify physicians of patients whose hypertension treatment was not intensified despite their having persistently elevated blood pressure. We will then randomize primary care physicians to one of three arms: academic e-detailing, social norming, or no intervention (control).

For Aim 2, we will conduct interviews with select physicians from each arm. We will then identify patient and physician characteristics that are associated with inertia and with responsiveness to each intervention.

3.2.1 Aim 1 Design

In Aim 1 of the study, we will conduct a three-arm randomized controlled trial to compare the effectiveness of two interventions compared to control on clinical inertia in hypertension treatment. We will recruit 45 primary care physicians (PCPs) in the Mass General Hospital (MGH) system caring for patients who are potentially in need of hypertension treatment intensification.

Using EHR data, we will first identify patients: (1) aged 18-79; (2) for whom the recent blood pressure (BP) history in the last 18 months is above goal, (3) whose most recent BP at an outpatient visit was above goal, and (4) who did not have their hypertension treatment regimens intensified (dose increase, new medication added, or medication exchange) at or since that time.

The BP goal for this study will be <140/90 for all patients. If there are multiple blood pressures on the same day, we will select which BP to use for the study. This will either be the lowest BP from that day (if this is routinely available in the EDW) or the last BP measured that day (this is available in the EDW). The choice of which BP to use will be applied uniformly to all patients after reviewing preliminary data on BP availability in the EDW. To accommodate changes in care delivery that occurred during the COVID surge, outpatient visits will include in-office and virtual visits that had vitals recorded in the EHR the same day. We will exclude patients who,

based upon EHR data, are excluded from the hypertension registry, are pregnant or post-partum 6 months, or who are receiving hospice care.

In order to ensure that sufficient patient visits occur during the intervention period for Aim 1 and enough patients per physician for our prediction model development in Aim 2, primary care physicians will need to have at least 2 patients on their panel meeting these criteria to be eligible for the study. We will also exclude physicians with fewer than 100 patients on their primary care panel or who practice less than 1 session per week.

