PROTOCOL TITLE:

Improving Hypertension Using a Smartphone-Enabled Personal Control Program: The Smart Hypertension Control Study

PRINCIPAL INVESTIGATOR:

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1.0 Purpose of the Study:

Purpose

Investigators at Northwestern University will partner with Omron Healthcare Co., Ltd. (hereinafter referred to as "Omron") to conduct a randomized controlled trial of a hypertension personal control program (HPCP), known as Lark HTN Pro with a home blood pressure monitoring device (HBMD) compared to a HBMD alone. The overarching goal of this study is to investigate the effects of the HPCP on blood pressure control, blood pressure self-management, and healthy lifestyle behaviors among adults with hypertension.

Specific Aims and Hypotheses

Our primary aims and hypotheses (H) are to:

- **Aim 1**: To determine the effects of the HPCP+HBMD compared with HBMD alone on blood pressure control in adults with hypertension.
  - ***H_1**: HPCP+HBMD will lower systolic blood pressure at 6 months compared with HBMD alone.*
  - ***H_2**: HPCP+HBMD will improve hypertension control rates at 6 months compared with HBMD alone.*
  - ***H_3**: HPCP+HBMD will lower diastolic blood pressure at 6 months compared with HBMD alone.*

- **Aim 2**: To determine the effects of the HPCP+HBMD compared with HBMD alone on antihypertensive medication use in adults with hypertension.
  - ***H_4**: HPCP+HBMD will increase number of antihypertensive medication classes used at 6 months compared with HBMD alone.*
  - ***H_5**: HPCP+HBMD will increase medication adherence at 6 months compared with HBMD alone.*

- **Aim 3**: To determine the effects of the HPCP+HBMD compared to HBMD alone on hypertension self-management among adults with hypertension.
  - ***H_6**: HPCP+HBMD will increase the proportion of months where a home blood pressure reading is obtained compared with HBMD alone in adults with hypertension*
  - ***H_7**: HPCP+HBMD will increase the number of home blood pressure readings per month compared with HBMD alone in adults with hypertension.*
  - ***H_8**: HPCP+HBMD will increase self-efficacy to monitor and control blood pressure at 6 months compared with HBMD alone.*

- **Aim 4**: To determine the effects of the HPCP+HBMD compared to HBMD alone on healthy lifestyle behaviors among adults with hypertension.
  - ***H_9**: HPCP+HBMD will lower weight at 6 months compared with HBMD alone.*
  - ***H_{10}**: HPCP+HBMD will improve diet quality score compared with HBMD alone.*
  - ***H_{11}**: HPCP+HBMD will increase physical activity compared with HBMD alone.*
  - ***H_{12}**: HPCP+HBMD will increase sleep duration compared with HBMD alone.*

2.0 Background / Literature Review / Rationale for the study:

Hypertension, defined by elevated blood pressure, is a major contributor to death and disability from heart and vascular diseases.[1] Currently, an estimated 86 million adults or 1 in every adults in the US have hypertension, and rates are projected to increase.[1] Clinical trials have consistently shown that antihypertensive medications can reduce important health outcomes like stroke by 30-40%, heart attacks by 20-25%, and heart failure by as much as 50%.[2] Therefore, reduction of raised blood pressure with healthy lifestyle modifications (diet, exercise, weight loss, alcohol moderation) and antihypertensive medications are a cornerstone of cardiovascular disease prevention strategies.[3-6]

Despite the impressive efficacy of antihypertensive medications in clinical trials, hypertension treatment and control rates remain suboptimal in the United States. According to data from the National Health and Nutrition Examination Survey (NHANES) 2009-2010, high blood pressure control rates among all individuals was 47% and among treated hypertensives was 64%.[7]

Strategies to promote self-monitoring of hypertension have been shown to reduce blood pressure and improve hypertension control rates.[8-10] However, many self-monitoring interventions require significant resources for face-to-face counseling and patient activation, which can be costly over time.

