Application for Review of Human Research: IRB Protocol Summary
Biomedical Research **Section II**

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PROTOCOL TITLE

1. Full Title
Connected Health Blood Pressure Monitoring In Stroke and TIA Patients

2. Brief Title
Connected BP Study

STUDY SPONSORSHIP

1. Funding Sponsor
Penn Medicine Center for Healthcare innovation

2. Primary Sponsor

Study Summary

The goal of this pilot project is to assess adherence with home blood pressure monitoring in hypertensive patients with a history of stroke and to determine if a social incentive improves adherence with monitoring. Enrolled subjects stroke (Ischemic stroke, intraparenchymal hemorrhage, or high-risk TIA)and uncontrolled blood pressure, defined by SBP>140 or DBP>90 mm Hg at the time of study screening. To be eligible subjects will also be required to own a smart phone (iOS or Android operating system). After enrollment, patients will be given a home blood pressure cuff with instructions to monitor their BP twice daily for 90 days. Subjects will be randomly assigned to a social incentive program, in which a social supporter receives updates via email and/or text message on the subject's adherence with BP monitoring and their average blood pressure. This study will provide important pilot data which will inform the design of future studies utilizing connected health and automated systems to improve home blood pressure monitoring and blood pressure control in patients with a history of stroke.

1. STUDY OBJECTIVES

1.1 Primary Objective

The primary objective of this pilot study is to quantify adherence to 90 days of home blood pressure monitoring and to determine if a social incentive improves adherence.

1.2 Secondary Objective

A secondary objective of this study is to determine if adherence with blood pressure monitoring is associated with change in blood pressure during the study period and to determine which individual factors are associated with adherence.

2. OUTCOME VARIABLES

2.1 Primary Endpoint

Adherence with home blood pressure monitoring, defined by the proportion of home blood pressure recordings successfully completed.

2.2 Secondary Endpoints

Secondary endpoints include the following:

- Change in blood pressure over the 90 day study period
- Number of physician visits
- Number of emergency department visits
- Number of phone calls to the study team
- Number of changes in antihypertensive medications (dose adjustment or addition of a new agent)
- Patients perception of blood pressure monitoring device ease of use
- Patients perception of the utility of blood pressure monitoring
- Patients perception of blood pressure control

3. BACKGROUND

Stroke is the fourth leading cause of death and a leading cause of adult disability in the US, with over 800,000 cases per year.[1] Total direct and indirect costs from stroke are expected to increase from 72 Billion in 2012 to 183 Billion in 2030.[2] Effective secondary prevention strategies exist, including blood pressure control, high dose statin therapy, smoking cessation, diet, and exercise. The goal of this proposal is to perform important preliminary work on the feasibility of connected health and behavioral/social incentives to improve blood pressure control in patients with TIA or stroke.

Hypertension is by far the most significant risk factor for both ischemic stroke and intracerebral hemorrhage, with a population attributable risk of 35 to 75% depending on the definition of hypertension used.[3] Approximately half of hypertensive patients with stroke continue to have suboptimally controlled blood pressure levels, and prior work suggests that stroke patients are even less likely to achieve target blood pressure goals than patients with coronary artery disease.[4] Importantly, treatment to lower blood pressure reduces future stroke in those with and without a prior history of stroke.[5-7] In a study of 227 ischemic stroke patients with symptomatic intracranial stenosis and a median follow-up of 32 months, 17% of subjects who achieved a systolic blood pressure of <140 (or <130 for diabetics) had a recurrent stroke, MI, or vascular death, compared to 29% in patients who did not achieve goal blood pressure.[8] All of these 227 patients were all enrolled in a clinical trial and were receiving protocol driven intensive medical therapy to optimize risk factor control. Despite this, only 121 of 227 (53%) reached their goal blood pressure.

Non-adherence to prescribed medications has been proposed as one major reason for suboptimal blood pressure control.[9] In one study of 4068 elderly subjects with hypertension, antihypertensive prescriptions were filled for only 49% of the prescribed medication days, and only 23% of subjects had good compliance (defined as taking > 80% of their recommended medication regimen).[9] Additionally, lack of insight into the benefit of aggressive blood pressure control, lack of awareness of actual blood pressure levels, and lack of effective strategies for triggering more intensive therapy for both patients and providers may all be important.[10]

One prior study compared home blood pressure monitoring with intermittent nurse support to usual care in patients with recent stroke.[11] At 12 month follow-up, more patients in the intervention group had changes to their antihypertensive therapy (60% vs. 48%, p=0.02), but there was no overall difference in change in mean systolic blood pressure from baseline to 12 month measurements. This study was limited in that the incentive (nursing support) is relatively resource intensive, patient report was used to assess compliance rather than automated device recording, and blood pressure was checked infrequently (weekly).