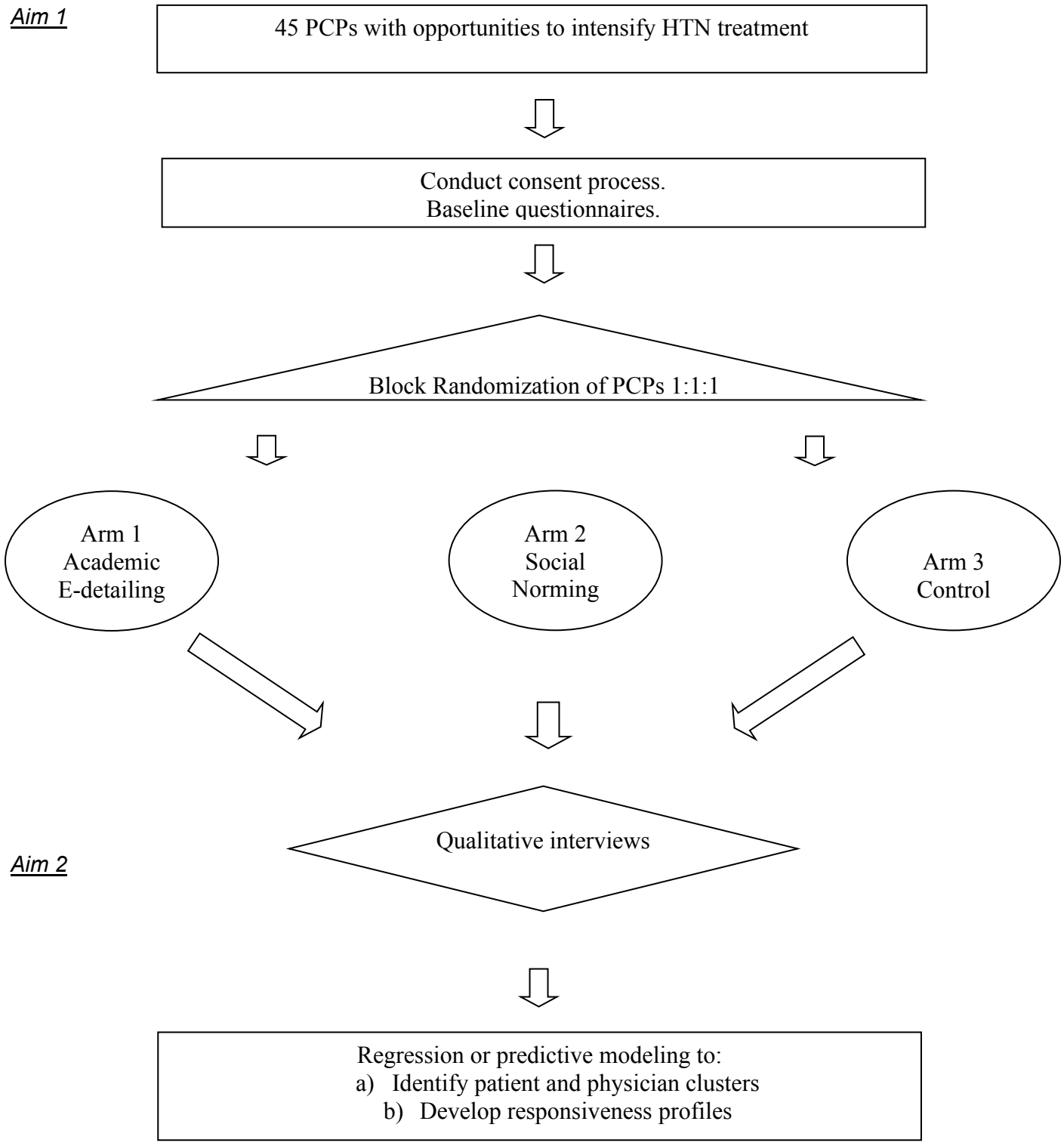
Physicians will be informed about the study and agree to participate using an online consent process through RedCap, and then will be asked to complete a set of behavioral surveys administered through RedCap. PCPs will then be randomized to one of the two intervention arms or control arm. To minimize imbalance between treatment groups, we will use block stratified randomization. Based on the number of sessions per week, providers will be determined to have a small (1-2 sessions), medium (3-4 sessions), or large (5 or more sessions) panel. Within each stratum, we will array physicians into blocks of 3 (note: could also be multiples of 3). All possible balanced combinations of assignment within the block will be allowed in each stratum. Ultimately, within each block and each stratum, physicians will have an equal probably of being assigned to one of the 3 arms.

3.2.2 Aim 2 Design

In Aim 2, we will conduct semi-structured interviews with select physicians across all study arms to further develop our understanding of what data elements are likely to be the most helpful or significant inputs for the predictive modeling analysis. Each interview will be moderated using a semi-structured interview guide.

Following this, we will develop a regression model to evaluate the association of patient and physician characteristics with a) the likelihood of hypertension treatment intensification overall and b) the responsiveness to the study interventions. Finally, we will construct a model to predict the most likely intervention to elicit treatment intensification given physician demographics, with or without patient data. This model, if successful, could assist health systems in selecting the most appropriate individualized intervention to improve treatment intensification.

3.3 Study Schema


Aim 1
45 PCPs with opportunities to intensify HTN treatment
Conduct consent process.
Baseline questionnaires.
Block Randomization of PCPs 1:1:1
Arm 1
Academic
E-detailing
Arm 2
Social
Norming
Arm 3
Control
Qualitative interviews
Aim 2
Regression or predictive modeling to:
a) Identify patient and physician clusters
b) Develop responsiveness profiles

3.4 Scientific rationale for study design

The use of a randomized trial design will be able to both provide stronger evidence of causality in the effectiveness of the interventions and allow for empiric derivation of patient and physician characteristics that may influence intervention responsiveness. An observational study design or physician self-report of factors that influence intervention responsiveness are more subject to bias.