Mobile health technologies such as smartphone apps provide a unique opportunity to augment self-monitoring interventions with health behavior coaching to promote behavior change for risk reduction.[11-13] However, there is limited high quality evidence to guide the optimal implementation of this intervention.[11] We seek to address this evidence gap with the proposed study.

3.0 Inclusion and exclusion criteria:

Screening for eligibility:

We will use structured language queries of electronic health record data from the Northwestern Medicine Enterprise Data Warehouse (NMEDW) to identify potentially-eligible participants with elevated blood pressure and exclude patients with clinical exclusion criteria from Northwestern Medical Group outpatient practices. We will provide primary care clinicians with lists of potential candidates and allow them two weeks to indicate which patients should not be contacted. We will then attempt to recruit from this remaining population. Potentially-eligible participants will be contacted by telephone by the research team for initial screening. Volunteers who remain candidates for participation as a result of the phone screening questions will be asked to schedule an on-site visit. During the on-site visit individuals will be asked to provide written informed consent and have blood pressure measured in a standardized fashion (described in section #4) to see if this inclusion criteria is met.

Inclusion and exclusion criteria:

We will use these criteria to determine who will be included or excluded in the final study sample.

Inclusion criteria:

- Adults aged 18 years to <85 years at the time of screening
- Standardized mean blood pressure measurement ≥135 to <180 mmHg systolic or ≥85 to <110 mmHg diastolic
- Have and use an iOS device(s) (iPhone generation 5s or newer)
- Able to provide written informed consent prior to participation in the study
- Receive their primary care from a Northwestern Medicine clinic site

Exclusion criteria:

- Current user of the HCPC (Lark HTN Pro)
- Standardized mean blood pressure measurement ≥180 mmHg systolic or ≥110 mmHg diastolic
- Persistent atrial fibrillation as indicated in the electronic health record (EHR)
- Pregnant or planning to become pregnant during the study period
- Severe kidney disease, defined as estimated glomerular filtration rate <30 per 1.73 m^2 or currently on renal replacement therapy (i.e. hemodialysis or peritoneal dialysis)
- Hearing impaired and unable to respond to phone calls
- Lack of fluency in English
- History of a cardiovascular event (stroke, transient ischemic attack, myocardial infarction, coronary artery bypass grafting) in the past 3 months
- Diagnosis of dementia as indicated in the electronic health record
- Diagnosis of psychosis as indicated in the electronic health record

- Terminal cancer diagnosis or NYHA III or IV heart failure
- Deemed unsuitable for study by primary care provider
- Individuals requiring BP monitor cuff size larger than 17 incles or 42cm

We will not recruit, enroll, or study special populations: adults who are unable to consent, individuals who are not yet adults (minors), pregnant women, or prisoners or other detained individuals.

4.0 Procedures Involved:

1. Describe the setting of the study, including all locations where research procedures will be performed.

This study will take place in Northwestern Medicine Group outpatient clinic settings. Northwestern Medical Group (NMG) is a multi-specialty group practice, with more than 1,200 physicians and other healthcare professionals, and is an integral component of Northwestern Medicine. NMG physicians work within Northwestern Memorial Hospital, Northwestern Lake Forest Hospital, Northwestern University Feinberg School of Medicine, and in more than 25 outpatient care locations spread across Chicago and the northern suburbs, offering primary, specialty and immediate care within and surrounding the communities where people live and work. Before contacting individual physicians within a practice, we will obtain permission from the clinical practice director to do so and will seek opportunities to introduce the study to the practice's clinicians at practice meetings and through email. We will initially recruit from the Galter 18 General Internal Medicine practice and subsequently extend recruitment to additional NMG practices as needed to achieve recruitment goals.