The proposed study builds on existing literature in several unique and important ways. First, the blood pressure monitor used in this study is a commercially available unit that will interact with the subject's smart phone. Software that comes with the device will allow the subject to track their own blood pressure. Blood pressure will be checked more frequently (twice daily). Finally, the incentive used in this study will provide real time feedback to the subject and to a social supporter that they identify, in an effort to improve adherence.

4. CHARACTERISTICS OF THE STUDY POPULATION

4.1 Target Population

Adult subjects with a history of acute ischemic stroke, intraparenchymal hemorrhage, or high risk transient ischemic attack (TIA) and uncontrolled hypertension, defined by SBP>140 mm Hg or DBP > 90 mm Hg.

4.2 Accrual

The study will enroll a total of 90 patients at the Hospital of the University of Pennsylvania (HUP).

The study will be powered on the primary objective of the study, which is to compare adherence with twice daily blood pressure monitoring in subjects with and without a social incentive. Based on data in other study populations, we expect a 50% adherence rate in subjects without a social incentive.

A sample size of 90 subjects will provide 80% power to detect a 30% difference in adherence between groups. This calculation is based on a two-sample comparison of means, with alpha=0.05.

Patients will be identified from the inpatient stroke service and the outpatient neurology clinic at the Hospital of the University of Pennsylvania. It is expected that we will complete enrollment in 15 months and the study will be completed in 2 years.

4.3 Inclusion Criteria

1. Adult, age ≥ 18 years
2. History of ischemic stroke, intraparenchymal hemorrhage, or high risk TIA (defined by ABCD2 ≥ 4) with the past 5 years prior to enrollment
3. Hypertensive at time of screening, defined by SBP>140 mm Hg or DBP >90 mm Hg
4. Enrollment must occur within 30 days of study screening
5. Must own a smart phone capable of interacting with the connected blood pressure cuff (Apple iPhone 3GS or higher; Android 4.0 or higher with Bluetooth connectivity)
6. Must be able to identify at least one adult (≥18) with internet access and/or a smart phone with text messaging capability who could serve as a social support person.
7. Willingness and ability to sign informed consent by patient

4.4 Exclusion Criteria

1. Moderate or severe disability, defined by modified Rankin Scale ≥ 3.
2. Moderate or severe cognitive impairment, defined by a Mini-Mental Status Examination Score of ≤20
3. Expected residence in a rehabilitation hospital, nursing facility or assisted living community during the study period.
4. Upper arm circumference <9 inches or >17 inches
5. Inability to monitor BP in upper arms (i.e. history of bilateral radical mastectomy, bilateral severe subclavian stenosis, or bilateral arterial venous fistulas for dialysis).
6. Inability to follow-up at 90 days and return BP monitor
7. Active participation in another clinical trial
8. Pregnant women

4.5 Vulnerable Populations

Children, fetuses, neonates, prisoners and pregnant women are not included in this research study.

4.6 Subject Recruitment

4.6.1 Participant Screening and Recruitment

Potential study participants will be identified from the inpatient stroke service at the Hospital of the University of Pennsylvania and the outpatient neurology clinic at the Hospital of the University of Pennsylvania. Additionally, the neurology residents and the stroke physicians at the Hospital of the University of Pennsylvania will be

informed of the study and provided with contact info for study personnel to refer eligible outpatients. The attending physician caring for the patient will be informed of eligible patients prior to enrollment. Screening visits may include an inpatient admission for stroke or TIA or any routine outpatient clinic visits in which blood pressure is measured. Inpatients who are considered for the study can only be enrolled if they are being discharged to home, and enrollment should occur on the date of discharge. Patients discharged to an inpatient rehabilitation hospital or skilled nursing facility are excluded from participation.

4.6.2 Informed Consent

Informed consent must be obtained (completed online by the participant) prior to initiation of any study-related activity. Consent will be obtained via the Way to Health online platform. Way to Health is secure and HIPAA compliant.

4.6.3 Consent Process

After an eligible subject is identified, a member of the study team will contact the attending physician responsible for the patient's care to ensure that the patient is clinically suitable for the study. If so, the patient will be approached by a member of the research team for consent. The full consent form is enclosed as attachment 1. The consent form will be described to the patient in plain language. The patient will also be given a copy of the consent form for their reference. Electronic informed consent will be obtained via the Way to Health platform prior to the onset of any study related activities. The patient will have the ability to withdraw consent and exit the study at any time.

