NYU Langone Health

Official Title:	Behavioral Economics Trial To Enhance Regulation of Blood Pressure (BETTER-BP)
NCT Number:	NCT04114669
Study Number:	19-00952
Document Type:	Study Protocol and Statistical Analysis Plan
Date of the Document:	• October 19, 2023

Behavioral Economics Trial To Enhance Regulation of Blood Pressure

(BETTER-BP)

Sponsor

NIH/NHLBI

Protocol Version

October 2nd, 2023

Version 19.0

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Synopsis

Study Purpose

BETTER-BP (Behavioral Economics Trial To Enhance Regulation of Blood Pressure) is a prospective, phase II, 2:1 randomized, unblinded, pragmatic clinical trial of a lottery incentive program ("regret lottery") to promote antihypertensive adherence, based in primary care and cardiology ambulatory clinics at Bellevue Hospital an NYULMC-affiliated safety net hospital in New York City, Gouverneur Hospital and NYU Brooklyn (NYU Langone Family Health Centers). BETTER-BP will build on foundational work in behavioral economics to implement a lottery incentive program that promotes adherence to antihypertensive medication, delivered via smartphone for 6 months. Participants will be followed for a total of 12 months to examine the effects of the lottery incentive program, measured by the following outcomes: (1) change of mean systolic blood pressure (SBP) of ≥10 mmHg from baseline to 6 months, and post-cessation from 6 months to 12 months; (2) antihypertensive adherence, defined as ≥80% of days adherent with medication (assessed by electronic monitoring device [EMD]), measured at 6 months and 12 months. We will consent 525 participants and randomize 435 outpatients diagnosed with hypertension and determined to have poor adherence (<80% adherence with one antihypertensive medication), in a 2:1 (intervention:control) ratio. BETTER-BP will represent a novel approach to improving adherence in vulnerable patients that combines principles of behavioral economics with easily scalable technology.

Primary Objective

The primary objective (efficacy) of BETTER-BP is to evaluate whether an incentive lottery, implemented for 6 months, improves systolic blood pressure (SBP) by greater than or equal to 10 mmHg compared with control when assessed at the 6-month ambulatory visit.

The primary objective (process) is to evaluate whether an incentive lottery improves antihypertensive adherence between baseline and 6 months compared to the control arm.

Secondary Objectives (if applicable)

The secondary objective (efficacy) is to evaluate whether an incentive lottery improves SBP between 6 and 12 months (6 months after the lottery cessation).

The secondary objective (process) is to evaluate whether an incentive lottery improves adherence between 6 and 12 months.

The engagement endpoint addresses patterns of adherence (e.g., improving adherence, deteriorating adherence, sustained non-adherence) among participants assigned to receive the study intervention.

General Design Description

BETTER-BP is a phase II, single-center, prospective, pragmatic randomized clinical trial with 2:1 randomization. Participants with a documented history of hypertension and a current prescription of at least one antihypertensive medication will be identified at a routine ambulatory visit, and after providing informed consent will be asked to self-report adherence to their antihypertensive medications using a brief questionnaire. Those deemed poorly adherent will then be randomized in a 2:1 ratio to receive a regret lottery or the control condition.

Study Date Range and Duration

The entire study is expected to be actively enrolling for 36 months from the first date of recruitment, with the last ambulatory follow-up visit occurring 12 months after the last enrollment. The entire study will be complete in 48 months.

Number of Study Sites

The trial will be conducted at both Bellevue Hospital and Gouverneur Hospital's ambulatory clinics within the New York City Health and Hospitals (NYC-H+H) public health system as well as NYU Brooklyn (NYU Langone Family Health Centers)

Primary Outcome Variables

To test the primary efficacy endpoint, change in SBP of ≥10 mmHg from baseline to 6 months will be assessed at the ambulatory follow-up visit.

To test the primary process endpoint, adherence (good adherence defined as ≥80% of days adherent) to one antihypertensive medication will be assessed from baseline to 6 months. Adherence assessments will be made based on the scheduling adherence metric, which is the proportion of days on which a patient takes his/her medication as prescribed divided by the total number of days that s/he is expected to take them in that period. Among participants assigned to receive the study intervention, we will calculate adherence on a weekly basis and analyze trajectories over time from baseline to 6 months.

Secondary and Exploratory Outcome Variables

To test the secondary efficacy endpoint, a maintained SBP change of ≥10 mmHg from 6 months to 12 months will be assessed at the 12-month ambulatory follow-up visit.

To test the secondary process endpoint, adherence (good adherence defined as ≥80% of days adherent) to one antihypertensive medication will be assessed at 12 months (6 months post-cessation). Adherence assessments will be made based on the scheduling adherence metric, which is the proportion of days on which a patient takes his/her medication as prescribed divided by the total number of days that s/he is expected to take them in that period. Among participants assigned to receive the study intervention, we will calculate adherence on a weekly basis and analyze trajectories over time from baseline to 12 months.

Safety endpoints. The intervention involves promoting antihypertensive medication adherence, which may have the unanticipated consequence of medication-related adverse effects. We will therefore capture any injury/adverse event that is, or might be, a result of the intervention, including any of the following: (1) fall-related injury; (2) syncope; (3) hypotension; (4) bradycardia; (5) renal or electrolyte abnormality. Safety events will be ascertained both by questionnaire at the 6- and 12-month follow-up visits and by periodic (monthly) EHR review of ambulatory visits and hospitalizations within NYC-H+H and NYU Brooklyn.

Study Population

Our study will recruit socioeconomically disadvantaged and/or minority participants attending an ambulatory care visit and under treatment for hypertension, given the high burden of hypertension-related sequelae and high rates of nonadherence in these individuals. Recruitment will take place through Bellevue Hospital's ambulatory clinics (primary care or cardiology) and Gouverneur Hospital's ambulatory clinics, both based in the New York City Health and Hospitals Corporation (NYC-H+H). By definition, H+H serves a vulnerable population, almost all of whom are either Medicaid-insured or uninsured. In addition, we will recruit participants from NYU Langone Brooklyn (NYU Langone Family Health Centers) who also serve socioeconomically disadvantaged and/or minority population.

Number of Participants

We anticipate that of 1934 participants eligible for initial screening, 75% (N=1450) will agree to in-person adherence screening. Of those who agree, we project 60% (N=870) will be eligible based on poor adherence, and 50% (N=435) of this population will then agree to participate by completing the informed consent. Of those who agree, we project 60% (N=870) will be eligible based on poor adherence, and 60.35% (N=525) of this population will then agree to participate by completing the informed consent. Of those who consent, we project 83% (N=435) will be randomized and 17% (N=90) will be screen failures.

Abbreviations

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
EHR	Electronic Health Records
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IRB	Institutional Review Board
MOP	Manual of Procedures
N	Number (typically refers to participants)
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OHSR	Office of Human Subjects Research
PI	Principal Investigator
QC	Quality Control
RC	Research Coordinator
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
US	United States

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1 Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

2 Background

Despite the well-established benefits of antihypertensive medications, human behavior remains a large source of variability in their effectiveness. Consistent control of blood pressure requires that patients take their prescribed medication on a daily basis, but poor adherence to daily regimens is a pervasive problem that represents a lost opportunity to improve health.[19] Observational studies have shown that estimates of poor adherence to antihypertensive medications, using the common definition of <80% days adherent, range from 25% to 77% after 1 year.[19—21] Adherence is even lower among vulnerable populations as seen in studies of patients insured by Medicaid, with adherence rates routinely below 40%.[1,3,21] For example, Bailey et al. reported that 60.6% of Medicaid-insured patients with hypertension in Tennessee were nonadherent with antihypertensive medications (using a threshold of days adherent <80%); the strongest risk factor for nonadherence was Black race (odds ratio 1.67).[1]

Poor adherence is a complex phenomenon with many causes. One commonly accepted model from the World Health Organization includes 5 interacting dimensions:[22] socioeconomic (age, race, sex, income), therapy-related (cost, adverse drug effects), patient-related (health beliefs, health literacy, readiness to change), system-level (clinician engagement, care coordination), and comorbid conditions. Due perhaps to this complexity, many interventions to improve antihypertensive medication adherence have yielded either negative or only marginal gains in adherence with little improvement in BP control.[23—25] Further, while selected interventions have demonstrated success,[26,27] they are commonly resource-intensive and/or institution-specific (e.g., case management, care coordination), which limits both scalability and applicability across different healthcare settings, particularly in vulnerable populations where resources may be scarce.

Behavioral economics, which combines principles from psychology and classical economics, represents a novel approach to improve medication adherence. The foundation of behavioral economics rests on the assertion that human beings' decision making is not entirely rational and is subject to predictable "decision errors." These errors include "present bias" (placing undue value on immediate outcomes and discounting future outcomes),[30,31] "social desirability bias" (behaving differently when actions are witnessed by others),[29,32] and "loss aversion" (loss of a certain size is more distressing than an equally-sized gain is reinforcing).[33,34] In healthcare settings, behavioral economics may be especially applicable to chronic conditions such as hypertension; these are largely asymptomatic and therapeutic benefits take years to accrue, while the immediate harms of nonadherence are not clinically apparent.

Vulnerable patients may stand to gain the most from these approaches: in hypertension, low income and Black race are both associated with considerable early cardiovascular morbidity including premature myocardial infarction[37] and stroke,[38] both of which can plausibly be reduced by adequate BP control. Vulnerable populations may also be more receptive to incentive lotteries: a 2015 meta-analysis of behavioral economic approaches found that when adjusting for incentive structure, higher income participants had a lower odds of successful behavior change than lower income participants with a lottery incentive intervention (odds ratio = 0.46, P=0.01).[12]

To our knowledge, no trials have examined behavioral economic approaches to antihypertensive adherence in an exclusively vulnerable population, despite these individuals having the lowest levels of medication adherence and the highest burden of premature CVD-related sequelae. In this setting, we are seeking to leverage ambulatory clinics within the largest public health system in the U.S. (New

York City Health and Hospitals [NYC-H+H]) in order to test whether a lottery incentive program ("regret lottery") improves antihypertensive adherence and lowers SBP. We will enroll participants at safety-net ambulatory practices in Bellevue Hospital and Gouverneur Hospital that serve a diverse group of patients who are mostly Medicaid-insured or uninsured. In addition, we will also recruit participants from NYU Brooklyn affiliated Family Health Centers (NYU Langone Family Health Center)

3 Rationale/Significance

3.1 Problem Statement

Decades of research have demonstrated the effectiveness of antihypertensive medications in reducing adverse outcomes including myocardial infarction, heart failure, stroke, and death.[18] For example, a 2017 meta-analysis of 42 randomized clinical trials (144,220 participants) demonstrated that a 10 mmHg reduction in SBP was associated with significant reductions in any CVD event (29%) and death (27%).[18] In current practice, the majority of antihypertensive medications are available at low cost and are generally well tolerated.

Adherence to antihypertensive medications, however, remains unacceptably low despite decades of research. This is especially true in vulnerable populations (socioeconomically disadvantaged and/or minority) who simultaneously experience the highest rates of adverse hypertension-related sequelae (such as myocardial infarction and stroke), and have the lowest levels of medication adherence.[1,2] For example, among Medicaid recipients at high cardiovascular disease (CVD) risk, long-term adherence to antihypertensive therapy has been reported below 40%.[1,3] Nonadherence to antihypertensive medications is associated with more hospitalizations for CVD events,[4,5] increased healthcare costs,[6] and increased mortality.[4,5] A program that successfully improves antihypertensive adherence would therefore represent a means of implementing a low-cost and readily available prevention strategy with known benefits.