2. Describe the study design including the rationale.

We will conduct a non-blinded randomized controlled trial among hypertensive adults in NMG outpatient clinics. We will randomize participants in a 1:1 fashion to the intervention group (HPCP + HBMD) or the comparator group (HBMD alone). We will recruit adults with elevated blood pressure as assessed by in-person standardized examination at baseline. We will measure change in blood pressure by in-person examination at 6 months. All in-person study procedures will be performed at NMG outpatient clinic sites or at Northwestern Univerisity locations. We will recruit between 350 to 400 participants in order to have 300 participants with analyzable data at the time of study completion. If changes are deemed necessary, a revision to the study protocol will be submitted to the IRB for review and approval prior to implementing these changes. Based on higher than predicted retention at 6 months, in discussion with our funder we will stop recruitment activities once 333 participants are enrolled.

3. Provide a description of all research procedures and activities.

Randomization

We will perform randomization with the use of a centralized computer-generated assignment sequence uploaded a priori to Northwestern University's REDCap (Research Electronic Data Capture) application. Randomization will be stratified by: age (<65 or ≥65 years of age) and baseline systolic blood pressure (<145 or ≥145 mmHg) to optimize the likelihood of obtaining similar populations in each treatment group.

Study assignments

Control group: Control group participants will be provided with a home blood pressure monitoring device (HBMD) (Omron BP761N Bluetooth Smart Automatic Upper Arm Blood Pressure Monitor) and will be instructed in its use at the baseline study visit. Participants will also receive an information sheet describing home blood pressure monitoring that gives advice for how to respond to different home readings (see attached form). At the baseline visit, participants will be instructed to install an Omron application to their smart phone device (to monitor use of the HBMD). Participants will

continue to receive all routine care, including anti-hypertensive medications as prescribed by their regular clinicians.

Intervention Group: The intervention group will receive all the interventions provided to the control group.Participants randomized into the intervention group will not be asked to download the Omron application to their smart phone device. In addition, intervention group participants will be sent a hyperlink to install the hypertension personal control program (HPCP) ("Lark HTN Pro"), which is a smartphone application. The intervention group will have the HPCP installed on their iOS device during their initial office visit (screening/baseline) and will successfully take a reading from their HBMD. The HPCP has blood pressure, medication, and weight monitoring, including periodic reminders for the user to measure blood pressure, measure weight, and take their medication(s). The HPCP provides real-time feedback based on user input, such as out-of-range measurements and has additional features designed to encourage behavior change in areas such as dietary intake, physical activity, sleep, and stress reduction. Users can set goals and receive guidance and feedback through the app.

Endpoints

- Primary:
    - Systolic blood pressure (mmHg) at 6 months (adjusted for baseline systolic blood pressure)
- Secondary:

    Blood Pressure
    - Diastolic blood pressure (mmHg) at 6 months (adjusted for baseline diastolic blood pressure)
    - Proportion with controlled blood pressure at 6 months (defined as BP <140/<90 mmHg)

    Medication use
    - Medication adherence, measured as 4-day recall of antihypertensive medications
    - Number of antihypertensive agents used at 6 months
    - Number of antihypertensive medication changes (increases or substitution) at 6 months
    - Number of health system contacts (telephone, office, or mychart encounters) at 6 months – derived from electronic health record (EHR)

    Self-management
    - Frequency of home blood pressure measurements per month – derived from HBMD device
    - Proportion of months where a home blood pressure reading is obtained – derived from HBMD device
    - Self-efficacy to monitor and control high blood pressure.

    Lifestyle behaviors
    - Weight at 6 months (lbs)
    - Diet quality score (as assessed by Dietary Approaches to Stop Hypertension questionnaire, DASH-Q)[14]
    - Self-reported physical activity
    - Self-reported sleep duration

4. Include when they are performed, and any procedures being used to monitor participants for safety or minimize risks.

Before initial visit

All potential participants will go through a telephone screening. The following information will be obtained during the telephone screening:

- Age

- Confirmation of hypertension diagnosis, use of antihypertensive medications, or being told by a healthcare professional of elevated blood pressure
- Smoking status
- Presence of any exclusion criteria

If participants express study interest and qualify based on the telephone screening, they will attend a screening visit at a study clinic site.