The physicians caring for the patient clinically will make judgments about capacity. All patients seen by neurology receive detailed neurologic examinations, which can be used to assess capacity. These examinations include an assessment of cognition, language function, and neglect/anosagnosia in addition to other domains of neurologic function. Additionally, the person obtaining consent will evaluate the subjects understanding of the risks/benefits of study participation by asking open-ended questions about the study and addressing any misperceptions or unanswered questions. Possible questions include: Can you describe the study in your own words? What more would you like to know? Would you please explain to me what we are asking you to do? What are your concerns? If a potential subject is not competent to consent for him or herself, they will be excluded from the study.

4.6.4 Waiver of Authorization

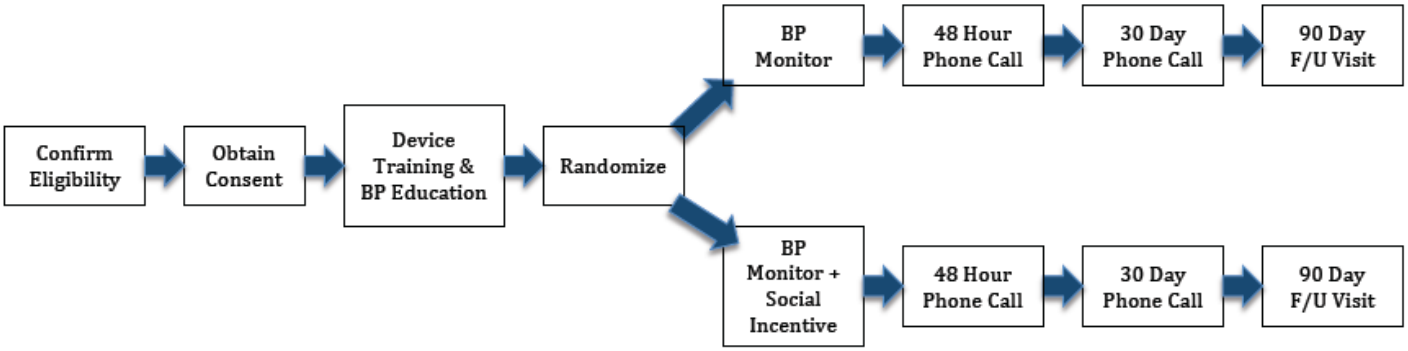
Not applicable

4.6.5 HIPAA Authorization

Following mandated federal HIPAA regulations and according to local IRB guidelines, the use and disclosure of the subject's protected health information (PHI) will be explained and participant authorization will be obtained as part of the informed consent process. The consent forms will list those individuals and organizations that may have access to the participant's research data. HIPAA authorization will be included in the informed consent process. The HIPAA authorization form is attached as a part of the informed consent form in attachment 1.

4.6.6 Patient Flow

A depiction of patient flow is presented below:



4.6.7 Follow-up Period

Participants will have a follow-up phone call at 48-72 hours after enrollment and either a phone or computer based encounter 30 days +/- 3 days after enrollment and an in-person visit at 90 days +/-7 days. Participation will be completed after the day 90 visit.

5. STUDY DESIGN

5.1 Phase

Phase 2 pilot trial.

5.2 Design

This is a single center randomized trial designed to assess the effectiveness of a social intervention to improve adherence with home blood pressure monitoring. Computer-based block randomization (block size=4) will be used to maintain relatively equal numbers of subjects in both arms of the study. This study will provide important preliminary data for future studies, which will use behavioral incentives to improve adherence to home blood pressure monitoring and titration of antihypertensive therapy.

5.3 Study Duration

Individual subjects will be in the study for a total of 90 days. They will receive a telephone call at 48 hours and either a computer based or telephone based interview at 30+/- 3 days and then will have an in-person visit at 90+/-7 days.

Total study duration is expected to last approximately 2 years. We expect to enroll about 6 subjects per month and should reach our target of 90 patients by 15 months. The final follow-up visit will occur 3 months after the last patient is enrolled. Data collection and analysis will be completed in the subsequent 6 months for total study duration of 24 months.

6. DRUGS OR DEVICES

All patients will receive a Withings wireless blood pressure monitor. This commercially available device measures heart rate and blood pressure. The device is operated by and communicates with both Apple and Android smart phones (Apple iPhone 3GS and newer, Android 4.0 and newer) via bluetooth. Blood pressure and heart rate readings will be automatically uploaded to Penn's *Way to Health* platform via the subject's smart phone. There are no risks associated with this device. All subjects will be instructed on the proper use of the device as well as best practices for measuring blood pressure at the time of study enrollment.