Novel approaches are needed to address the persistent problem of low adherence to antihypertensive medications among vulnerable populations. Historically, patient education and counseling interventions have shown some benefit[7,8] but are resource-intensive and may not translate across health systems. While initial reports showed that direct financial incentives for patients improved adherence, subsequent studies yielded mixed results,[9—11] and questions have been raised concerning their long-term sustainability. Recently, several behavioral economic approaches have been developed to enhance purely financial incentives; these strategies aim to leverage innately human tendencies (such as overweighting of immediate benefits) in order to improve health behaviors.[12—14] Results of several studies using a lottery incentive program ("regret lottery") approach, whereby participants are encouraged to undertake healthy behaviors through the desire to avoid regret over losing financial incentives, have been promising.[13,15] However, whether these incentives translate to sustainable behavior change in vulnerable populations is unclear.

BETTER-BP will build on these foundational works in behavioral economics[16,17] to design a lottery incentive program that promotes adherence to antihypertensive medication, delivered via smartphone for 6 months. Our approach is based on self-determination theory (SDT), a theory of human motivation that postulates that individuals are more likely to pursue healthy behaviors when actions are autonomously (intrinsically) motivated. Individuals are autonomously motivated to the degree that their actions reflect a true sense of choice due to the personal importance of the specific behavior (e.g., taking medications because one believes it is personally important for their health) rather than feeling pressured or coerced to.[39,40] SDT defines competence as a general indicator of an individual's

confidence in their ability to carry out a behavior. SDT hypothesizes that competence and autonomous motivation are correlated such that autonomy "concerns the experience of initiating behaviors whereas perceived competence concerns the feelings about achieving the outcome."[41] Thus, in terms of medication regimens, adherence will be most likely when individuals feel both autonomous and competent in their health behaviors.[42] While it may seem counterintuitive to pair a short-term lottery incentive, based on principles of behavioral economics (an extrinsic motivator) with the concept of building autonomous motivation and competence for behavior change, several studies in health-related behaviors have found that behavioral economic interventions do not "crowd out" intrinsic motivation.[43,44] Instead, previous research has shown that when incentives are small they serve as a "nudge" that can strengthen autonomous motivation to increase engagement and adoption of healthy behaviors (i.e., antihypertensive adherence).[45,46] Importantly, the resultant increase in autonomous motivation reinforces the individual's feelings of competence, which can in turn sustain the behavior change even when the incentive is extinguished.[47,48]

We hypothesize that the lottery incentive in BETTER-BP will increase participants' perceived autonomous motivation for adhering to their antihypertensive medications, which will then be sustained due to increased feelings of competence (i.e., self-efficacy) once the incentive is withdrawn.[49]

3.2 Purpose of Study/Potential Impact

Poor adherence to antihypertensive medications is a pervasive problem that particularly harms vulnerable patients. The burden of hypertension-related premature stroke, myocardial infarction, heart failure, and death among this population could be substantially reduced with a successful intervention that improves adherence; however, many interventions to date have failed, are prohibitively expensive, or lack scalability. BETTER-BP is innovative because it represents a novel approach to improving adherence in vulnerable patients that combines principles of behavioral economics with easily scalable technology. This study is enabled by relatively recent insights into human behavior in healthcare (e.g., loss aversion) coupled with the development of a software platform that can automatically administer a daily lottery incentive program by linking with an electronic monitoring device (EMD). While recent studies have shown promising results with this platform in selected populations,[16,35] to our knowledge none has exclusively targeted antihypertensive adherence in vulnerable patients. While recruitment of vulnerable populations can be challenging, we have collected preliminary data (C.1.1.) that demonstrate the feasibility of enrollment and retention within the NYC-H+H ambulatory network, as well as the use of EMDs for evaluation of adherence in this patient group. The innovation of our study is enhanced through application of advanced statistical methods that will allow greater exploration of patterns of adherence in participants receiving the lottery incentive program (through the use of unbalanced randomization), which will lead to an understanding of which subgroups may benefit most. In addition, the study's maintenance phase (intervention participants will be monitored for 6 months after cessation of the lottery incentive) will permit us to examine whether a short-term intervention can lead to sustained behavior change. This phase, which is often absent in healthcare-focused behavioral economics trials, will help to inform policymakers about whether investment in a short-term lottery incentive can lead to long-term health benefits that may justify the cost.

BETTER-BP has the potential to extend previous work to understand whether a behavioral economic approach in vulnerable patients (socioeconomically disadvantaged and/or minority) with hypertension

can achieve improved medication adherence and reductions in SBP. If positive, this trial will have important implications for reducing CVD events in real-world clinical practice.

3.3 Potential Risks and Benefits

3.3.1 Potential Risks

Risks associated with study procedures and intervention:

The primary safety concern is adverse events related to increased adherence with antihypertensive therapy (medication-related adverse events not previously clinically apparent due to nonadherence). Adverse events are defined as follows:

- Fall-related injury: defined as any fall requiring medical care (including emergency department visit, inpatient hospitalization, or outpatient evaluation).
- Syncope (defined as hospitalization for loss of consciousness with loss of postural tone; may or may not be associated with fall).
- Hypotension (recorded SBP <90 mmHg or DBP <50 mmHg at ambulatory visit).
- Bradycardia: (heart rate <50 BPM at ambulatory visit).
- Renal or Electrolyte abnormality: abnormal sodium (≤132 or >150 mEq/L), potassium (<3.0 or >5.5 mEq/ L), or serum creatinine (increase by at least 50% from value closest to baseline visit to a level ≥1.5 mg/dL). As trial is pragmatic, judgment based on any labs ordered as part of routine clinical care (rather than labs obtained at study follow-up visit).

Adverse events will be assessed in-person by questionnaire at the 6- and 12-month follow-up visits, and by a monthly review of the EHR by research coordinators that includes review of laboratory values, clinic notes, hospitalizations, and blood pressures recorded as part of clinical care. Participants assessed with high risk of an adverse event will be discontinued from the study and the DSMB will be notified.

Participant risks are also minimized by the following protections:

- Pre-specified criteria for participant withdrawal to protect participant safety;
- Pre-specified criteria for study termination or suspension to protect participant safety;
- Scheduled safety monitoring by an external independent DSMB

Risks associated with confidentiality:

All patient data will be kept strictly confidential, except when published for purposes of reporting data. In that case, the patients are never identified. All electronic data will be de-identified and transmitted and stored with secure systems that meet or exceed Federal guidelines. The Principal Investigator will maintain files with identifying information in a locked cabinet in a locked room or in password-protected files on a password-protected computer.

No identifiers will be recorded in the research database. All data retrieved from study software and devices will be reviewed and stripped of identifiers prior to database lock and data analysis. Since hypertension is a common condition and the study is being conducted in a densely populated area, it is extremely unlikely that participants could be identified from an anonymized dataset.

Risks associated with financial incentives:

Low-income participants (e.g. Medicaid beneficiaries) may be vulnerable to financial incentives to enroll in the research study. We will therefore delineate in the informed consent that compensation should not be the sole grounds for participation in the research project, and should not cause participants to assume risks that they would not ordinarily find acceptable. We designed study compensation to be modest in order to not unduly influence participation. Simultaneously, we will also aim to ensure that participants do not incur additional costs from the study that may be burdensome. Participant compensation for the 6- and 12-month follow-up visits take to account the cost for time and travel spent by the participant. In addition, study equipment will be provided to participants at no charge, and a toll-free number will be provided to reach the research coordinator for ongoing communication as necessary. There are no anticipated out-of-pocket costs for participants using the Way to Health platform.

3.3.2 Potential Benefits

There is no definitive direct benefit to participants from study treatment or other study procedures during the course of the study. If the adherence intervention turns out to be beneficial, then participants assigned to this study arm will benefit, although this will not be known until conclusion of the study.

4 Study Objectives

4.1 Hypothesis

To test the effect of a lottery incentive program, designed to improve adherence with antihypertensive medications, on:

- **Mean systolic blood pressure (SBP) of ≥10 mmHg from baseline, measured at 6 months**. Hypothesis: The program will reduce mean SBP ≥10 mmHg at 6 months compared with control.
- **Antihypertensive adherence measured at 6 months**. Hypothesis: The program will lead to improved antihypertensive adherence at 6 months compared with control.

To test the durable effect of the lottery incentive program (6 months post-cessation) on:

- **Mean SBP reduction, measured at 12 months**. Hypothesis: 6 months after cessation of the intervention, mean SBP reduction will be maintained in the intervention arm.
- **Antihypertensive adherence measured at 12 months.** Hypothesis: 6 months after cessation of the program, improved antihypertensive adherence will be sustained in the intervention arm.

To examine differing patterns of adherence among participants assigned to the intervention group:

- Hypotheses: Among participants assigned to receive the intervention, (1) there will be distinct trajectories of adherence (e.g., improving adherence, deteriorating adherence, sustained non-adherence); and (2) there will be significant adherence differences among groups defined by motivation, self-efficacy, age (≥65 years), sex, race/ethnicity, comorbidities, patient-reported health status, depressive symptoms, and medication burden.

4.2 Primary Objective

The primary objective (efficacy) of BETTER-BP is to evaluate whether an incentive lottery, implemented for 6 months, improves systolic blood pressure (SBP) by greater than or equal to 10 mmHg compared with control when assessed at the 6-month ambulatory visit.

The primary objective (process) is to evaluate whether an incentive lottery improves antihypertensive adherence between baseline and 6 months compared to the control arm.

4.3 Secondary Objectives

The secondary objective (efficacy) is to evaluate whether an incentive lottery improves SBP between 6 and 12 months (6 months after the lottery cessation).

The secondary objective (process) is to evaluate whether an incentive lottery improves adherence between 6 and 12 months.

The engagement endpoint addresses patterns of adherence (e.g., improving adherence, deteriorating adherence, sustained non-adherence) among participants assigned to receive the study intervention.

5 Study Design

5.1 General Design Description

BETTER-BP is a phase II, single-center, prospective, pragmatic randomized clinical trial with 2:1 randomization. Participants with a documented history of hypertension and a current prescription of at least one antihypertensive medication will be identified at a routine ambulatory visit, and as part of pre-screening will give verbal consent to self-report adherence to their antihypertensive medications using a brief questionnaire. The research coordinator will obtain verbal consent from these potential subjects using an IRB-approved script. The information is destroyed immediately if subjects are not eligible or are determined eligible, but decide not to participate. Otherwise, if subjects are eligible and consent to participate in the study, the de-identified information is kept with their study file. Those deemed poorly adherent (reported missing at least 2 doses of medication over the past 7 days) will then go through the written informed consent process with the research coordinator. The participant will berandomized in a 2:1 ratio to receive a regret lottery or the control condition only if their baseline SBP is ≥130 mmHg. If the participants SBP is <130 mmHg they will be considered a “screen failure” and the participant will not be randomized.

5.1.1 Study Date Range and Duration

The entire study is expected to be actively enrolling for 36 months from the first date of recruitment, with the last ambulatory follow-up visit occurring 12 months after the last enrollment. The entire study will be complete in 48 months.

5.1.2 Number of Study Sites

The trial will be conducted within the ambulatory clinics of Bellevue Hospital and Gouverneur Hospital which are within the New York City Health and Hospitals (NYC-H+H) public health system. In addition, we will also recruit participants from NYU Brooklyn affiliated Family Health Centers (NYU Langone Family Health Centers)

5.2 Outcome Variables

5.2.1 Primary Outcome Variables

The primary study outcome is systolic blood pressure (SBP), assessed as follows: Three seated blood pressure (BP) assessments will be measured after a rest period (5 minutes) using the same automated device (Omron 907 XL, Lake Forest, IL) on the participants non-dominant arm which will reduce the potential for observer bias. There will be a 1-2 minute interval between each measurement. The study participant will be in a seated position, with feet on the floor and back supported, and will be instructed to empty their bladder prior to measurement. Clothing covering the cuff position will be removed; rolling up shirtsleeves for measurement is prohibited. A cuff size will be selected in order for the cuff bladder to cover 75% to 100% of the arm. Manual BP will be recorded if an automated device fails or is unavailable. For purposes of standardization, all research coordinators will undergo a formal half-day training session on BP measurement offered at NYU. While the primary endpoint is SBP, diastolic BP and pulse will also be recorded for exploratory analyses.