3.5 Justification for intervention

Social norming[10,11] and academic detailing[10,12,13] interventions are effective tools to change physician behavior and improve hypertension management. However, few studies have evaluated specific patient and physician characteristics that might influence intervention effectiveness. With the results of this study, we hope to be able to target interventions more precisely to increase their effectiveness. This research could provide direct benefit to patients through improved blood pressure control and may increase physicians' awareness and knowledge of hypertension treatment.

3.6 End-of-study definition

The active interventions in aim 1 are expected to last for no more than 6 months, and the post-intervention qualitative interviews will be completed within 2 months after the intervention period is complete. Study data collection for the secondary outcome of blood pressure control will continue for 6 months after the intervention period is complete. Development of the prediction models will be done concurrently during that time. We expect to complete the full study including all analyses by July 2022. Participants will be notified by email of study completion.

3.7 Data sources

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 EHR data, supported by Epic Systems, Inc. The data warehouses for this organization 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.

Linkages to subjects, access to subject identities

Individually-identifiable data are maintained for patient care purposes within the MGB network and are needed to identify patients for evaluation and to monitor care recommendations by physicians. Without this linkage, we could not fulfill the study's objectives. To protect the confidentiality of these data, only the minimal necessary research staff will have access to personal identifiers. This will be necessary for linking data and contacting physicians. After linkage is completed and study variables are created, all identifiable information will be deleted from the study database. All research staff are properly trained in research management and will be approved by the IRB. All personally identifiable health information will be kept under lock and key.

3.8 Schedule of activities

	Screening	Enrollment	Intervention	Analysis
Identification of eligible physicians	X			
Recruitment of physicians	X			
Consent Process		X		
Physician surveys		X		
Randomization		X	X	
Control & Experimental Interventions			X	
Physician Interviews				X
Primary outcome analysis				X
Predictive modeling analysis				X

4. Study Population

The study will include primary care physicians at MGH.

4.1 Inclusion Criteria

We will include primary care physicians meeting the following criteria:

1. Practicing in primary care at Massachusetts General Hospital.
2. Caring for at least 2 patients: (1) aged 18-79, (2) for whom the recent BP history in the last 18 months is above goal, (3) whose most recent BP at an outpatient visit was above goal, and (4) who did not have their hypertension treatment regimens intensified (dose increase, new medication, or medication exchange) at or since that time. The BP goal will be <140/90 for all patients. To accommodate changes in care delivery that occurred during the COVID surge, outpatient visits will include in-office and virtual visits that had vitals recorded in the EHR the same day. We will exclude patients who were excluded from the hypertension registry, are pregnant or post-partum 6 months, or who are receiving hospice care.

4.2 Exclusion Criteria

Providers will be excluded if they have fewer than 100 patients on their primary care panel or practice less than one session per week. These will be identified using data available from the primary care tableau dashboard and/or the baseline surveys.

Patients will not directly receive intervention, but their clinical parameters will be used to identify eligible providers and upcoming visits with potential opportunities for treatment intensification. For this study, we plan to exclude patients age 80 and older. The SPRINT[14] and HYVET[15] trials enrolled patients aged ≥75 and ≥80 years respectively and demonstrated the safety and efficacy of blood pressure control to <130/80 or <150/80, suggesting that medication intensification in this age group is safe and effective. However, another recent trial of de-prescribing for patients >80 years with controlled BP on two or more medications was non-inferior to usual care,[16] suggesting that medication de-escalation may also be appropriate for some patients. In both of these cases, patients who participated in these trials were selected by their physicians who had detailed knowledge of their clinical history and functional status. Because we will not be directly seeking PCP input on patients to include in this trial, and because blood pressure treatment decisions are more nuanced and individualized in this age range, we will exclude patients ≥80 years of age from this pilot study.