Way to Health is an integrated research platform that uses online tools to connect with and collect data from wireless devices. Blood pressure and heart rate data will be collected and stored in a secure, HIPAA complaint format. The platform will provide automatic reminders for all patients to use the blood pressure cuff twice daily. Additionally, the platform will automatically apply the social incentive to randomized subjects. The social incentive is described in more detail later (section 7.1).

7. STUDY PROCEDURES

7.1 ENROLLMENT

At the time of enrollment the following data will be collected: Age, sex, race, ethnicity, handedness (left arm dominate, right arm dominate), date of stroke, etiology of stroke (large vessel disease, small vessel disease, cardioembolic, other defined etiology, cryptogenic), past medical history (including prior history of: hypertension, diabetes, hyperlipidemia, atrial fibrillation, congestive heart failure, coronary artery disease and/or myocardial infarction, chronic kidney disease, peripheral artery disease, stroke prior to the enrolling event, and other), current medications, smoking history (current, former, never smoker), employment status (currently employed, disabled, retired), living situation (lives alone yes/no, if no, number of people and relationship of people living in the home), annual household income (<$20,000, $20,000-39,999, $40,000-64,999, $65,000-104,999, $105,000+), insurance status (private health insurance, medicare, medicaid, none), primary care provider (yes/no), cardiologist (yes/no), nephrologist (yes/no). We will also obtain contact information for follow-up phone calls and for scheduling the 90 day visit. Social security numbers will be collected for subject reimbursement purposes.

Figure 1. Modified Rankin Scale

Modified Rankin Scale
0 – No symptoms
1 – No disability; able to carry out all previous activities despite some symptoms
2 – Slight disability; unable to carry out all previous activities but able to look after own affairs
3 – Moderate disability; requires some help but able to walk unassisted
4 – Moderately severe disability; unable to attend to own bodily needs and unable to walk unassisted.
5 – Severe disability; requires constant nursing care and attention, bedridden.

Study Measurements at enrollment

1. Upper arm circumference. Measured using a tape measure in the mid-portion of the upper arm. Circumference <9” or >17” is an exclusion criteria.

2. Mini-Mental Status Examination (MMSE) – the MMSE is a brief, standardized cognitive assessment . Subjects will be excluded if they score ≤ 20 on the MMSE, which corresponds to moderate or severe dementia.

2. Modified Rankin Scale (mRS). The mRS is a 5 point scale which ranges from no disability to severe disability (figure 1). It is assessed using a brief, structured interview. Study personnel will be trained and certified in the use of the mRS. Subjects with mRS >2 are excluded.

3. National Institute of Health Stroke Scale (NIHSS). The NIHSS is a brief, structured neurologic examination, designed to assess deficits from stroke (figure 2). Study personnel will be trained and certified in the use of the NIHSS.

4. Heart Rate and blood pressure – Heart rate and blood pressure will be measured at least 30 minutes after exercise. The patient will have been sitting for at least 5 minutes before blood pressure is checked. The patient will be asked to sit in a chair with their back straight and supported and their feet flat on the floor. The arm will be supported on a flat surface at approximately the level of the heart. Blood pressure and heart rate will be assessed in the non-dominate arm using an

NIH Stroke Scale

1a. LOC
0 alert
1 drowsy ____
2 stuporous
3 coma
1b. LOC ?'s
0 both correct
2 incorrect ____
1c. LOC Commands
0 both correct
1 one correct ____
2 incorrect
2. Best Gaze
0 normal
1 partial gaze palsy ____
2 forced deviation
3. Visual Fields
0 no visual loss
1 partial hemianopasia ____
2 complete hemianopsia
3 bilateral hemianopsia
4. Facial Palsy
0 normal
1 minor ____
2 partial central
3 complete
5. Motor Arm
a. Left Arm
0 no drift
1 drift ____
2 cannot resist gravity
3 no effort against gravity
4 no movement
z amputation/joint fusion
b. Left Arm
0 no drift
1 drift ____
2 cannot resist gravity
3 no effort against gravity
4 no movement
z amputation/joint fusion
6. Motor Leg
a. Left Leg
0 no drift
1 drift ____
2 cannot resist gravity
3 no effort against gravity
4 no movement
z amputation/joint fusion
7. Limb Ataxia
0 absent
1 present in one limb ____
2 present in two limbs
8. Sensation
0 normal
1 partial loss ____
2 severe loss
9. Best Language
0 no aphasia
1 mild-mod aphasia ____
2 severe aphasia
3 mute
10. Dysarthria
0 none
1 mild-mod ____
2 severe/mute
z intubated
11. Extinction
0 no neglect
1 partial neglect ____
2 complete neglect

Total Score ____

Figure 2. NIH Stroke Scale

automated sphygmomanometer. This will be repeated for a total of three measurements, which will be averaged to determine the baseline blood pressure.