5.2.2 Secondary and Exploratory Outcome Variables

Secondary Endpoint

The secondary study endpoint is adherence, measured continuously using the Adheretech wireless EMD, which transfers data via cellular network to a secure web portal on a daily basis. Data are viewable on the Adheretech dashboard, including daily adherence and timing of doses. We will define adherence using the scheduling adherence metric, which is the proportion of days on which a patient takes his/her medication as prescribed divided by the total number of days that s/he is expected to take them in that period.[24] Detailed records of all patient emergency room visits and hospitalizations will be kept and accounted for in the analyses.

Safety Endpoints

We will assess the safety endpoints of antihypertensive medication-induced adverse effects (fall-related injury, syncope, hypotension, bradycardia, renal or electrolyte abnormality) via monthly electronic health record (EHR) review within the NYC H+H system, as well as questionnaires at the 6- and 12-month follow-up visits to capture out-of-system utilization.

Exploratory mediators and moderators of intervention effect

Exploratory outcomes will be measured to examine differing patterns of adherence among participants assigned to the intervention group. We hypothesize that: (1) there will be distinct trajectories of adherence (e.g., improving adherence, deteriorating adherence, sustained non-adherence); and (2) there will be significant engagement differences among groups. We will test whether the following characteristics are significant: age (≥65 years), sex, race/ethnicity, motivation (based on TSRQ), self-efficacy (based on MASES), comorbidity burden, and depressive symptoms.

We will capture mediators of adherence based on our theoretical model including intrinsic versus extrinsic motivation (TSRQ)[50] and self-efficacy (MASES).[51] We will also capture moderators to explain effects in different subgroups based on prior studies of adherence. These include comorbidity burden (Charlson Comorbidity Index),[58] depression (PHQ-8),[59]

patient reported health status (SF-12),[60] number of chronic medications prescribed, and demographic characteristics (age, sex, race, ethnicity). Measures are captured as follows:

Motivation will be measured with the Treatment Self-Regulation Questionnaire (TSRQ)[50] which assesses an individual's quality of motivation to achieve a particular outcome along a spectrum of autonomy. For this study, we will calculate scores for the Intrinsic and Extrinsic motivation subscales. TSRQ will be administered at baseline, 6 months, and 12 months to evaluate change over time.

Self-efficacy will be measured by the Medication Adherence Self Efficacy Scale (MASES),[51] a 26-item scale used to assess patients' confidence in their ability to take antihypertensive medications. MASES will be administered at baseline, 6 months, and 12 months to evaluate change over time.

Comorbidity burden will be evaluated (baseline) using the Charlson Comorbidity Index (CCI)[58], a weighted index that includes 19 chronic medical conditions, each of which is weighted on a scale of 1-6. The CCI has been used extensively to quantify comorbidity in previous studies of medication adherence.[77,78]

Depression will be measured (baseline) by the PHQ-8,[59] a validated screening tool consisting of 9 symptom questions that are scored on a scale of 0 ("not at all") to 3 ("nearly every day"). A score of ≥10 is consistent with at least moderate depression.

Patient-reported health status will be measured (baseline) using the Short Form 12 (SF-12).[60] Physical (PCS) and Mental (MCS) Component Summary scores based on SF-12 responses will be calculated automatically using a proprietary algorithm (Optum Labs, Eden Prairie, MN), with higher scores indicating better health.

Number of medications prescribed will be collected (baseline) and includes the total number of medications prescribed for chronic medical conditions.

5.3 Study Population

Antihypertensive nonadherence is a major public health problem associated with high rates of morbidity and mortality and associated high health care costs. These adverse sequelae are particularly high in vulnerable patients (socioeconomically disadvantaged and/or minority). Observational studies have shown that estimates of poor adherence to antihypertensive medications, using the common definition of <80% days adherent, range from 25% to 77% after 1 year.[19—21] Adherence is even lower among vulnerable populations as seen in studies of patients insured by Medicaid, with adherence rates routinely below 40%.[1,3,21] By design, our study recruits socioeconomically disadvantaged and/or minority participants attending an ambulatory care visit and under treatment for hypertension, given the high burden of hypertension-related sequelae and high rates of nonadherence in these individuals. However, we are excluding persons from enrollment who are members of the following vulnerable populations: children, pregnant women, and incarcerated individuals. Rationale is as follows:

- The target condition (hypertension) is overwhelmingly a disease of adults (age ≥18), and we are therefore excluding children from eligibility.
- We are excluding pregnant women since this represents a vulnerable population where individualized management of hypertension is required as a standard of care. Study

participants who become pregnant after the baseline visits will be discontinued from study participation and will be referred to her medical provider for appropriate follow-up treatment.

- In addition, participants who are incarcerated are not eligible to participate in this research study, the study intervention (EMD and possible smartphone lottery incentive use) is not feasible in the setting of incarceration. Participants who become incarcerated after randomization will be discontinued from study participation and will be referred to his/ her medical provider for appropriate follow-up treatment.

To our knowledge, no trials have examined behavioral economic approaches to antihypertensive adherence in an exclusively vulnerable population, despite these individuals having the lowest levels of medication adherence and the highest burden of premature CVD-related sequelae. In this setting, we are seeking to leverage ambulatory clinics within the largest public health system in the U.S. (New York City Health and Hospitals [NYC-H+H]) in order to test whether a lottery incentive program ("regret lottery") improves antihypertensive adherence and lowers SBP. We will enroll participants at Bellevue Hospital and Gouverneur Hospital, both safety-net ambulatory practices that serves a diverse group of patients who are mostly Medicaid-insured or uninsured and participants from NYU Brooklyn (Family Health Centers). Eligible participants include adults age 18 and older with a diagnosis of hypertension, prescribed 1 or more antihypertensive medication, with at least one measured SBP greater than or equal to 140within the prior 6 months.

Vulnerable patients may stand to gain the most from these approaches: in hypertension, low income and Black race are both associated with considerable early cardiovascular morbidity including premature myocardial infarction[37] and stroke,[38] both of which can plausibly be reduced by adequate BP control. Vulnerable populations may also be more receptive to incentive lotteries: a 2015 meta-analysis of behavioral economic approaches found that when adjusting for incentive structure, higher income participants had a lower odds of successful behavior change than lower income participants with a lottery incentive intervention (odds ratio = 0.46, P=0.01).[12]

5.3.1 Number of Participants

Based on review of preliminary data, over the course of 3 years of baseline enrollment (month 6 through month 42) we anticipate 1934 participants will be eligible for initial screening, and 75% (N=1450) will then agree to in-person adherence screening. Of those who agree, we project 60% (N=870) will be eligible based on poor adherence, and 60.35% (N=525) of this population will then agree to participate by completing the informed consent. Of those who consent, we project 83% (N=435) will be randomized and 17% (N=90) will be screen failures.

5.3.2 Eligibility Criteria/Vulnerable Populations

Inclusion criteria:

- Male or female age ≥18 years
- Diagnosis of hypertension
- An active prescription for ≥1 antihypertensive medication (any of the following classes: thiazide diuretic, ACE inhibitor, angiotensin receptor blocker, beta blocker, calcium channel blocker, centrally acting alpha agonist, direct vasodilator)
- ≥1 measured ambulatory BP ≥140 mmHg within the past 6 months
- Self-reported suboptimal adherence (<80% days adherence) at screening

Eligible participants include adults age 18 and older with a diagnosis of hypertension, prescribed 1 or more antihypertensive medication, with at least one measured SBP greater than or equal to 140 within the prior 6 months. In addition, we will require self-reported poor adherence with medication (less than 80% days adherent). Participants will be recruited from Bellevue Hospital and Gouverneur Hospital, both safety-net ambulatory clinical sites that are a part of New York Health and Hospitals Corporation (NYC-H+H), the public hospital system serving New York City and from NYU Langone Brooklyn (NYU Langone Family Health Centers)

Exclusion criteria include individuals who are incarcerated, pregnant, unable to use study software (Way to Health) in English or Spanish, unable/unwilling to consent, clear barrier to technology use (e.g. visual or hearing impairment), projected life expectancy <12 months.

By design, our study recruits socioeconomically disadvantaged and/or minority participants attending an ambulatory care visit and under treatment for hypertension, given the high burden of hypertension-related sequelae and high rates of nonadherence in these individuals. However, we are excluding persons from enrollment who are members of the following vulnerable populations: children, pregnant women, and incarcerated individuals.

6 Methods

6.1 Intervention

6.1.1 Description of Intervention

Participants assigned to the intervention arm will receive a lottery incentive ("regret lottery") for 6 months. This is delivered via the Way to Health platform, which operates via Short Message Service (SMS) text messages sent to participants' smartphones. By design, SMS enables messages of only 160 characters or fewer. Participants are eligible to receive a potential monetary reward (disbursed via ClinCard) if they are adherent with their antihypertensive medication the day before, which is monitored via electronic monitoring device (EMD) from AdhereTech. Each participant is assigned a 2-digit number for the trial, and each day the Way to Health platform randomly generates a 2-digit number. Participants will receive $50 if both digits match (1 in 100 chance) and will receive $5 if one digit matches (18 in 100 chance). If they are not adherent with their medication, but would have won if they were adherent, they receive a text message that they would have won ("regret" component).

The specific components of the study intervention are as follows:

Way to Health. Way to Health is a technology platform developed at the University of Pennsylvania that is broadly focused on patient engagement and clinical trial administration. A primary feature of Way to Health is the ability to deliver behavioral health interventions on portable electronic devices (tablet or smartphone), including lottery incentive programs. These lotteries are customizable including the amount, frequency of administration, and probability of winning. The platform is capable of surveillance, patient communication (via text message, email, or automated phone call), and data capture. The platform automates connections among other devices (including a previously developed integration with the AdhereTech EMD), as well as feedback to patients, and self-administered surveys. Only intervention participants will receive SMS text messages, although Way to Health will be also used for study administration tasks (e.g., adherence data integration) in both the intervention and control arms. Text messages will be delivered to participants in their primary language (English or Spanish). We selected the Way to Health platform because of its comprehensive functionality and its prior successful implementation in lottery incentive studies, and given that 75% of ambulatory patients in NYC-H+H ambulatory clinics own a smartphone, there will be general familiarity with text messaging. The actual messages delivered will first be piloted among a sample of outpatients seen at

Bellevue Hospital who are unaffiliated with the main study, in order to ensure they are appropriately tailored to the target population. This is further described in Section 6.3.8 (“User Testing”).

Electronic adherence monitoring. An EMD is necessary to determine lottery eligibility and to measure the process outcome of antihypertensive adherence. Adherence will be assessed via a wireless pill bottle provided to each participant (AdhereTech, New York, NY), which has been previously integrated with Way to Health software and is currently being used in other trials supported by Way to Health. Bottles are connected to a cellular network; when opened, the bottle sends a wireless signal to Way to Health. While all participants in the intervention arm are entered in the lottery each day, they are eligible to win only if the bottle is opened the day before. While the AdhereTech EMD is capable of medication reminders (chime or blinking light), we will turn off these reminder functions to isolate the effect of the lottery incentive on adherence.