4.3 Recruitment and retention

We will send email invitations to eligible Primary Care Physicians in the MGH healthcare system. Based on preliminary data, we expect that 100 or more physicians will have at least 2 qualifying patients each and thus will be eligible for the study. Assuming approximately 50% of physicians will agree to participate, we expect to be able to recruit 45 physicians for the study. Our research team includes the Chief of the MGH Division of General Internal Medicine and Associate Medical Director of the Massachusetts General Physician Organization, who will help us achieve our enrollment targets and retention rates.

Physicians will receive $75 for completion of the baseline surveys. After that time, physicians will receive the interventions and will be able to choose whether or not to incorporate that information into their routine clinical practice, but they will not be required to complete any additional study-specific tasks. We expect that the compensation for their time and minimal study-specific tasks will help ensure retention.

4.3.1 Informed consent considerations

Potentially eligible physicians will be contacted by email and provided with an informational fact sheet. Physicians will then click a link to a RedCap form that will contain the same information in the fact sheet. The fact sheet includes information about baseline questionnaires, potential study interventions (if randomly assigned to one of these arms), and potential for contact at the end of the study to participate in a semi-structured interview. We have allocated approximately 12 weeks for the process of recruitment and consent.

4.3.2 Inclusivity of study subjects

MGH primary care consists of over 200 PCPs who care for more than 200,000 patients across the Boston area. Based on preliminary data, we expect that 100 or more physicians will have at least 2 qualifying patients each and thus will be eligible during the proposed study period. We expect that ≥50% of the physicians will agree to participate and that therefore we will be able to recruit 45 physicians for the study. Providers will be excluded if they have fewer than 100 patients on their primary care panel or practice less than one session per week. These will be identified using data available from the primary care tableau dashboard and/or the baseline surveys. The chief of the MGH Division of General Internal Medicine (DGIM), and the Director of Population Health and

Quality for MGH DGIM are engaged in support of this project and will help with study recruitment and retention.

5. Study Interventions

5.1 Therapeutic areas

The focus on the proposed study is uncontrolled hypertension treatment guidelines, defined based upon MGH hypertension treatment quality metrics.

5.2 Study interventions

Eligible physicians who agree to participate will be randomized to one of three treatment groups:

- In arm 1 (academic e-detailing), we will first generate a list of patients who meet the definition for clinical inertia in hypertension care and have an upcoming visit with the PCP in the next few weeks. An MGH clinical pharmacist will then review each patient's chart in advance and provide a personalized recommendation for how to modify the specific patient's antihypertensive regimen based on clinical practice guidelines. For example, the clinical pharmacist might recommend adding an additional medication based on the patient's comorbid conditions and could suggest a starting dose and timeframe for dose escalation. The academic e-detailing recommendations will be sent via an Epic in-basket message for each patient 1-3 days in advance of the patient's scheduled visit.
- In arm 2 (social norming), a report of the physician's hypertension control rates compared to benchmarks will be displayed using principles of social norming. The dashboards will be prepared using EHR data to calculate blood pressure control rates for each individual PCP and for his or her practice mean and practice top performer. Every Thursday, we will send each PCP a list of patients who meet the definition for clinical inertia in hypertension care and have an upcoming visit that week. Every 2-4 weeks, we will additionally attach the physician performance review dashboard.
- In arm 3 (control), physicians will not receive outreach**.**

5.3 Measures to minimize bias: randomization and blinding

Physicians will be informed about the study and agree to participate using an online consent process through RedCap, and then will be asked to complete a set of behavioral surveys also administered through RedCap. PCPs will then be randomized to one of the two intervention arms

or the control arm. To minimize imbalance between treatment groups, we will use block stratified randomization. Based on the number of sessions per week, providers will be determined to have a small (1-2 sessions), medium (3-4 sessions), or large (5 or more sessions) panel. Within each stratum, we will array physicians into blocks of 3 (note: could also be multiples of 3). All possible balanced combinations of assignment within the block will be allowed in each stratum. Ultimately, within each block and each stratum, physicians will have an equal probably of being assigned to one of the 3 arms.