Screening/Baseline study visit

Participants will be given a hard copy of both privacy and use documents for both Omron and Lark mobile applications to be reviewed before they will receive informed consent.

After providing informed written consent, the following information will be obtained during the screening/baseline study visit.

- Height and weight
- Measurement of blood pressure using standardized procedures.[15] Research assistants will perform standardized measurements of blood pressures and pulse using an automated device (Omron HEM-907XL Pro Blood Pressure Monitor). Participants will be asked to be seated quietly with their feet and back supported for 5 minutes before blood pressure is obtained. Patient positioning, arm selection, cuff size selection and other techniques will follow the procedures for blood pressure measurement outlined in guidelines from the American Heart Association.[15] Three recordings will be performed and the mean of the 2nd and 3rd readings will be used to indicate the blood pressure. For participants meeting eligibility, this mean blood pressure value will also serve as the baseline systolic and diastolic blood pressures.

If participants meet eligibility criteria for the study, we will also obtain:

- Detailed review of chronic daily antihypertensive medication and other cardiovascular (including cholesterol lowering medications) the patient is taking at the start of the trial. Adherence to antihypertensive medications will be measured for each prescription medication using a 4-day assessment of pills taken/pills prescribed based upon patient self-report. Missing any doses will be considered non-adherent for that medication.
- Questionnaire data to measure:
    - General self-efficacy[16] as well as self-efficacy to monitor and control high blood pressure
    - Diet quality as assessed by the DASH-Q[14]
    - Physical activity
    - Sleep duration

After screening, all participants will be provided with an Omron Bluetooth-enabled HBMD (Omron BP 761N) and taught how to use it for home blood pressure monitoring. Participants randomized to the HPCP group, will install the HPCP application to their iOS device. Study staff will instruct participants how to collect and transmit data from the HBMD to their phone and assist participants in their initial conversation with the HPCP coach, including an initial conversation about blood pressure reading from their HBMD. Participants in the HPCP group will be prompted to enter the Lark HTN Pro application frequently (as much as every day) via notification on their iOS device.

Participants' physicians will continue to manage blood pressure for both groups according to standard of care.

6-month study visit

Study participants will be required to return for a 6-month study visit (within 2 weeks before to 8 weeks after). During the 6-month visit, subjects will have their height/weight and blood pressure measured again. Participants will also repeat questionnaires related to their current cardiovascular medications. They will also complete questionnaires measuring: medication adherence, self-efficacy, diet, physical

activity, and sleep duration. An exit survey will also be provided to participants at the end of the 6-month follow up visit to obtain feedback on Lark and Omron apps usability.

EDW data extraction from Epic electronic health record
Study participants will be asked to consent to the automated collection of data from their Northwestern Medicine electronic health record. We will collect EHR data using the Northwestern EDW to measure during the study period: the frequency of office visits, telephone and patient portal (email contacts), and antihypertensive medications prescribed, changed, or discontinued.

Procedures to monitor participants for safety or minimize risks
Individuals involved in any aspect of this study will be subject to minimal risk through their participation. This study collects personal health information and information that identifies study participants. While we work to keep this information confidential, there is a risk of loss of confidentiality. There is a risk that personal identifying information could be released.

Participants will be informed in all cases about their rights as research participants. They may withdraw at any time during the study without penalty or loss of any healthcare benefit or service to which they are entitled. Participants will be assigned a unique identification number; the research database will be password protected and accessible only to the research team and the Institutional Review Board. Information linking participants' names and contact information with their unique identifier will be kept in a separate password protected file on a password and firewall protected FSM network server as well as 3 encrypted study laptops. The laptops are whole disk encrypted utilizing Symantec Endpoint Encryption. Whole Disk Encryption (WDE) provides protection for computers by preventing data loss with strong access control and powerful disk encryption. It is important that Northwestern University personnel storing sensitive information such as Protected Health Information (PHI), Personally Identifiable Information (PII) or research data, protect their machines and data with whole disk encryption software. We believe that in using these methods we will be compliant with the "Standards for Privacy of Individual Identifiable Health Information" under the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy Rule. Information obtained during the delivery of clinical care at the Northwestern Medicine clinic sites (such as documentation of clinical encounters with the nurse) may be recorded in patients' medical records and will be subject to the confidentiality protections for medical records under HIPAA.