In the event that a study participant is prescribed >1 antihypertensive medication, only one EMD will be given to the participant to track a single antihypertensive medication. Preference will be given to once-daily medications in this selection process. If there are more than one once daily medications prescribed, they will be chosen according to the following hierarchy:

1. ACE inhibitor or angiotensin receptor blocker
2. Calcium channel blocker
3. Beta blocker
4. Diuretic (thiazide or aldosterone antagonist)
5. Other (e.g. clonidine)

This hierarchy is based on our discussions with several practicing physicians in the Bellevue ambulatory clinic where enrollment will take place. Diuretics were placed lower in the hierarchy based on the consensus that improving diuretic adherence in this target population may lead to untoward side effects (frequent urination) that would decrease acceptability of the study intervention.

Our strategy of choosing a single medication simplifies the intervention, which is especially important in participants with low health literacy.

Way to Health is designed to be simple (text messaging only), and the AdhereTech EMD synchronizes automatically to administer the lottery, requiring no special capabilities on the part of the participant.

Lottery incentive. The lottery is administered through the Way to Health application. The lottery will be designed as a "combined lottery" with a low frequency chance of winning a large reward and a higher frequency chance of winning a small reward: participants will receive $50 if both digits match (1 in 100 chance), and will receive $5 if one digit matches (18 in 100 chance). The expected daily value (EDV) for this lottery, which is calculated by multiplying the incentive amounts by the probabilities of winning, is $1.40. The lottery also includes the powerfully motivating "regret" feature: patients whose number matches (for either a small or a large prize) are informed of the result whether or not they were adherent the previous day. Those who did not take their antihypertensive medication receive a message indicating that had they been adherent, they would have won either a small or large prize. When participants accrue winnings, payments are calculated automatically through Way to Health and a ClinCard deposit will be disbursed to participants by the research team monthly. The lottery will run for 6 months; adherence will be monitored (without lottery) for an additional 6 months to examine durable effects. If a participant does not own a smartphone (estimated 25% based on pilot work by Dr.

Schoenthaler in NYC-H+H populations) we will provide a device for the duration of the study. For participants with smartphones, we will provide a data card to reimburse the cost of text messaging.

The proposed study attempts to improve clinical care of patients already prescribed antihypertensive medications, through incentivizing adherence to a single antihypertensive medication. There are no investigational medications being studied, and no new medications being prescribed as part of the study intervention. The intervention is harmless, painless, and not physically invasive. The main risk to participants is that, with improved adherence to an already prescribed medication, there is a potential for new medication-induced adverse effects (previously not present due to nonadherence). There is no anticipated lasting impact of the intervention on the subjects; however, if the adherence intervention turns out to be beneficial, then participants assigned to this study arm will benefit, although this will not be known until conclusion of the study. Though current data on implementing financial incentives among the targeted vulnerable population are scarce, it is strongly believed that the intervention will not be offensive or embarrassing to subjects as it is aimed to improve adherence in antihypertensive medications, which may proliferate more continuing health benefits to the participant.

6.1.2 Method of Assignment/Randomization

Participants with suboptimal self-reported adherence during screening and a SBP ≥130 mmHg at the baseline visit will be randomized by a centralized, interactive system in a 2:1 ratio to either the intervention (daily lottery incentive program) or control, using permuted block randomization with variable block sizes of 6 and 9. Variable sized blocked randomization code will be created by an independent biostatistician, and given to a CTSI staff member. A backup copy of the randomization code will be retained by the independent biostatistician in the event that this code is lost. More participants will be enrolled in the intervention than in control in order to have an adequate sample size to understand engagement trajectories (an endpoint). Randomization will be stratified by ambulatory clinic specialty (Cardiology or Internal Medicine) to ensure balance across treatment arms given population-level and clinic-level differences. Due to the nature of the intervention, research coordinators and participants will not be blinded to intervention arm. However, outcome assessment (BP and adherence) is automated; for BP we will use an electronic cuff, and for adherence we will use an EMD (AdhereTech). Automated outcome assessment reduces the potential for measurement bias between study arms. The investigators and data analytic team will remain blinded to arm assignment until the trial is complete and the database has been cleaned and locked. The randomization procedure will be implemented within the Way to Health software platform.

6.1.3 Selection of Instruments/Outcome Measures

Instruments for Primary and Secondary Endpoints

All participants who have consented and are enrolled into the study will be administered the following instruments during the baseline and follow-up visits throughout the duration of study involvement:

Systolic Blood Pressure (SBP) will be assessed at baseline, 6 month, and 12 month visits. Three seated BPs will be measured after a rest period (5 minutes) using an automated device (Omron 907 XL, Lake Forest, IL) which will reduce the potential for observer bias. Manual BP will be recorded if an automated device fails or is unavailable. While the primary endpoint is SBP, diastolic BP as well as pulse will be recorded for exploratory analyses. BP assessment methodology is further described in 5.2.1.

Adherence will be measured continuously using the AdhereTech wireless EMD which transfers data via cellular network to the Way to Health platform, including daily adherence and timing of doses. We will define adherence using the scheduling adherence metric, which is the proportion of days on which a patient takes his/her medication as prescribed divided by the total number of days that s/he is expected to take them in that period.[75] Detailed records of all patient emergency room visits and hospitalizations (where participant may have been nonadherent due to an acute medical issue) will be kept and accounted for in the analyses.[76]

Instruments for exploratory mediators and moderators of intervention effect

We will capture mediators of adherence based on our theoretical model including intrinsic versus extrinsic motivation (TSRQ)[50] and self-efficacy (MASES).[51] We will also capture moderators to explain effects in different subgroups based on prior studies of adherence. These include comorbidity burden (Charlson Comorbidity Index),[58] depression (PHQ-8),[59] patient reported health status (SF-12),[60] number of chronic medications prescribed, and demographic characteristics (age, sex, race, ethnicity). Measures are captured as follows:

Motivation will be measured with the Treatment Self-Regulation Questionnaire (TSRQ)[50] which assesses an individual's quality of motivation to achieve a particular outcome along a spectrum of autonomy. For this study, we will calculate scores for the Intrinsic and Extrinsic motivation subscales. TSRQ will be administered at baseline, 6 months, and 12 months to evaluate change over time.

Self-efficacy will be measured by the Medication Adherence Self Efficacy Scale (MASES),[51] a 26-item scale used to assess patients' confidence in their ability to take antihypertensive medications. MASES will be administered at baseline, 6 months, and 12 months to evaluate change over time.

Comorbidity burden will be evaluated (baseline) using the Charlson Comorbidity Index (CCI)[58], a weighted index that includes 19 chronic medical conditions, each of which is weighted on a scale of 1-6. The CCI has been used extensively to quantify comorbidity in previous studies of medication adherence.[77,78]

Depression will be measured (baseline) by the PHQ-8,[59] a validated screening tool consisting of 9 symptom questions that are scored on a scale of 0 ("not at all") to 3 ("nearly every day"). A score of ≥10 is consistent with at least moderate depression.

Patient-reported health status will be measured (baseline) using the Short Form 12 (SF-12).[60] Physical (PCS) and Mental (MCS) Component Summary scores based on SF-12 responses will be calculated automatically using a proprietary algorithm (Optum Labs, Eden Prairie, MN), with higher scores indicating better health.

Number of medications prescribed will be collected (baseline) and includes the total number of medications prescribed for chronic medical conditions.

Interventional Instruments

Platforms used in the administration of the intervention were described earlier in *Section 6.1.1 Description of Intervention*. Briefly, participants randomized to the intervention arm will receive an (1) AdhereTech electronic monitoring device (EMD) and (2) instructions Way to Health functionality (communication via text message). Participants will receive training from the research coordinator at the baseline ambulatory visit.

Data Management

The data used for analysis will come from two main sources: Way to Health, and the NYC-H+H electronic health record (EHR). Way to Health will record data on randomization assignment, data on adherence measured using the AdhereTech EMDs, and clinical data from each study visit (baseline, 6 months, 12 months) entered into the Way to Health portal by the study research coordinators; this clinical data includes measurement of BP, and measurement of potential mediators assessed by patient self-report using validated questionnaires (i.e, TSRQ, MASES, PHQ-8). The NYC-H+H EHR will be the source to verify clinical events including hospitalizations, outpatient blood pressure readings, laboratory values, and medications. These two data sources will be merged into a final analytic dataset that will be managed by NYU Langone Health's data management team.

6.1.4 Intervention Administration

Participants randomized to the intervention arm will receive an AdhereTech electronic monitoring device (EMD) that communicates with the Way to Health platform. Way to Health prompts are delivered via SMS text messaging and do not require installation of a separate software application. Participants will receive training from the research coordinator at the baseline ambulatory visit. Description of study interventions can be found in *Section 6.1.1 Description of Intervention.*

6.1.5 Reaction Management

To minimize risk, the study will only enroll clinically stable participants who meet eligibility criteria under the direct supervision of the Principal Investigator and other research personnel with appropriate training and licensure.

In the event that a participant is experiencing stress as a result of the study intervention, the Principal Investigator will evaluate the participants' symptoms directly and if necessary, refer the participant to a psychologist at NYU Langone Health immediately for further evaluation.

6.2 Assessments

6.2.1 Efficacy

Change in SBP of ≥10 mmHg (measured at 6-month ambulatory visit) from baseline to 6 months, and maintenance of SBP change from 6 to 12 month (measured at 12-month follow-up visit), is measured to assess for the efficacy endpoint outcomes. A 2017 meta-analysis of 42 randomized clinical trials (144,220 participants) demonstrated that a 10 mmHg reduction in SBP was associated with significant reductions in any CVD event (29%) and death (27%).[18]

6.2.2 Safety

The intervention involves promoting antihypertensive medication adherence, which may have the unanticipated consequence of medication-related adverse effects. We will therefore capture any injury/adverse event that is, or might be, a result of the intervention, including any of the following: (1) fall-related injury; (2) syncope; (3) hypotension; (4) bradycardia; (5) renal or electrolyte abnormality. Safety events will be ascertained both by questionnaire at the 6- and 12-month follow-up visits to capture both in-system and out-of-system utilization, and electronic health records will also be reviewed on a monthly basis to evaluate for in-system events that may occur sooner than follow-up assessment (especially those unlikely to be reported by the participant, e.g. laboratory abnormality). Elements will be entered into a secure Research Electronic Data Capture (REDCap) database created by NYU DataCore. All potential safety endpoints will also be reported directly to the Principal

Investigator and subsequently the DSMB. Given that our enrollment criteria include at least one prior SBP ≥140 mmHg, we anticipate that adverse events related to hypotension from better adherence with a single medication (e.g. fall-related injury, syncope, hypotension) are relatively unlikely.

6.2.3 Adverse Events Definition and Reporting

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related.

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

The following guidelines will be used to describe severity of adverse events.

- Mild — Events require minimal or no treatment and do not interfere with the participant's daily activities.
- Moderate — Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe — Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

All adverse events (AEs) must have their relationship to study intervention assessed by the investigator who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- Related — The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- Not Related — There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

OR

- Definitely Related — There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals.

The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

- Probably Related — There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- Potentially Related — There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- Unlikely to be related — A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- Not Related — The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

The Principal Investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The project coordinator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

We will further classify AEs as cardiovascular or non cardiovascular. Cardiovascular AEs include hospitalization for any of the following: myocardial infarction, ischemic stroke, heart failure, arrhythmia, critical limb ischemia, percutaneous coronary intervention, cardiac surgery.