Education

At the time of enrollment, the patient will receive general education about hypertension, including proper technique for blood pressure measurement, goal blood pressure, and appropriate actions to take if blood pressure is severely elevated or abnormally low. Additionally patients will be educated on the proper use of the Withings Blood Pressure monitor. The appropriate software will be downloaded onto their smart phone and they will be supervised as they measure their own blood pressure with the device. Subjects will be encouraged to measure blood pressure in their non-dominate arm for ease of monitor placement. Subjects will be instructed to take their BP prior to or at least 2 hours after moderate or high intensity exercise. Subjects will be instructed to take their BP twice daily, once between 6:00am-11:59am and once between 4:00pm-9:59pm. Finally, patients will be enrolled onto the Way to Health platform and will choose whether they prefer to receive study communications via email or text message. The subject will also be given a telephone number that they may call if they encounter any technical difficulties with the Withings device.

Connected Health Monitoring

The Withings blood pressure cuff provides the subject with a graphical display of their blood pressure after it is measured as well as prior blood pressure readings. Blood pressure readings are color coded to indicate Normal blood pressure, mild, moderate, and severe hypertension. BP readings will be automatically uploaded form the subject's device to Way to Health. If subjects have not completed their morning BP check by 11:00am they will receive a reminder via their chosen form of communication (email or text). In the evening they will receive a reminder if they have not checked their BP by 9:00pm. In addition to the standard feedback provided within the Withings app, subjects will receive automated feedback from the Way to Health platform on a weekly basis. This message will contain the subject's mean blood pressure over the preceding 7 days. This message will also note whether the subject's blood pressure is above or below a goal of <140/90 mm Hg and will report their compliance with scheduled BP checks.

Social Incentive

Patients will be randomly assigned (1:1) to either receive a social incentive or not. The social incentive will require the subject to identify a social supporter. This individual can be a family member, friend, or other community member selected by the subject. The social supporter will need to assent to the study and register on the Way to Health platform. The social supporter will receive education on the importance of hypertension, how to measure blood pressure, and how to operate the Withings monitor. If the social supporter is not present at the time of subject enrollment, they may assent to the study via telephone and/or by registering online at the Way to Health platform. In this scenario they will receive education via telephone and/or online.

The social supporter will choose whether they prefer to receive study communications via text message or email. The social supporter will receive a text or email message alert at 11:00am if the subject has not completed their morning BP reading and at 9:00pm if the subject has not completed their evening BP reading. The social supporter will also receive feedback on the subject's BP control from the Way to Health platform on a weekly basis. This message will summarize the subject's adherence to home monitoring in the preceding 7 days. It will also contain the subject's mean BP over the preceding 7 days and note whether the subject's BP is above or below a goal of <!40/90 mm Hg. The expectation is that the social support person will provide further feedback to the subject in order to improve both adherence and BP control

Non-adherence

BP readings will be automatically uploaded from the subject's smartphone to the Way to Health platform. If the subject goes 7 days without a single BP measurement, Way to Health will alert study personnel. Study personnel will contact the subject by phone to remind them to check their BP and troubleshoot any potential technical

problems. If the subject indicated that they do not wish to continue BP monitoring, study alerts will be discontinued and the study team will setup a time for the subject to return the BP device. Even if the subject completely stops monitoring their BP, they will still remain in the study and be encouraged to complete the 30 and 90-day follow-up assessments. For analysis, if a subject completely stops BP monitoring, they will remain in the final analytic dataset but be considered "non-adherent" for the remaining study days (further details in section 8).

7.2 48 Hour Follow-up Phone Call

Enrolled subjects will be contacted at 48 hours +/- 24 hours after enrollment. The purpose of this call will be to ensure the subject is able to properly use the device. We will ask subjects if they have had any difficulty using the Withings blood pressure monitor or interacting with Way to Health. If the patient is having difficulty using either system, troubleshooting will occur via the telephone. If the issue cannot be resolved, the subject will be offered an additional in-person visit to trouble shoot the device and/or repeat device training. The subject will also be screened for adverse events during this telephone call.