It will not be possible to blind physicians to the interventions, as they will directly receive either e-consults, dashboards, or no intervention. Because physicians have individual panels, hypertension is typically treated via routine follow-up visits with the PCP, and the interventions are specific to each physician, risk of practice-level contamination is low.

6. Study Assessments and Procedures

6.1 Baseline data

We will collect baseline data using a combination of provider surveys and the EHR. From the provider surveys, we will collect physician age, gender, race/ethnicity, years in practice, practice location, and the behavioral scales detailed below. We will also collect data on providers from the EHR, including, but not limited to: hypertension prescribing trends (frequencies of medications utilized, BP control rates, time to treatment intensification) and information about the PCP's panel such as panel size, demographic characteristics (e.g. age, gender, race/ethnicity), and clinical characteristics (e.g. comorbidities). We will also collect data specific to the patients who meet the definition for clinical inertia and whose visits are targeted by the interventions. This will include sociodemographic data, medical history and comorbidities, baseline resource utilization in prior 12 months (i.e., number of visits), and biometric values (e.g., serum creatinine, systolic/diastolic blood pressures).

The surveys that physicians will complete were selected to capture personality traits and behavioral tendencies that might contribute to clinical inertia or intervention responsiveness. These surveys will include measures of:

- risk aversion (Physicians' Reactions to Uncertainty Scale)[17]
- long and short term orientation (Individual Cultural Values Scale)[18]
- conscientiousness (Ten-Item Personality Inventory)[19]

- need for cognition (Need for Cognition Scale)[20]
- resistance to change (Resistance to Change Scale)[21]
- susceptibility to social norms (Social-Norm Espousal Scale)[22]
- burnout (Professional Fulfilment Index)[23]
- automaticity (Self-Report Behavioural Automaticity Index).[24]

6.2 Outcomes

The *primary outcome* will be whether physicians intensified treatment at the visit targeted by the intervention. Intensification of treatment will include an increase in dose of an existing antihypertensive medication, adding an additional medication, or rotation of one medication to another that is stronger or more appropriate for the patient (e.g. changing hydrochlorothiazide to furosemide for a patient with chronic kidney disease). These will be measured using prescribing information from the EHR on the day of the patient's visit.

The *secondary outcome* will be the change in systolic blood pressure over 6-months of follow-up in each intervention arm compared to control. The initial value will be the systolic blood pressure at the time of enrollment that determined the patient's eligibility for participation. The follow-up blood pressure will be the last blood pressure available in the EHR within 6 months after the visit targeted by the intervention. Based on prior studies in a similar local healthcare system, we anticipate approximately 20% missingness rate for the follow-up blood pressure within 6 months, and that this will likely be non-differential between treatment arms.[25] Should there be sufficient missing data (e.g., >10%), we will use multiple imputation to handle this. In specific, we will use 20 imputations with Proc MI in SAS to impute any estimated values using fully conditional specification. Analyses will then be conducted on each imputed dataset and combined using Rubin's rules.[26] We will perform a complete case analysis as a sensitivity analysis.

Each post-intervention interview will be moderated by trained study staff using a semi-structured interview guide that asks physicians about barriers to hypertension treatment intensification, perspectives on different intervention arms, and suggestions for improvement.

We will use results from the physician interviews and study staff expertise to select variables for inclusion in the predictive modeling analysis. These variables will all be available in either the EHR or baseline physician surveys and will include, but are not limited to: physician age, gender,

practice setting, baseline trends in hypertension prescribing, practice location, and patient case-mix. We will also collect patient data that include but are not limited to: sociodemographic data, medical history and comorbidities, baseline resource utilization in prior 12 months (i.e., number of visits), and biometric values (e.g., serum creatinine, systolic/diastolic blood pressures).

6.3 Adverse events and unanticipated problems

Oversight:

Oversight of the pilot will be the responsibility of Drs. Haff and Choudhry, the Principal Investigators.

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

De-identified study data will be accessible at all times for the MGH PI 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.

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.

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 clinical inertia. 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.