The Principal Investigator will immediately report to the sponsor and to the reviewing Institutional Review Board (IRB) any serious adverse event related to the study intervention, including an assessment of whether there is a reasonable possibility that the study intervention caused the event.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the study sponsor and should be provided as soon as possible.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

6.3 Study Procedures

6.3.1 Study Schedule

Each participant (control and intervention group) will complete a total of 3 in-person study visits, approximately one hour each. These will take place at baseline, 6 months, and 12 months. The 6- and 12-month assessments are primarily for purposes of measuring the primary efficacy endpoint (SBP), although safety events and mediators of adherence (Treatment Self-Regulation Questionnaire (TSRQ), Medication Adherence Self Efficacy Scale (MASES) will also be obtained. A window of +/- 21 days will be allowed for scheduled 6- and 12-month follow up study visits. Medication adherence will be measured on a continuous basis via the AdhereTech EMD which sends information (whether EMD is opened daily, and time of opening) to Way to Health. The baseline visit will take place in dedicated space within the NYU-HHC Clinical & Translational Science Institute (CTSI), which is located in Bellevue Hospital in Manhattan, an NYU Langone Health-affiliated NYC-H+H hospital. Bellevue Hospital is also the recruitment site for this study; Bellevue Hospital ambulatory clinic space and CTSI research space are located less than a 5 minute walk apart. The 6- and 12-month follow-up visits will take place in the same location as the baseline visit for purposes of convenience for study participants. For participants enrolled at Gouverneur Hospital as well as NYU Brooklyn, a designated private research room has been identified to complete study visits.

6.3.2 Informed Consent

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting study procedures/administering study intervention. The following consent materials are submitted with this protocol:

- Sample Key Study Information Form
- Sample Informed Consent Form

6.3.3 Screening

We will screen consecutive patients attending ambulatory clinic visits (primary care or cardiology) at Bellevue Hospital in Manhattan, an NYU Langone Health-affiliated NYC-H+H hospital, Gouverneur Hospital, and NYU Brooklyn (NYU Langone Family Health Center). There are two phases of screening:

(1) **Potentially eligible individuals will be identified by review of the EHR within 1 week prior to their clinic visit**. The research coordinator will use a simple algorithm to identify adult ambulatory patients who meet inclusion criteria identifiable by EMR (age 18 and older, diagnosis of hypertension, active prescription for 1 or more antihypertensive medication, 1 or more ambulatory SBP greater than or equal to140 mmHg in the past 6 months- on therapy). Exclusion criteria are as follows: incarcerated, pregnant, unable to use study software (Way To Health) in English or Spanish, unable/unwilling to consent, clear barrier to technology use (e.g. visual or hearing impairment), projected life expectancy less than 12 months.

(2) **Patients deemed eligible by this initial screen will be contacted via telephone by the research coordinator prior to their clinic visit.** They will be offered a brief screening questionnaire that ascertains antihypertensive adherence over the past 7 days. If the participant is deemed nonadherent to medications from the questionnaire, s/he will then be offered informed consent at their next ambulatory clinic visit. If the research coordinator is unable to reach the patient via phone call, then the research coordinator will approach the patient on the day of their clinic visit to introduce the study and administer brief screening questionnaire. Participants deemed non-adherent will be offered informed consent. In practice, screening will most often take place prior to the visit (e.g. in a private waiting area of primary care or cardiology clinic, or while waiting in the exam room), while the baseline assessment will take place after this visit. While we will offer the baseline assessment on the same day as their clinic visit, we understand that some patients may not have adequate time to complete on the same day due to other commitments, and we will therefore allow them to return within 1 month of screening for completion. Informed consent will be completed at the time of this scheduled visit.

Two research coordinators will be simultaneously screening (and subsequent enrollment) from the multiple clinics.

6.3.4 Recruitment, Enrollment and Retention

Recruitment: Recruitment will take place through ambulatory clinics (primary care or cardiology) based at Bellevue Hospital and Gouverneur Hospital in Manhattan, both a part of New York City Health and Hospitals Corporation (NYC-H+H) medical center. Recruitment will also take place at NYU Brooklyn (NYU Langone Family Health Center).

Screening: To achieve randomizing 435 study participants, we anticipate needing to initially identify 1934 eligible participants from the electronic health record (EHR) over the 3-year baseline enrollment period (month 6 through month 42). There will be two phases to screening: first, EHRs will be reviewed on the day prior to clinic sessions by the research coordinators, in order to find patients who meet initial eligibility study criteria (age ≥18 years, diagnosis of hypertension, active prescription for ≥1 antihypertensive medication, ≥1 ambulatory SBP ≥140 mmHg recorded within the past 6 months on therapy). The nexteligibility criteria (poor adherence) can only be determined by patient interview. The research coordinator will call potentially eligible patients, introduce the study and if interested will administer pre-screening questionnaire. If the research coordinator is unable to reach patient via phone they will approach potentially eligible patients (based on EHR screening) in the waiting area for

their clinic visit, or in the exam room while waiting for their clinician, and if they are interested in participating they will be asked to complete a brief de-identified pre-screening questionnaire in private. The questionnaire can be administered in less than 5 minutes. Study participants who report less than 80% adherence with their antihypertensive medication based on this survey will qualify for the clinical trial.

Enrollment and Informed Consent. Following screening, eligible patients will be offered a baseline study visit on the same day or within 1 month of screening, based on individual preference. Informed consent will be completed at the time of the baseline study visit (rather than immediately after screening). All study personnel responsible for obtaining informed consent will receive appropriate human subjects training, as required by institutional and NIH policies, and protocol-specific training prior to initiating any study related activities. Informed Consent procedures will take place in dedicated research space within the NYU-HHC CTSI, where participants will be provided with the informed consent form to read. S/he will be explicitly informed that participation in the study is voluntary and will not affect their normal standard of care, the care that they receive even if they do not participate in the research study.

Interested patients will be provided with the informed consent form and given unlimited time to review the document and ask questions. Once the potential participant has read the consent form and had all questions answered to his/her satisfaction, S/he will be asked to sign the consent form. The individual obtaining informed consent will subsequently sign the form, and a copy of the signed form will be given to the participant for his/her records. Only individuals capable of self-consent will be eligible for the study. Participants who are unable to or have difficulties in understanding or performing study procedures (i.e. obvious barriers to technology use such as visual or hearing impairment, or inability to use mHealth software in English or Spanish) will be excluded from participating in the research study.

Should enrollment fall behind target, the study team will meet to discuss barriers to recruitment. A corrective action plan will be developed and initiated to ensure that enrollment rates improve and the study can be completed on schedule. In addition, the Clinical and Translational Science Institute (CTSI) Recruitment and Retention Unit (RRU) will be engaged to provide expert consultation.

Retention: Study participants will be provided with compensation for their time and effort while they are participating in the research study. At the time of participant enrollment, the research coordinator will complete a participant contact sheet which will include the participant's name, address, phone number and preferred time for study-related phone calls. The participants will also be asked to provide the contact information (phone numbers) for at least two relatives or close friends as additional contact persons. These individuals will only be contacted in the event that the study participant is unresponsive to at least three communication attempts or if the participant missed a scheduled study visit. In addition, we will implement additional strategies that have led to successful retention of racial/ethnic minority patients in clinical trials such as regular phone calls to remind participants of visits, provision of a toll-free study telephone number, continuity of staff to maintain a personal connection to the study, and flexible scheduling.

6.3.5 Study Visits

Baseline (ambulatory visit)**.** All study participants will be required in to complete this study visit. All study procedures and data collection by the research coordinators. While all data listed below are not necessarily part of the prespecified analysis, they will be used for purposes of describing the study

sample as well as for potential exploratory analyses. Whenever possible, descriptive data (e.g. medications, laboratory values, demographics) will be obtained from the EHR through chart abstraction in order to minimize the burden on study participants. All questionnaires will be administered digitally (on a portable electronic tablet device or designated workstation with computer access). Total estimated time for the baseline assessment is 60-75 minutes.

- Chart Abstraction (NYC-H+H and NYU Langone Medical Center EHR) will be performed by the research coordinator. Elements will be entered into a secure Research Electronic Data Capture (REDCap) database created by NYU DataCore.
    - Laboratory values: hemoglobin, platelet count, white blood cell count, sodium, potassium, BUN, creatinine, glucose, troponin (all based on admission blood draw).
    - Demographic data: sex, race, ethnicity, insurance status.
    - Medications.
- Research Coordinator Assessment. Procedures listed below will be electronically administered using standardized instruments on a secure, portable tablet computer or designated workstation using Research Electronic Data Capture (REDCap) database created by NYU DataCore.
    - Physical examination: Height, weight, and BP.
    - Additional demographic data: Marital status, education level.
    - Treatment Self-Regulation Questionnaire (TRSQ). Motivation will be measured with the Treatment Self-Regulation Questionnaire (TSRQ) which assesses an individual's quality of motivation to achieve a particular outcome along a spectrum of autonomy.
    - Medication Adherence Self Efficacy Survey (MASES). MASES is a 26-item scale used to assess patients' confidence in their ability to take antihypertensive medications.
    - Charlson Comorbidity Index, a weighted index that includes 19 chronic medical conditions, each of which is weighted on a scale of 1-6. Calculation of the Index will be performed by the research coordinator based on chart abstraction; participants will be asked to clarify the presence/absence of specific comorbidities if there is ambiguity.
    - Patient Health Questionnaire 8 (PHQ-8), a validated screening tool consisting of 8 symptom questions that are scored on a scale of 0 ("not at all") to 3 ("nearly every day"). A score of greater than or equal to 10 is consistent with at least moderate depression.
    - Short Form 12 (SF-12) questionnaire. Physical (PCS) and Mental (MCS) Component Summary scores based on SF-12 responses will be calculated automatically using a proprietary algorithm (Optum Labs, Eden Prairie, MN), with higher scores indicating better health.

*Note: Questionnaires will be administered via phone call in the event participant is not able to complete baseline visit in person.

Screen Fail Criteria

Since this trial is focused on treating HTN, a second criteria is necessary in order for the study intervention to achieve clinically meaningful reduction in SBP. Therefore, a screen fail criteria will be implemented during the baseline visit. Specifically, if the participant's baseline SBP is <130 mmHg, this will be considered a "screen fail" and they will not be randomized. However, the participant will be compensated for the baseline visit.

Study intervention components. Participants randomized to the intervention arm will receive an AdhereTech electronic monitoring device (EMD) and an overview of the Way to Health text messages. The platform is customizable and capable of surveillance, communication via text message, and data capture. Participants will receive training from the research coordinator at the baseline ambulatory visit. Description of study interventions can be found in Section *6.1.1 Description of Intervention.*

Control. Participants randomized to the control condition arm will receive an AdhereTech EMD for assessing daily adherence, and a brochure on hypertension management developed by the American Heart Association.

1-week call: All enrolled participants will be contacted by telephone one week after the baseline visit to ensure understanding of bottle use, and to provide opportunity for troubleshooting if needed.

6-month follow-up visit (ambulatory visit): All study participants will be required in to complete this study visit. The research coordinator will schedule an ambulatory visit to take place 6 months after the baseline visit. A window of +/- 21 days will be allowed for 6-month follow up visit after the baseline visit. However, any visits that are not scheduled within 3 months from participants 6-month follow up due date will be considered missed. This visit will be led by the same research coordinator who performed the baseline assessment. The estimated time for the 6-month visit is 30-45 minutes. Measures at 6 months will include a repeat of several baseline instruments to evaluate change over time (BP, TRSQ, MASES), and ascertainment of hospital admissions from the study participant. The research coordinator will also perform chart abstraction to verify hospital admissions, and capture BP and laboratory values recorded during ambulatory visits within the 6 months.

1-week call after 6-month follow-up visit: All participants will be contacted by telephone one week after the 6-month visit to ensure understanding of bottle use, and to provide opportunity for troubleshooting if needed.