7.3 30 Day Interview

Enrolled subjects will be contacted at 30 days +/- 3 days after enrollment via electronic messaging (text message and/or email). The subject will be asked to log into Way to Health and complete a short form. This form will screen for adverse events and collect 30 day outcome data. Blood pressure readings and adherence to twice daily blood pressure monitoring will be collected automatically via Way to Health and will not need to be assessed over the telephone. Secondary outcomes assessed will include:

- TIA or stroke since enrollment
- Number of physician visits since enrollment (Primary care, cardiology, other)
- Number of emergency department visits since enrollment and reason for each visit
- Number of changes in antihypertensive medications since enrollment (dose adjustment and/or addition of a new agent)
- Patients perception of blood pressure monitoring device and study protocol ease of use (very difficult, moderately difficult, mildly difficult, easy to use)
- Patients perception of the utility of blood pressure monitoring (very useful, moderately useful, mildly useful, not useful)
- Patients perception of blood pressure control (adequately controlled, not adequately controlled)

Subjects who do not complete the online form will be contacted by telephone in order to assess the same information.

7.4 90 Day Follow-up Visit

At 90 +/- 7 days from enrollment the subject will be seen for an in-person visit. They will be asked to return the blood pressure monitor at that time and be screened for adverse events. Outcomes will again be assessed. Blood pressure readings and adherence to twice daily blood pressure monitoring will be collected automatically via Way to Health and will not need to be assessed during this in-person visit. Secondary outcomes assessed will include:

- TIA or stroke since 30 day phone call
- Number of physician visits since 30 day phone call (Primary care, cardiology, other)
- Number of emergency department visits since 30 day phone call and reason for each visit
- Number of changes in antihypertensive medications since 30 day phone call (dose adjustment and/or addition of a new agent)
- Patients perception of blood pressure monitoring device and study protocol ease of use (very difficult, moderately difficult, mildly difficult, easy to use)

- Patients perception of the utility of blood pressure monitoring (very useful, moderately useful, mildly useful, not useful)
- Patients perception of blood pressure control (adequately controlled, not adequately controlled)

Heart rate and blood pressure will be assessed in the non-dominate arm using an automated cuff. This will be repeated 3 times and averaged to determine final blood pressure. The modified Rankin Scale and NIHSS will also be assessed, as described in section 7.1. Research personnel assessing both the mRS and the NIHSS will be trained and certified in its use. Finally, for each subject we will tabulate the number of telephone calls to the study team initiated by the subject and the purpose of the call (blood pressure reading high/low, technical difficulty with device, other).

7.5 Study Visits

Subject visits will follow a standard visit schedule:

	Eligibility Confirmation & Enrollment	48 +/- 24 Hours	Day 30 +/- 7	Day 90 +/-7
Screening	X			
Informed Consent	X			
Eligibility [Inclusion & Exclusion	X			
Blood Pressure	X			X
mRS	X			X
NIHSS	X			X
Outcomes	X		X	X
AE Screening		X	X	X

8. STATISTICAL ANALYSIS

Demographics and past medical history variables will be summarized for all subjects using means or medians as appropriate for continuous variables and proportions for categorical variables. We will compare the two study arms using Student's t-test or Wilcoxon rank sum as appropriate for continuous variables and χ^2 test for categorical variables.

The primary outcome measure is adherence with blood pressure monitoring during the study period. Adherence will be defined by dividing the number of successfully completed BP measurements (numerator) by the expected number of BP measurements (denominator). The expected number of BP measurements is the number of days that the subject is in the study multiplied by 2. Most subjects will be enrolled in the study for 90 days and will therefore be expected to check their BP 180 times. Adherence in this case is the number of completed BP measurements divided by 180. The 90-day follow-up visit has a window of +- 7 days, so for subjects that complete the study protocol the denominator will be adjusted accordingly. Subjects whom withdrawal from the study and/or stop monitoring their BP before the 90-day follow-up visit will remain in the analysis. These subjects will be considered non-adherent for all BP measurements after they cease taking measurements and the denominator will be set at 180. As an example, if a subject checks their BP 60 times in the first 75 days of the study and then ceases all BP measurements, adherence will be calculated as 60/180=33.3%. After adherence has been calculated for all subjects we will evaluate the distribution of adherence for normality and compare adherence between the two study arms using Student's t-test or Wilcoxon rank sum as appropriate. A sample size of 90 will give us 80% power to detect a 30% difference between groups with α=0.05.

Additional analysis will compare the change in blood pressure between the two groups. The mean systolic and diastolic blood pressure in the first 7 days of the 90 day study period and the last 7 days of the 90 day study period will be calculated for each subject. The average change in blood pressure will be compared between study arms using Student's t-test or Wilcoxon rank sum as appropriate. We will also compare the proportion of subjects with an average blood pressure <140/90 mm Hg in the final week of the study between groups using χ^2. Subjects who drop out of the study or cease monitoring their BP prior to day 90 will be included in these analyses if they have a minimum of 14 days of monitoring. For these subjects, we will utilize BP readings from the last 7 days of monitoring. The use of earlier readings carried forward should be conservative and bias the results toward the null. Exclusion of subjects with less than 14 days of monitoring may truncate our sample and introduce bias, so we will conduct a sensitivity analysis in which we impute a change in BP for subjects with less than 14 days of monitoring of zero.