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 Massachusetts General Hospital. 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 DGIM 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. Daniel Horn, MD Director of Population Health and Quality for MGH DGIM and the Associate Medical Director of the Massachusetts General Physician Organization is 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 NIA Program Officer and to the Safety Officer (SO) within 24 hours. Any unexpected SAEs will be reported to the NIA PO, SO 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 NIA Program Officer and to the SO quarterly, unless otherwise requested by the Safety Officer or Roybal Center Program Data Safety Monitoring Board (DSMB).

7. Statistical Considerations

7.1 Statistical Hypotheses

The null hypothesis is that rates of hypertension treatment intensification will be equal in each of the intervention groups when compared to control.

7.2 Sample size determination

Because we are selecting specifically for patients with clinical inertia, we expect the control arm rate of medication intensification at the target office visit to be no more than 15%. Assuming an ICC of 0.05, a type I error rate of 5%, and 12 patients per physician over the study period, a sample size of 45 physicians (i.e. 15 per arm) will provide more than 80% power to detect a 15% difference in treatment intensification between each intervention group and control. If the control arm intensification rate is higher than anticipated, we will still be sufficiently powered for reasonable effect sizes (i.e. if the rate of the primary outcome in the control arm was 0.2%, we will be able to detect an effect size of 17%). These data are intended to provide pilot data for larger evaluations, and any positive signal from this pilot trial will help inform next steps. If we have more eligible and

consented physicians than originally anticipated, we will adjust our allocation scheme so that additional physicians are allocated to the control arm to maximize power.

7.3 Statistical analyses

7.3.1 Analysis of the primary endpoint

The primary outcome of this trial will be whether physicians intensified treatment at the visit targeted by the intervention. These data will be collected through EHR data from MGB. We will evaluate the primary outcome using generalized estimating equations (GEE) to adjust for provider-level clustering and multiple patient observations per physician with a logit link function and binary distributed errors; these models will also adjust for the block-randomized design. Because this is a randomized trial, our primary analyses are planned as unadjusted; however, if there are strong predictors of the outcomes not balanced by block randomization, we will adjust for these in the primary analyses. We will conduct analyses using intention-to-treat principles and each intervention arm will be compared to control. Given the nature of the data and how the outcome is being measured, there should not be missing values for our primary outcome.

7.3.2 Analysis of secondary endpoints

The secondary outcome of this trial is change in systolic blood pressure control in each arm over 6 months. For this secondary outcome, we will use GEE with an identity link function and normally-distributed errors to account for provider-level clustering, adjusting for the block-randomized design. As in the primary analysis, we will perform analyses unadjusted and adjusted for provider and patient-level covariates to accommodate any imbalance across arms. We will conduct analyses using intention-to-treat principles and each intervention arm will be compared to control. Based on prior studies in a similar local healthcare system, we anticipate approximately 20% missingness rate for the follow-up blood pressure within 6 months, and that this will likely be non-differential between treatment arms.[25] Should there be sufficient missing data (e.g., >10%), we will use multiple imputation to handle this. In specific, we will use 20 imputations with Proc MI in SAS to impute any estimated values using fully conditional specification. Analyses will then be conducted on each imputed dataset and combined using Rubin's rules.[26] We will perform a complete case analysis as a sensitivity analysis.

7.3.3 Baseline descriptive analyses

We will report the means and frequencies of baseline variables for physicians and their eligible patients.

7.3.4 Subgroup analyses

In subgroup analyses, we will explore whether there were any modifiers of the effects of the different intervention arms both using standard methods and predictive modeling. For example, we will explore whether providers that score highly on a measure of conscientiousness were more likely to respond to the social norming intervention, or if there were observable differences in patients who were less likely to receive treatment intensification, such as gender or race/ethnicity.

7.3.5 Exploratory analyses

Additional exploratory analyses will be performed based on predictive modeling analyses to develop a predictive model for responsiveness to each intervention.