12-month follow-up visit (ambulatory visit): All study participants will be required in to complete this study visit. The research coordinator will schedule another ambulatory visit 12 months after the baseline visit. There will be a window of +/- 21 days for 12-month follow-up visit to be completed. The study team will have six months after a participant's window has ended to attempt to gather time point data. Any visits that are not scheduled within 6 months from the participants 12-month time point will be considered lost to follow up. Similar to the 6-month visit, the estimated time is 30-45 minutes. Measures at 12 months will include a repeat of the instruments taken at baseline and 6-month visits (BP, TRSQ, MASES) and ascertainment of hospital admissions from the study participant. For admissions that occur outside the NYC-H+H system, hospital records will be obtained when feasible. The research coordinator will also perform chart abstraction to verify hospital admissions, and capture BP and laboratory values recorded during ambulatory visits between 6 and 12 months.

6.3.6 End of Study and Follow Up

The end of study visit will be conducted at the 12-months ambulatory follow-up visit. Measures at 12 months will include a repeat of the instruments taken at baseline and 6-month visits (BP, TRSQ, MASES) and ascertainment of hospital admissions from the study participant. For admissions that occur outside the NYC-H+H system or NYU Langone Medical Center, hospital records will be obtained when feasible. The research coordinator will also perform chart abstraction at the 12-months follow-up visit to verify any hospital admissions, capture blood pressure values, and record laboratory values during ambulatory visits between the 6 and 12 months-visits for both adjudication of safety events and for potential exploratory analyses.

Assessments of safety events, which include adverse events plausibly related to better antihypertensive adherence (fall-related injury, syncope, hypotension, bradycardia, renal or electrolyte abnormality), will be recorded during the 6- and12-month follow up visits.

Study Discontinuation Criteria. Participants may be removed if they request to withdraw informed consent or experience an adverse event determined to be related to the study intervention. For all subjects withdrawn, the reason for discontinuation will be documented and reported to the DSMB and NHLBI.

Participants wishing to withdraw or that are terminated from the study will be asked if they may continue to be monitored for safety endpoints to capture AEs, SAEs, and unanticipated problems. Survival data on all participants who are lost to follow-up will be kept in the REDCap database (Research Electronic Data Capture), a secure, web-based Electronic Data Capture (EDC) system. Participants who withdraw or are terminated will not return for the 6- or 12-month ambulatory assessment. Participants will be contacted by the study team personnel via phone call at least three times and/or contact with next-of-kin, if possible, before being considered as lost to follow-up. A certified letter will be sent by the study personnel to the participants as final proof of contact.

Car service to study visits. A cost-free car service option will be offered to study participants for transport to and from all in-person research visits at study sites for the purposes of eliminating barriers to enrollment and follow-up.

6.3.7 Removal of Subjects

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The participant meets an exclusion criterion not caused by study procedures (either newly developed or not previously recognized) that precludes further study participation

6.3.8 User testing

The incentive lottery involves delivery of text messages via the Way 2 Health application. In order for these messages to have maximum impact on the target population, we will first pilot the wording of these messages among a sample of patients prior to initiation of the main study, as described below:

Focus groups: We will conduct focus groups of 3-5 English-speaking patients. The focus group will last for approximately 1 hour in duration. Patient focus groups will be conducted to provide feedback

on the clarity and relevance of the text messages that will be delivered throughout the duration of the intervention period. These groups will be convened by Dr. Schoenthaler (Co-Investigator). Participants will be compensated with a $30 gift card upon completion of the focus group.

Recruitment: A random sample of patients who participated in Dr. Schoenthaler' s IRB approved projects #s11-0053, s15-00229 or s14-00414 and indicated on the main project consent form that they are willing to be re-contacted in the future will be contacted for purposes of the focus groups. In order to contact these patients, the following information will be obtained from Dr. Schoenthaler's trial: Name, mailing address, and phone number. This information will be used to contact the patients via a letter and then by a phone call. The letter will include a brief description of the project and the reason why they are being contacted to participate. It will also provide information about how to get in touch with Dr. Schoenthaler and it will inform participants that Dr. Schoenthaler or a RA will be contacting them soon via a phone call.

During the call, Dr. Schoenthaler or the RA will explain that the purpose of the project is to obtain feedback on a text message incentive lottery to improve medication adherence for patients with high blood pressure. In addition, the potential subjects will be informed that all information collected during the feedback sessions is anonymous, no identifying information will be collected and that all responses will be kept confidential. If the person expresses interest in participating in the Focus Group and agrees to participate at this point, the participant will be scheduled for the visit. Prior to the start of the focus group, participants will be asked to sign an informed consent form. These recordings will be labeled only with a code number, which will be kept in the investigators files for one year from time of interview.

In order to randomly select participants to receive an interest letter, each participant (patient) that completed project #s11-0053, s15-00229 or s14-00414 will be assigned a number. Using a random number table, three patients will be chosen to receive a letter. We will then use the following procedures: If the first person chosen refuses to participate when called, research personnel will approach the second person chosen, and so on until a participant agrees to the project or the list is exhausted. This process will continue until all potential subjects are contacted and invited to participate in the user testing study.

6.4 Statistical Method

6.4.1 Statistical Design

Statistical comparisons will be performed using two-sided significance tests and two-sided confidence intervals. We will begin all analyses with descriptive summary statistics and graphical displays of all variables, with attention to assessing balance in these characteristics by intervention group, and with an assessment of the distribution of variables, relevant to the choice of statistical tests.

6.4.2 Sample Size Considerations

A sample of poorly adherent patients will first be identified to avoid a "ceiling effect" whereby high-adherence individuals have little room for improvement with the lottery incentive. Patients will be screened for low adherence on the day of their clinic visit using a rapid, previously validated 2-page screening form developed by Voils et al.[61] Those identified as having poor medication adherence (<80%) based on this screening will then be offered informed consent.

We estimate that randomizing 435 participants will provide adequate power to achieve the study aims. These participants will be randomized in a 2:1 allocation (intervention:control), resulting in 290 participants in the intervention group and 145 participants in the control group. While we will aim to minimize participant dropout, we include adjustment for up to 20% dropout in each arm, so that we expect about 348 participants with evaluable endpoints (232 intervention, 116 control). Endpoints for efficacy (≥10 mmHg reduction in SBP) and process (≥80% days adherent) were selected based on clinically meaningful thresholds derived from prior literature. For SBP, we wish to be able to detect a between-group difference in change in BP from baseline to 6 months of 10 mmHg. Assuming 232 intervention and 116 usual care participants with an evaluable endpoint, and a conservative standard error estimate of 28 mmHg,[94] we have approximately 88% power to detect a difference between groups of 10mmHg, using a two-sided, 0.05-level test; there is 80% power to detect a difference between groups as small as 8.9 mmHg. For the outcome of adherence (dichotomized at ≥80% adherent vs. <80% adherent), we will have 93% power to detect a 20% difference in adherence between groups, and 80% power to detect a 15% difference, assuming a baseline adherence rate in the control group of about 25%.

While every effort will be made to minimize missing data, procedures have been designed to handle missing data. We will compare participants with missing and complete data to identify characteristics that contribute to missing data. Missing outcomes of the primary efficacy endpoint will be imputed with multiple imputations using baseline information to predict missing values. We will conduct sensitivity analyses incorporating different assumptions about missing data mechanisms to enable assessment of the robustness of results.

6.4.3 Planned Analyses

Primary and secondary clinical endpoints:

1. The primary endpoint (efficacy) is reduction in mean systolic BP (SBP) between baseline and 6 months. The primary endpoint (process) is antihypertensive adherence between baseline and 6 months. Both endpoints will be evaluated after completion of the incentive lottery, which will take place for a duration 6 months.

2. Additionally, we will evaluate maintenance of mean SBP reduction (Aim 2A) and antihypertensive adherence (Aim 2B) between 6 and 12 months.

3. The engagement endpoint (Aim 3) addresses patterns of adherence (e.g., improving adherence, deteriorating adherence, sustained non-adherence) among participants assigned to receive the study intervention.

Primary endpoint analysis.

Aim 1A: To test the effect of a lottery incentive program on change in SBP of ≥10 mmHg from baseline, measured at 6 months. We will compare the change in SBP between groups by calculating difference scores for each participant and comparing the intervention and usual care groups with an independent groups t-test allowing for unequal variances. We will also regress 6-month BP on a binary indicator of treatment group, with adjustment for baseline BP and the stratification factor (clinic specialty). While randomization should obviate the need for additional adjustment, we will explore whether adjustment for participant-level characteristics (e.g., race, ethnicity, sex) is necessary, using the change-in-estimate criterion.[79,80]

Aim 1B: To test the effect of a lottery incentive program on antihypertensive adherence, defined as ≥ 80% of days covered (assessed by EMD), measured at 6 months. We will summarize antihypertensive adherence using the scheduling adherence metric (days in which a patient takes his/her medication as prescribed divided by the total number of days that s/he is expected to take them in that period). For the primary outcome, we will classify participants in the intervention and control arms as adherent versus nonadherent based on this 80% threshold (i.e., total number of days adherent divided by 183 days). We will use the chi-squared test to evaluate differences between groups. As in Aim 1A, we will explore whether adjustment for participant-level characteristics is necessary despite randomization, and if necessary fit logistic regression models for the binary outcome of "adherent" at the level of ≥ 80%. We will also explore different thresholds for "adherent" (e.g., (≥ 60%) in sensitivity analyses.

Because we will also collect daily adherence information from participants in both arms using the Adheretech EMDs, we will take advantage of the granularity of these data and undertake longitudinal modeling of adherence. We will calculate a weekly adherence rate, ranging from 0 (zero days adherent out of seven) to 1 (seven days adherent out of seven). We will fit longitudinal generalized linear mixed models using these repeated assessments.[81] The models will include fixed effects for time; these could take the form of a linear effect, a polynomial model (e.g., including terms for time and time^2), a piecewise model allowing different shapes in different time periods (e.g., a different slope in the first three months and the second three months), or a completely unspecified model using indicator variables for each assessment to allow for the most flexibly shaped trajectories. We will include an indicator of treatment arm, as well as interaction terms between the time effects and the treatment indicator; these interaction terms will afford a procedure for testing whether the trajectory of adherence over time differs between the intervention and control groups. These models include random effects for individuals, to accommodate the correlation of repeated assessments over time within the same patients, and also allow additional adjustment, using fixed effects, for stratification factors or other characteristics that may be unbalanced despite randomization. These analyses will help us understand the trajectories of adherence over time and lay the groundwork for the trajectory modeling proposed in Aim 3.

To assess whether intrinsic motivation serves as a mediator of our intervention effect, we will estimate a just-identified path model[82] using the robust weighted least squares estimator that examines changes in patients' autonomous and controlled motivation at 6 months. Based on our conceptual model (Figure 1), we will test the direct effects from the theoretical constructs of autonomous and controlled motivation (measured via the TSRQ) to the adherence proportion. In addition to the direct effects, the indirect effects of autonomous and controlled motivation to SBP via adherence will be estimated as the product of component direct effects and tested using bootstrapped 95% confidence intervals. Finally, we will estimate the direct effects of the predicted model of adherence on SBP reduction. We will take similar steps with the MASES to determine whether self-efficacy serves as a mediator of the intervention effect.

Aims 2A and 2B: Analysis of these Aims, which test the durable effect of the lottery program after cessation (6 to 12 months) on BP and adherence respectively, will proceed in a similar manner to Aims 1A and 1B. We will fit longitudinal mixed effects models of the three repeated SBP measures (baseline, 6 months, 12 months), modeling time using indicator variables, or using piecewise linear splines to allow differential rates of change from baseline to 6 months and from 6 months to 12 months. To examine durable effects of the incentive lottery on intrinsic motivation, we will assess

trajectories of TSRQ from baseline to 6 months and from 6 months to 12 months between the two treatment arms. Interaction terms between randomized arm assignment and time effects will address the hypothesis of differential patterns over time between arms. As with the mixed effects models described above, we will include random individual effects to accommodate natural positive correlation among repeated SBP measures within an individual participant.