5. Describe the study timelines including: the duration of an individual participant's participation in the study and the overall anticipated duration of the project.
The duration of an individual participant's participation in this study is approximately 6 months. Overall, we anticipate that this project will last from May 1, 2017 to January 1, 2019.

6. Describe the actual source records or measures that will be used to collect data about participants. (All surveys, interview scripts, and data collection forms will be attached elsewhere in the application. Do not add other documents to the protocol.) Describe what data will be collected and how it will be collected at all measurement/data collection time-points.

Source records used to collect data about participants
We will administer a baseline survey at enrollment consisting of demographics, past medical information, medications and other questions as detailed in the survey instruments (attached).

During the course of study, blood pressure and pulse will be measured by the HBMD and transmitted together with measurement time to the patient's iPhone via Bluetooth Low Energy (BLE) communication. An iPhone application will then send the transmitted data to an Omron server. Data collected from the Lark HTN Pro app will be stored on a Lark server. Lark will make available a research file with the participants' unique identifier consisting of all data collected by the Lark app: physical activity times and duration, foods logged, sleep duration, and patient-entered messages (see attached list).

At the 6 month visit, we will assess medication lists and administer structured questionnaires to measure medication adherence, self-efficacy, diet score, and physical activity. For participants randomized to the intervention group, we will also administer survey questions to assess the usability of the HPCP application.

7. If doing online research, include the URL where the data collection will occur.
Not applicable.

8. If your research is conducted outside of Northwestern University, please identify any site-specific regulations or customs affecting your project, including any local scientific and ethical review structure.
Not applicable. This research will not be conducted outside of Northwestern University

9. Describe any approvals that will be obtained prior to commencing the research. (e.g., school, external site. funding agency.)
Not applicable. This research will be commenced after obtaining IRB approval from Northwestern University.

10. If the research involves individuals who are vulnerable or susceptible to coercion or undue influence[1], describe additional safeguards included to protect their rights and welfare.
Not applicable. This research will not involve individuals who are vulnerable or susceptible to coercion or undue influence.

5.0 Multiple sites:
Not applicable. This is not a multi-site study.

6.0 Incomplete Disclosure or Deception:
Not applicable. This study will not use incomplete disclosure or deception.

7.0 Recruitment:
1. Describe when, where, and how potential participants will be recruited.
2. Describe the types of strategies and materials that will be used to recruit participants.
Note: Do not attach recruitment documents to the protocol but for additional guidance on the recruitment process and documents see: http://irb.northwestern.edu/process/new-study/requirements/recruitment-materials-guidelines.

Participant recruitment
We will apply structured language query to data within the NMEDW to screen for participants who are likely to meet study eligibility criteria. In phase 1 of our recruitment, we will identify patients in the NMEDW whose most recent in-office blood pressures are ≥145 mmHg systolic or ≥ 95 mmHg diastolic. If we are not meeting recruitment targets, we will expand NMEDW screening criteria to identify patients with in-office blood pressure ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic.

Once potentially-eligible patients are identified, research assistants will send primary care physicians a secure message within the EHR notifying them of their patients who may be eligible for this study.

[1] Coercion occurs when an overt or implicit threat of harm is intentionally presented to obtain compliance. Undue influence, by contrast, often occurs through an offer of an excessive or inappropriate reward or other overture in order to obtain compliance (http://www.hhs.gov/ohrp/policy/faq/informed-consent/what-does-coercion-or-undue-influence-mean.html). For example, the threat of the loss of reputation, good standing in class or of a bad grade if a student does not participate in a study would be an example of coercion. The offer of excessive money or special treatment or rewards for participation could be an example of undue influence.