8. Ethical and regulatory requirements

8.1 Ethical conduct

General oversight of the project by the principal investigators (Drs Haff and Choudhry) will occur throughout the study period, including regular contact with clinical leadership to obtain ongoing feedback. In addition, this protocol will undergo Institutional Review Board (IRB) evaluation by an institutional IRB. Study data will be accessible at all times for the principal investigators and co-investigators to review, if applicable. The principal investigator will review study conduct (e.g., protocol deviations) on a monthly basis. The principal investigators will also ensure that all protocol deviations for the trials are reported to the NIH and the IRB according to the applicable regulatory requirements.

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 specifically physician-focused and delivered through interventions that use information already available to

physicians. 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 others. However, as noted above, 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.

The primary 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 EHR. The data extracts obtained are continuously used by MGH clinical operations staff for quality assessment and improvement, and undergo routine, rigorous review by experienced data analysts to ensure accuracy and completeness. Dr Haff will work with the research project staff to ensure the accuracy of these data throughout the study period. For the purpose of conducting analyses of the study outcomes, this will involve creating scrambled patient and physician identifiers and sharing only limited Protected Health Information (PHI) with investigators for the purposes of analysis. All team members have received appropriate training in data privacy.

8.2 Informed consent

This study involves enrolling physician-subjects and the use of routinely collected data from patient-subjects.

Physician subjects:

Physician subjects will be invited to participate via email. A fact sheet will be attached to the email with information about the study, their participation, and the names and contact information for study staff who can be reached for a phone or video conversation if they have any questions or concerns. In the email, if interested in participating, physicians will be asked to click on a link to open a secure RedCap survey. There, physicians will again view an electronic copy of the fact sheet. If the physician agrees to participate, he or she will click a button indicating "I agree".

The fact sheet will include information about baseline questionnaires, receipt of study interventions, and potential for contact at the end of the study to participate in a semi-structured interview. We will provide sufficient information to the prospective physician-subjects about the nature of the study and their rights. We will obtain IRB approval for all consent materials that are used. Physicians can keep the copy of the fact sheet in the invitation email for their records.

For this consent process, we therefore request a waiver of documentation of informed consent for physician subjects in this study. We feel this is appropriate for this study because it is minimal risk, the surveys and interventions are similar to existing quality initiatives for which physicians do not need to provide consent, physician subjects are knowledgeable about randomization and study design, and requiring a formal consent conversation with documentation would be a barrier to participation that would limit the sample size and generalizability of the study.

Patient subjects:

For use of routinely collected patient data, we request waiver of patient consent and HIPAA authorization. We plan to use routinely collected EHR data to identify eligible providers, administer interventions, and assess study outcomes. Because this is of minimal risk to patients, the study team will have no interaction with patients, and it would be impracticable to obtain patient consent, we feel that a waiver of consent and HIPAA authorization is needed for this study. This is similar to what we have done in prior work. We believe this waiver is justified as investigators will have no direct patient contact and all prescribing decisions are made under the care of licensed physicians.

Finally, the goal of this project is to improve existing decision support for hypertension control, consistent with MGH-specific professional guidelines and quality metrics. Therefore, the intervention is exclusively provider-facing with the underlying goal of promoting chronic disease management in accordance with widely adopted clinical practice guidelines.

8.3 Confidentiality and privacy

This study involves physician subjects who will receive the study interventions and data from physicians and patients. We believe that the risks to participation are no more than minimal. The primary risk to patients will be privacy of health information. We will minimize this risk as follows:

For Aim 1, we request a HIPAA waiver of patient authorization to access the EHR data necessary for study completion.

For Aim 2, all interviews will take place on a secure MGB Zoom platform. Only audio will be recorded from the interviews and will be used to generate transcriptions which will be de-identified. The data will be securely stored in a manner determined by the IRB, and audio recordings will be destroyed after study completion.