We will compare secondary outcomes across study arms including number of calls to the study team, number of physician visits, number of emergency department visits, number of changes in antihypertensive medications, and the patient perception of: study protocol, utility of blood pressure monitoring, and blood pressure control. We will also determine the relationship between adherence to blood pressure monitoring and change in blood pressure during the study period. For this analysis, we will first determine the average adherence in the study population. We will compare the change in blood pressure in those with above average adherence to those with below average adherence. This will be done in the full study population and then stratified by study arm. In an exploratory analysis multivariable regression will be utilized to determine which factors were associated with a high level of adherence to the study protocol, defined as adherence above the study median. We will investigate the following variables in a univariate analysis: age, sex, race, ethnicity, income, social support in the home, employment status, MMSE score, NIHSS, and modified Rankin Scale. Variables in the univariate analysis with $p<0.10$ will be incorporated into a multivariable logistic regression model. We will test for an interaction between the social incentive and the variables in the multivariable model.

9. Data Handling and Record Keeping

9.1 Confidentiality.

- ☒ Paper-based records will be kept in a secure location and only be accessible to personnel involved in the study.
- ☒ Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords.
- ☐ Prior to access to any study-related information, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information.
- ☒ Whenever feasible, identifiers will be removed from study-related information.

☐ A Certificate of Confidentiality will be obtained, because the research could place the subject at risk of criminal or civil liability or cause damage to the subject's financial standing, employability, or liability.
☐ A waiver of documentation of consent is being requested, because the only link between the subject and the study would be the consent document and the primary risk is a breach of confidentiality. (This is not an option for FDA-regulated research.)
☒ Precautions are in place to ensure the data is secure by using passwords and encryption, because the research involves web-based surveys.
☐ Audio and/or video recordings will be transcribed and then destroyed to eliminate audible identification of subjects.
☐ Other *(specify):* _____

9.2 Source Documents

Source documents are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in this research.

Trained members of the research team may review source documents at the time of enrollment/consent in order to ensure patient eligibility. Necessary data from the source documents will be recorded on the case report form. Copies of source documents will not be needed for this study.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. Hard copy of all case report forms will be kept secure in a locked cabinet accessible to the study primary investigator and study coordinator. Data for this study will also be stored in an electronic database via the Way to Health platform. Way to Health is secure and HIPAA compliant. Data contained within Way to Health will only be accessible to appropriately trained study personnel.

9.4 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

We will retain all case report forms and the electronic databases for a minimum of two years after completion of the study.

Personal identifiers will not be released to other investigators under any circumstances. If at any time the data is to be shared with other investigators for future research, it will be de-identified prior to release. The data collected in this study will not become a part of the subject's permanent record.

9.5 Subject Privacy/Protected Health Information

The following protected health information (PHI) will be collected:

- Name
- Address
- Social Security Number

- Medical record number
- Phone number
- Email address
- Medical history
- Current and past medications or therapies
- Information from a physical examination that generally also includes blood pressure reading, heart rate, breathing rate and temperature
- Information from laboratory and imaging tests such as echocardiograms, MRI and CT scans.

Collected PHI will be recorded on the case report form, which will be secured as detailed above. It will otherwise not be disclosed to anyone outside of key study personnel.

The HIPPA authorization for this study will be incorporated into the informed consent form. In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts will be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.6 Tissue Specimens

Not applicable

9.7 Genetic Testing

Not applicable

10. RISK/BENEFIT ASSESSMENT

10.1 Potential Study Risks

There are no risks associated with the blood pressure monitor used in this study. The study team will take every possible step to maintain your privacy, including using password protected files and minimizing the use of identifying information on study documentation, but whenever private health information is collected there is always a small risk that a breach of confidentiality could occur.

10.2 Potential Study Benefits

This study has the potential to benefit all subjects. Hypertension is the most important modifiable risk factor for stroke and an important risk factor for myocardial infarction, chronic kidney disease, and other serious medical conditions. Study education about the importance of hypertension, goal blood pressure levels, and regular monitoring of blood pressure may lead to improved blood pressure control in subjects, which in turn has the potential to lower the risk of serious medical conditions, including heart attack and stroke. There is also a potential societal benefit, as this study will provide important insights into adherence with home monitoring in patients with cerebrovascular disease and may be useful for future larger studies which combine home monitoring with therapeutic interventions to lower blood pressure with the goal of reducing the risk of future stroke.