Aim 3: To examine differing patterns of adherence among participants assigned to the intervention group. We hypothesize that: (1) there will be distinct trajectories of adherence (e.g., improving adherence, deteriorating adherence, sustained non-adherence); and (2) there will be significant engagement differences among groups. We will test whether the following characteristics are significant: age (≥65 years), sex, race/ethnicity, motivation (based on TSRQ), self-efficacy (based on MASES), comorbidity burden, and depressive symptoms. We selected these factors based on literature related to medication adherence.[21,83—86] We will conduct latent class analysis[87] to identify profiles of adherence and explore whether these factors indicate membership in a class; these models use maximum likelihood estimation, implemented with the iterative EM algorithm,[88] to identify a latent class solution for the set of indicators. We will evaluate model fit using the G^2 statistic[89]and compare models with the likelihood-difference test for nested models and the Akaike and Bayesian information criteria (AIC, BIC)[90,91] for non-nested models. While we have identified four potential classes a priori, we will use the parametric bootstrap likelihood ratio test[92] to select the optimal number of classes supported by the data in conjunction with the AIC and BIC. The output of the model will be a set of "item-response" probabilities giving the likelihood of a particular characteristic within each latent class, and a set of posterior predicted probabilities of latent class membership; uncertainty in predicting class membership will be summarized using the odds of correct classification (OCC) diagnostic tool.[93]

All comparisons between the randomized groups in this trial will be performed according to the principle of "intention-to-treat;" that is, participants will be analyzed according to the treatment group to which they were randomized, regardless of receipt of the actual intervention. We note, however, that it will be impossible for participants assigned to the control arm to have access to the lottery intervention; participants assigned to the lottery intervention, however, may not engage with the program. The intention-to-treat (ITT) population will include all subjects who are randomized to one of the two study conditions, except for those found subsequently to have a documented violation of trial eligibility criteria.

6.4.3.1 Primary Analyses

The primary study outcome is systolic blood pressure (SBP), assessed as follows. Three seated blood pressure (BP) assessments will be measured after a rest period (5 minutes) using an automated device (Omron, Lake Forest, IL) which will reduce the potential for observer bias. Manual BP will be recorded if an automated device fails or is unavailable. While the primary endpoint is SBP, diastolic BP and pulse will also be recorded for exploratory analyses.

We will compare the change in SBP between groups by calculating difference scores for each participant and comparing the intervention and usual care groups with independent groups t-test allowing for unequal variances. We will also regress 6-month BP on a binary indicator of treatment group, with adjustment for baseline BP and the stratification factor (clinic specialty). While randomization should obviate the need for additional adjustment, we will explore whether adjustment

for participant-level characteristics (e.g., race, ethnicity, sex) is necessary, using the change-in-estimate criterion.

6.4.3.2 Secondary Objectives Analyses

The secondary study endpoint is adherence, measured continuously using the Adheretech wireless EMD, which transfers data via cellular network to a secure web portal on a daily basis. Data are viewable on the Adheretech dashboard, including daily adherence and timing of doses. We will define adherence using the scheduling adherence metric, which is the proportion of days on which a patient takes his/her medication as prescribed divided by the total number of days that s/he is expected to take them in that period. Detailed records of all patient emergency room visits and hospitalizations will be kept and accounted for in the analyses.

We will summarize antihypertensive adherence using the scheduling adherence metric (days in which a patient takes his/her medication as prescribed divided by the total number of days that s/he is expected to take them in that period). For the primary outcome, we will classify participants in the intervention and control arms as adherent versus nonadherent based on this 80% threshold (i.e., total number of days adherent divided by 183 days). We will use the chi-squared test to evaluate differences between groups. We will explore whether adjustment for participant-level characteristics is necessary despite randomization, and if necessary fit logistic regression models for the binary outcome of "adherent" at the level of ≥ 80%. We will also explore different thresholds for "adherent" (e.g., (≥ 60%) in sensitivity analyses.

Because we will also collect daily adherence information from participants in both arms using the Adheretech EMDs, we will take advantage of the granularity of these data and undertake longitudinal modeling of adherence. We will calculate a weekly adherence rate, ranging from 0 (zero days adherent out of seven) to 1 (seven days adherent out of seven). We will fit longitudinal generalized linear mixed models using these repeated assessments. The models will include fixed effects for time; these could take the form of a linear effect, a polynomial model (e.g., including terms for time and time), a piecewise model allowing different shapes in different time periods (e.g., a different slope in the first three months and the second three months), or a completely unspecified model using indicator variables for each assessment to allow for the most flexibly shaped trajectories. We will include an indicator of treatment arm, as well as interaction terms between the time effects and the treatment indicator; these interaction terms will afford a procedure for testing whether the trajectory of adherence over time differs between the intervention and control groups. These models include random effects for individuals, to accommodate the correlation of repeated assessments over time within the same patients, and also allow additional adjustment, using fixed effects, for stratification factors or other characteristics that may be unbalanced despite randomization. These analyses will help us understand the trajectories of adherence over time and lay the groundwork for the trajectory modeling.

To assess whether intrinsic motivation serves as a mediator of our intervention effect, we will estimate a just-identified path model using the robust weighted least squares estimator that examines changes in patients' autonomous and controlled motivation at 6 months. We will test the direct effects from the theoretical constructs of autonomous and controlled motivation (measured via the TSRQ) to the adherence proportion. In addition to the direct effects, the indirect effects of autonomous and controlled motivation to SBP via adherence will be estimated as the product of component direct effects and tested using bootstrapped 95% confidence intervals. Finally, we will estimate the direct

effects of the predicted model of adherence on SBP reduction. We will take similar steps with the MASES to determine whether self-efficacy serves as a mediator of the intervention effect.

6.4.3.3 Analysis of Subject Characteristics

We will test whether the following characteristics are significant: motivation, self-efficacy, age (≥65 years), sex, race/ethnicity, comorbidities, patient-reported health status, depressive symptoms, and medication burden. These factors have been chosen based on literature related to medication adherence. Latent class analysis will be conducted to identify profiles of adherence and explore whether these factors indicate membership in a class; these models use maximum likelihood estimation, implemented with the iterative EM algorithm to identify a latent class solution for the set of indicators. We will evaluate model fit using the G^2 statisticand compare models with the likelihood-difference test for nested models and the Akaike and Bayesian information criteria (AIC, BIC) for non-nested models. While we have identified 3 potential classes a priori, we will use the parametric bootstrap likelihood ratio test to select the optimal number of classes supported by the data in conjunction with the AIC and BIC. The output of the model will be a set of "item-response" probabilities giving the likelihood of a particular characteristic within each latent class, and a set of posterior predicted probabilities of latent class membership; uncertainty in predicting class membership will be summarized using the odds of correct classification (OCC) diagnostic tool.

6.4.3.4 Interim Analysis

There are no formal interim statistical analyses planned. The goal of the intervention (improved BP control) has known benefits; the novelty of our trial is the delivery system for the intervention, which we anticipate will only have the (relatively low) risk of adverse events associated better with adherence.

6.4.3.5 Health economic evaluation, if applicable

There are no planned analyses to assess the health economic impact of the study.

6.4.3.6 Other

No other special analyses will be performed.

6.4.4 Subsets and Covariates

No analyses of subsets and covariates are planned.

6.4.5 Handling of Missing Data

While every effort will be made to minimize missing data, we have procedures in place to handle missing data. Rules for missing values will be discussed in appropriate places in the analysis plan below. In general, all available data will be included in data listings and tabulations. Population denominators will be displayed in column headers. Individual denominators will be displayed for each summary such that the amount of missing values will be evident. Patients who withdraw from the study or are lost to follow-up will still be included in the denominators for any proportions where data are available. We will compare participants with missing and complete data to identify characteristics that contribute to missing data. Whenever possible, the reason for missing data will be captured to inform possible approaches to imputation and/or sensitivity analyses. Missing outcomes of the primary efficacy endpoint will be imputed with multiple imputation using baseline information to predict

missing values. We will conduct sensitivity analyses incorporating different assumptions about missing data mechanisms to enable assessment of the robustness of results.

7 Trial Administration

7.1 Ethical Considerations: Informed Consent/Assent and HIPAA Authorization

Consent forms will be Institutional Review Board (IRB)-approved and the participant/legally authorized representative (LAR) will be asked to read and review the document. The research coordinator will explain the research study to the participant and answer any questions that may arise. This conversation will take place in a private room.

Participants/LAR will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants/LAR should have the opportunity to discuss the study with their family or surrogates, or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants/LAR must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants/LAR for their records.

Assent will not be obtained. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants.

Our research involves no more than minimal risk. Due to the study design that will require initial screening through the EHR system to identify eligible participants, the research coordinator will screen medical records for eligibility criteria only, preserving confidentiality by not recording any of the 18 identifiers restricted under HIPAA in the screening form. A unique study-specific ID will be used and no PHI will be recorded by the research coordinator on the screening form prior to obtaining consent. Basic, non-identifying demographic data of patients screened and not enrolled will be recorded and stored in REDCap, a password protected IRB approved database on a secure NYUSOM server, maintained and protected by the IT Department and Medical Center firewall. Due to the volume of patients having a diagnosis of hypertension, it is not feasible nor practical to approach and obtain HIPAA authorizations from all participants to review medical record information for screening purposes. It is not feasible to conduct the study with only provider referral, as physicians are busy and waiting for referrals may lead to unidentified eligible patients. While there is no more than minimal risk of loss of confidentiality, the benefits of the study far outweigh the risks.

A Waiver of HIPAA Authorization granted by the NYU Langone IRB will be used to conduct standard screening and recruitment procedures outlined in section 6.3.3 at both Bellevue and Gouverneur NYC H+H Hospitals.

Whenever appropriate, the subjects will be provided with additional pertinent information.

7.2 Institutional Review Board (IRB) Review

The protocol will be submitted to the IRB for review and approval. Approval of the protocol must be obtained before initiating any research activity. Any change to the protocol will require an approved IRB amendment before implementation. The IRB will have final determination whether informed consent and HIPAA authorization are required.

A study closure report will be submitted to the IRB after all research activities have been completed.

Other study events (e.g. data breaches, protocol deviations) will be submitted per New York University Langone Medical Center's IRB's policies.

7.3 Subject Privacy, Confidentiality & Data Management

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s)/funding agency. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval.

All research activities will be conducted in as private a setting as possible.

Representatives of the Institutional Review Board (IRB), regulatory agencies or study sponsor/funding agency may inspect all documents and records required to be maintained by the investigator for the participants in this study. The study site will permit access to such records.

The study participant's contact information will be securely stored at the study site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, regulatory, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored into a secure Research Electronic Data Capture (REDCap) database created by NYU DataCore in the NYU Translational Research Building. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used will be secured and password protected. At the end of the study, all study databases will be de-identified and archived into a secure Research Electronic Data Capture (REDCap) database created by NYU DataCore in the NYU Translational Research Building.

7.4 Deviations/Unanticipated Problems

A protocol deviation is any noncompliance with the clinical trial protocol. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site investigator to identify and report deviations within 5 working days of identification of the protocol deviation. All deviations must be addressed in study source documents, reported to the study sponsor, and the reviewing Institutional Review Board (IRB) per their policies.