Data for the study will be safeguarded by state-of-the-art security protocols. The facilities have 24-hour security and are protected by locked entrances. MGB has computer networks in place that employ up to date virus protection software and enable password protected access only to study investigators. The setup for analysis of these data will be the same as all the other IRB applications that our MGB research division submits for secondary use of data. All the datasets, including limited protected health information (PHI), will be stored only on secure servers at MGB's data center and will only be accessed by a limited number of individuals in the study team from this division who are all trained in data security and patient privacy.

To ensure the confidentiality and security of all data, the research team operates a secure, state-of-the-art computing facility housed at MGB'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 256-bit AES encryption, 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.

We will also safeguard any identifiable information from the physicians in accordance with IRB practices, limit access to any information in accordance with IRB practices, limit access to the information to study investigators actively involved in the research who have all undergone human subjects research training, and destroy any recordings from the qualitative interviews upon completion of the research.

All members of the research team have completed or will complete appropriate human subjects research training and patient privacy training related to the Health Insurance Portability and Accountability Act (HIPAA). The setup for analysis of these HIPAA-limited data will be exactly the same as all of the other IRB applications that our MGB research division submits for secondary use of data. All of the datasets, including limited PHI, will be stored only on secure servers at the MGB data center and will only be accessed by a limited number of individuals in the study team from this division who are all trained in data security and patient privacy.

8.4 Safety oversight

General oversight of these particular projects by the PIs (Dr. Haff and Choudhry) will occur throughout the study period, including regular contact with clinical primary care leadership to obtain ongoing feedback. In addition, this protocol will undergo Institutional Review Board (IRB) evaluation. Our trial has been registered with clinicaltrials.gov.

We will have oversight from both the NIA Director-approved Roybal Centers Program Data Safety Monitoring Board (DSMB) and a Program Officer-approved independent Safety Officer (SO) for all aspects of this research. The DSMB will act in an advisory capacity to the NIA to monitor participant safety, evaluate the progress of the study, and review procedures and management of the study. The SO will provide the Program DSMB with periodic safety reports. Our plan for data and safety monitoring also includes oversight by the project principal investigators (Drs. Choudhry and Haff) throughout the study period.

Meetings of the DSMB will be held regularly (e.g., every six to nine months) at the call of NIA or the DSMB Chair and review data related to study protocols and ensure protection of patient confidentiality and safety. At each meeting, the DSMB will make recommendations as to whether the studies should continue or if changes to the protocol are necessary for continuation. The DSMB will also review periodic safety reports from SO, as needed. This trial has been registered with clinicaltrials.gov.

8.5 Benefit risk assessment

8.5.1 Known potential risks

We believe there is no more than minimal risk involved to the physician subjects, as the physicians will receive interventions designed to help with the provision of guideline-concordant hypertension care. In terms of patient-subjects, all medical decisions are ultimately made by the physician. This trial will otherwise not interfere with the usual workings of primary care practices.

8.5.2 Known potential benefits

Social norming and academic e-detailing interventions could help reduce clinical inertia in managing chronic hypertensive patients. 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.

8.5.3 Assessment of potential risks and benefits

We will enroll physician-subjects based on their being employed by MGB. We will provide physicians with information about the study and they can choose whether or not to participate. We also request a HIPAA waiver of patient authorization to access the EHR data necessary for outcome evaluation.

To protect against the risk of inappropriate disclosure of personal health information, the investigators at MGH will only access study data with encrypted identifiers. As described, all members of the research team have completed or will complete appropriate human subjects research training and patient privacy training related to the Health Insurance Portability and Accountability Act (HIPAA). We have a history of collaborative evaluations with delivery

organizations that involves transfer of the minimum data necessary to complete rigorous evaluations, involving the use of encrypted identifiers to ensure patient confidentiality.

To ensure the confidentiality and security of all data, the research team operates a secure, state-of-the-art computing facility housed at MGB'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 256-bit AES encryption, 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.

We will also safeguard any identifiable information from the physicians in accordance with IRB practices, limit access to any information in accordance with IRB practices, and limit access to the information to study investigators actively involved in the research who have all undergone human subjects research training.

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