10.3 Alternatives to Participation

Participation in this research study is voluntary. Subjects may choose not to participate; their decision to participate or not will not affect their regular medical care in any way.

10.4 Risk/Benefit Assessment

Considering the minimal risk to participants and the potential benefit both to individual participants and to society, the risk to benefit ratio is favorable.

11. Data and Safety Monitoring

This study will be monitored by:

☒ Principal Investigator
☐ Sponsor or contract research organization
☐ NCI sponsored cooperative group
☐ Cancer Center (if mandated by CTSMRC)
☐ Medical monitor
☐ Safety monitoring committee
☐ Data and safety monitoring board

11.1 Definitions

Adverse Event

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- Results in study withdrawal
- Is associated with a serious adverse event
- Is associated with clinical signs or symptoms
- Leads to additional treatment or to further diagnostic tests
- Is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- Fatal
- Life-threatening
- Requires or prolongs hospital stay
- Results in persistent or significant disability or incapacity
- A congenital anomaly or birth defect
- An important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the serious criteria will be regarded as ***non-serious adverse events***.

Adverse Event Reporting Period

The study period during which adverse events must be reported is defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 90 days from enrollment, or at the final study visit, whichever comes first.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event will be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events will be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the FDA and IRB of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization will be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery will be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

11.2 Recording of Adverse Events

At each contact with the subject, study personnel will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures with their results will be recorded in the source document, grouped under one diagnosis.

All adverse events occurring during the study period will be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

11.3 Reporting of Serious Adverse Events

Reports of all serious adverse events (including follow-up information) must be submitted to the IRB promptly. All serious adverse events, regardless of relatedness or expectedness to the study drug, will be submitted via PennAEs. Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's binder.

11.4 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of this study. Safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above. There will not be an internal or independent data and safety monitoring board.

12. AUDITING, INSPECTING

12.1 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities. Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

13. SUBJECT COMPENSATION

Subjects will be compensated $50 in the form of a Greenphire ClinCard. Compensation will cover the subjects transportation costs to/from study visits and their time for participation in study visits. The ClinCard is a prepaid card which the subject can use for in-store or online purchases similar to a credit or debit card. It can also be used at an ATM or bank to receive cash. The will be given to the subject upon completion of all study visits and after they have returned the Withings Blood Pressure monitor to the study team.

14. RESOURCES NECESSARY FOR HUMAN RESEARCH PROTECTION

This research protocol will be conducted by the clinical research section of the stroke division of the department of neurology. The research team consists of three full time clinical research coordinators, one nurse practitioner, three vascular neurology fellows, and five vascular neurology attendings. All members of the research team will be required to have Patient Oriented Research training through the University of Pennsylvania Knowledge Link training system. All members of the research team who will be assessing NIHSS and mRS will be trained in the administration of these scales using web-based training systems. The research team will maintain training records, including copies of all pertinent certificates.

Prior to initiation of the study, the research team will have an in-service session to review the study protocol and procedures in detail. While the study is underway, the research team will meet weekly to discuss the study, including enrollment, follow-up, and any other issues which may arise.

15. STUDY FINANCES

15.1 Funding Source

Funding for this study will be provided by an internal pilot grant awarded from the Penn Medicine Center for Health Care Innovation as well as an internal pilot grant awarded from the University of Pennsylvania Department of Neurology Robbins Fund.

15.2 Budget

	Cost/Unit	Number of Units	Total Cost
Blood Pressure Monitors	$ 130	30	$ 3,900
Way to Health Platform Development	$18,000	1	$ 18,000
Way to Health Monthly Costs	$500	15	$7,500
Way to Health 2-way messaging	$1,250	1	$1,250
PI Salary	$25,601	1	$25,601
Research Coordinator	$8,435	1	$8,435

Miscellaneous Office Supplies	$200	1	$200
Greenphire ClinCards	$50	90	$4,500

Total Cost: $69,386.00

15.3 Conflict 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 a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All University of Pennsylvania investigators will follow the University conflict of interest policy.

16. PUBLICATION PLAN

Dr. Mullen, the principal investigator for this protocol, is responsible for publishing the results of this study. Neither the complete nor any part of the results of the study carried out under this protocol will be published or passed on to any third party without the consent of the principal investigator. Any investigator involved with this study is obligated to provide the principal investigator with complete test results and all data derived from the study.

17. REFERENCES

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