Unanticipated problems involving risks to participants or others include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.5 Data Collection

Data collection will take place by research coordinators under supervision of the Principal Investigator, who will ensure the accuracy of all data reported. All data elements collected directly by the research coordinators from study participants will be entered through the Way to Health portal. These elements include blood pressure recordings and participant-administered survey instruments (e.g., TSRQ, MASES, PHQ-8). Adherence data from AdhereTech will also synchronize with Way to Health. Way to Health servers are managed by Penn Medicine Academic Computing Services (PMACS), and all data are assumed to be electronic protected health information (ePHI). Multiple steps are in place to ensure security including encryption of data in-transit and at-rest, as well as audit logging and access monitoring. For purposes of analysis, Way to Health data will be merged with NYC-H+H ambulatory data (medications, laboratory values, hospital admissions) by NYU Langone Health DataCore, which will maintain the final analytic dataset.

No PHI will be collected through the intervention platforms or the mobile device. Patients will be provided with a random study number that is linked to a master file in the core dataset, therefore ensuring confidentiality of data from devices. All data obtained from the intervention platforms will be initially stored in a secure HIPAA-compliant cloud-based platform provided by its respective companies (Way to Health and AdhereTech) and later securely transferred to research staff at NYU for storage in the REDCap database.

All study participants in the intervention arm will be advised during the consenting process to only use the provided study device (if applicable) for research-related purposes only in order to prevent leakage of PHI-related data.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by NYU IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the NYU Translational Research Building in password-protected computers and physically locked in cabinet files at the desks of the research coordinator. The study data entry and study management systems used by clinical sites and by NYU Langone Medical Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NYU Langone Medical Center.

To further protect the privacy of study participants, a Certificate of Confidentiality will be obtained from the NIH. This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

7.6 Data Quality Assurance

QC procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP).

The investigational site will provide direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing and inspection by local and regulatory authorities.

7.6.1 Quality Assurance Plan- Way to Health

Background

On 9/29/20, we discovered that 5 out of 11 trial participants in the intervention arm received a series of incorrect text messages from our software vendor, Way 2 Health (WTH). As an example, if a patient was nonadherent with their medication, they may have received a text message stating that they were actually adherent (and eligible for lottery winnings). We discussed this error on a conference call with WTH on 10/13/20, for purposes of root cause analysis. In summary, their software was not programmed to deliver the lottery correctly after 28 days, since it was still in test phase. Therefore after 28 days, random text messages were delivered. This error has been corrected by WTH moving forward. We agreed that better communication at the time of study launch could have prevented this issue from happening. In addition, after presenting our findings to the BETTER-BP DSMB on 10/15/20, the DSMB recommended we come up with a formal Quality Assurance Plan to monitor fidelity of intervention delivery (detailed below).

Purpose

The purpose of the Quality Assurance Plan is to establish quality management guidelines for WTH moving forward. The quality assurance plan will outline the ongoing processes that will be used to monitor performance of delivery of text messages from WTH to study participants.

I. Way to Health (WTH) Information

WTH is a software platform utilized for the BETTER-BP Trial (s19-00952). The technology platform utilizes a lottery incentive program that has the ability to deliver behavioral health interventions on electronic devices (cellphones). Only intervention participants receive SMS text messages, although WTH will be also used for study administration tasks (e.g., adherence data integration) in both the intervention and control arms. Text messages will be delivered to participants in their primary language (English or Spanish).

II. QA Schedule

Rigorous quality reviews will be conducted bi-weekly until the first enrolled participant reaches 6-month milestone. Following this period, quality reviews will be done quarterly to ensure compliance of study protocol.

Specifically, on a biweekly basis, a BETTER-BP research coordinator (RC) will review each enrolled participants' profile on WTH dashboard and review WTH text messages delivered. The RC will ensure that the messages match adherence data from AdhereTech electronic monitoring device.

The RC will create a Quality Assurance (QA) log documenting the review process and verifying that all text messages are in accordance with adherence data from AdhereTech dashboard. QA logs will be stored in study regulatory binder housed in a locked study cabinet as well as the digital regulatory binder located in secured research shared drive, (R: BETTER-BP). RC performing QA check will initial after every review certifying completion of assessment.

If any discrepancies are found, the RC will report errors to WTH within 24 hours of discovery. The RC will create a table listing participants affected, date improper message was received, and text message they should have received. This table will be emailed to pertinent study staff as well as WTH team in order to expedite corrective action plan. Lastly, per NYU Institutional Review Board (IRB), deviations will be reported during the next scheduled continuing review submission.

These data will also be presented to the DSMB at the next scheduled call.

III. Additional QA Activities

A. Meetings

Study team will meet weekly to discuss any findings resulted from the QA check. The site staff will determine actions to be taken and implement corrective action plan, if needed.

B. Use of checklists

RCs will create and use checklist to assure each subject has been carefully reviewed. Checklist will serve as another safety net to help RC certify and document that participants are receiving correct text messages via Way to Health Platform. Checklists will be housed under BETTER-BP R: Shared Drive. This checklist will be ceased once the first enrolled participant reaches their 6-month follow up.

C. Monthly Clincard Payment Distribution

Lottery winnings are distributed to intervention participants on a monthly basis. This checkpoint will be another opportunity to verify accuracy of WTH text messages delivered. The RC will perform a thorough check utilizing both WTH and AdhereTech dashboards to verify that text messages are in accordance with monitored daily adherence. Upon verification, RC will disperse lottery winnings to participants ClinCard. Should there be any discrepancies, RC will create a note-to-file and notify Way to Health's support center at support@waytohealth.org or utilize their portal at https://support.waytohealth.org.

7.7 Study Records

The research material will be the prospectively collected data from described study procedures comprised of informed consent forms, clinical data collection, questionnaires, and physiological data recordings collected from each participant. Additionally, regulatory documents, including the study protocol and case report forms (and electronic case report forms), will also be considered research material.

7.8 Access to Source

For intervention participants, data on adherence via the study devices and platform (AdhereTech and Way to Health) will initially be stored in a secure HIPAA-compliant cloud-based platform provided by AdhereTech and Way to Health, which has been previously used in both clinical and research settings. For analytic purposes, these data will then be securely transferred to staff at NYU Langone Health DataCore.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study by the research coordinator. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record by the research coordinator and project coordinator. Clinical data (including AEs, concomitant medications, and expected adverse reactions data) will be entered into REDCap, a 21 CFR Part 11-compliant data capture system provided by the NYULH DataCore. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

7.9 Data Storage/Security

All records with identifying information for NYU participants will be kept in a locked cabinet in the office of the contact Principal Investigator or as a password-protected file on the secure NYU network or in a password protected computer. For intervention participants, data on adherence will initially be stored in a secure HIPAA-compliant cloud-based platform provided by AdhereTech and Way to Health, which has been previously used in both clinical and research settings. For analytic purposes, these data will then be securely transferred to staff at NYU Langone Health DataCore.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) will be entered into REDCap, a 21 CFR Part 11-compliant data capture system provided by the NYULH DataCore. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

7.10 Retention of Records

Study documents will be retained for the longer of 3 years after close-out, 5 years after final reporting/publication, or 2 years after the investigation is discontinued. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

7.11 Study Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of

the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

- At the NYU site, the contact Principal Investigator (PI), Dr. Dodson, will be responsible for ensuring participants' safety through targeted random review on a monthly basis throughout the study period.
- Independent audits will be conducted by the DSMB to ensure monitoring practices are performed consistently across all participating sites.

The Principal Investigator, Dr. Dodson, will be responsible for ensuring participants' safety on a daily basis. The DSMB will act in an advisory capacity to the NHLBI Director to monitor participant safety; evaluate the progress of the study; and review procedures for maintaining the confidentiality of data, the quality of data collection, management, and analyses.

Establishment of a DSMB will be achieved for the study. Four members will be identified (3 cardiologists and 1 biostatistician) and subsequently reviewed by the NHLBI for approval. Should there be any questions regarding the independence of the safety officer, they will be addressed and corrected if necessary at that time.

Safety reports are sent to the DSMB twice a year and will include a detailed analysis of study progress, data and safety issues.

The content of the safety reports will include:

- A detailed accrual report, by hospital and month of enrollment
- A detailed disposition report, listing the number of participants at various stages of the study protocol (e.g., screening, enrollment, follow-up, completed)
- A listing of all AEs and SAEs by intervention arm

7.12 Dissemination of Decision by DSMB

The Chairman of the DSMB will send a communication by email containing its recommendations to the Principal Investigator (Dr. Dodson) within 14 days after each meeting. The Principal Investigator will then communicate the decision from the DSMB to the IRB within 24 hours.

7.13 Study Modification

At the time of study modification, the research coordinator, with the approval by the Principal Investigator, will submit the modification to the NYU IRB. The protocol will be updated accordingly within the next 36 hours of the decision and submitted with the modification to the IRB. Once approval by the IRB is obtained, the study team can then implement the modification effective immediately.

7.14 Study Discontinuation

Recommendations for stopping of the trial due to evidence of benefit or harm will be based on statistical guidelines specified before the start of the trial and other internal and external factors considered relevant by the Committee members.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants

  - Major risks include fall-related injury requiring medical care (inpatient hospitalization) that occurs during study-directed exercise, hospitalization for acute coronary syndrome, or hospitalization for unstable arrhythmia.

- Demonstration of efficacy and engagement that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Recommendations for stopping of the trial due to evidence of futility will not be based on pre-specified criteria, but rather will be based on a consensus that a combination of recruitment shortfall and/or other problems with adherence to the study protocol have created a situation in which the likelihood of successful assessment of the study aims is very low and not amenable to remediation through revision of the study protocol.

A decision to override the pre-specified stopping points must be based on a sound scientific analysis derived from internal or external data (e.g., ethical, statistical, practical, or financial) that provides a clear rationale for study continuation and must be unanimously approved by all DSMB voting members. After appropriate discussion, the Chairperson will summarize and encourage a consensus opinion.

7.15 Study Completion

The study is expected to complete in July 2024. A study closure report will be submitted to the IRB after all research activities have been completed.

7.16 Conflict of Interest Management Plan

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership in conjunction with the appropriate conflict of interest review committee has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by The Conflicts of Interest Management Unit at NYU Langone Health with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All investigators will follow the applicable conflict of interest policies.

7.17 Study Finances

7.17.1.1 Funding Source

Salary support for this study is provided by the National Institutes of Health - National Heart, Lung, and Blood Institute.

7.17.1.2 Participant Reimbursements

Participants, intervention and control group, will be provided compensation (via ClinCard) at the time of the following follow up visits due to the cost for time and travel spent by the participant:

- $50 at Baseline
- $50 at 6 Months
- $50 at 12 Months

Payments will be disbursed through ClinCard, a payment card that will be provided for participants by the research coordinator after completion of the baseline assessments during the first visit.

In addition, study equipment will be provided to participants at no charge, and a toll-free number will be provided to reach the research coordinator for ongoing communication as necessary. There are no anticipated out-of-pocket costs for participants using the Way to Health platform.

7.18 Publication Plan

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

FDAAA mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials":

- Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations of a product subject to FDA regulation;
- Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric postmarket surveillance studies.
- NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA.

7.19. Notification of Clinical Team in the Event of Depressive Symptoms.

The BETTER-BP study aims to improve adherence to antihypertensive medications prescribed by patients' clinicians (for practical purposes given enrollment sites, this will be a primary care physician or cardiologist). The baseline screening instrument includes a variety of questionnaires intended to

understand variations in responsiveness to the study intervention. One of these instruments, the PHQ-8, identifies depressive symptoms. Since patients' clinicians may be unaware of the presence of depression that is identified by the study, we believe that ethically they should be made aware, as this may influence therapeutic decisions (e.g. referral to psychotherapy or prescribing of antidepressants).

Accordingly, for study participants who score ≥10 on the PHQ-8 (considered positive for depression based on the original description of the instrument),[59] their primary care physician or cardiologist (depending on clinic of enrollment) will be notified by the study research coordinator through the electronic health record. Further management of depressive symptoms will be at the discretion of the primary care physician or cardiologist.

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9 Appendices

Study Flow Chart