Physicians will be asked to review the list and identify patients who they feel we should not contact. If a physician does not respond within 10 business days, we will recruit their eligible patients. Once physician approval has been received, eligible patients will be sent a recruitment opt-out letter that describes the study, instructs patients that they are eligible for this study, and informs them that a study staff member will be contacting them via email or telephone to discuss the study. The letter will include a phone number and e-mail address to call and leave a voicemail/message if they choose not to be contacted further about the study. We have attached the opt-out letter within eIRB+ application. Potential participants will not receive more than one letter per year about the trial. In order to avoid an individual receiving multiple letters, the list will be reviewed for duplicate names first by a computer analyst and re-examined by study staff. Individuals may request to not receive future recruitment letters. Five days later, a research assistant will begin telephone recruitment. We will contact patients by telephone to ask if they are interested in hearing more about the study. Up to 3 telephone contacts will be made within a one-week time frame. If a voicemail greeting is identified as the patient, a brief message will be left asking patient to return call. We will also give clinicians at participating practices study contact information so they may refer patients with uncontrolled hypertension directly to the study.

During the telephone recruitment, patients interested in possibly participating in study will be asked a series of questions to screen for eligibility (attached in eIRB). Patients who screen positive for study participation will be asked to schedule a study visit.

8.0 Consent Process (see also the Process of Obtaining Consent guidance on the web site.

Consent location

Consent will occur at NMG outpatient clinic or Northwestern University sites on the day of the screening/baseline study visit.

Ongoing consent process

Not applicable to this study. There will be no reconsenting over time.

Details of consent process

I. ***Role of investigators.*** The investigator is responsible for ensuring that the participant understands the potential risks and benefits of participating in the study, including answering any questions the participant may have throughout the study and sharing in a timely manner any new information that may be relevant to the participant's willingness to continue his or her participation in the trial.
The investigator is ultimately responsible for ensuring that informed consent is given by each participant before the study is started. This includes obtaining the appropriate signatures and dates on the informed consent form prior to the performance of any protocol procedures.

II. ***Amount of time devoted to the consent discussion.*** We will devote approximately 5 minutes to the consent discussion and use standardized language per an informed consent document to structure the consent discussion.

III. ***Steps to minimize the possibility of coercion or undue influence.*** Trial recruitment will be performed by Northwestern study staff using structured recruitment scripts (attached). Research staff will receive training that includes didactic review of these materials and role play practice. Participants will also be informed that they withdraw from the study at any time.

IV. ***Steps to ensure participants' understanding.*** The informed consent process will be used to explain the potential risks and benefits of study participation to the participant in simple terms before he or she is entered into the study, and to document that satisfaction and understanding of the potential risks and benefits of participating in the study. The research assistant will make sure the participant understands what procedures and clinical data will be collected.

We will not include:

- Non-English speaking participants
- Participants who are not yet adults (infants, children teenagers)
- Cognitively impaired adults
- Adults unable to provide consent.

9.0 Process to Document Consent:

The research assistant will review the informed consent document with the participant and answer any questions. Participants will provide written informed consent. We have attached consent script within eIRB+ application.

10.0 Risks to Participants:

1. List the reasonably foreseeable risks, discomforts, hazards, or inconveniences related the participants' participation in the research. Describe the probability, magnitude, duration, and reversibility of the risks.
2. Consider physical, psychological, social, legal, and economic risks as well as community or group harms.

Participant risks in this study are minimal. Any potential risks that might exist fall into four categories: (a) risks associated with the Intervention. The main intervention risk is that patients may try to access the mobile phone or participate in assessments while driving. Risks associated with cell phone use and driving will be managed by informing the participants that they are not permitted to use the phones while driving; (b) risks associated with research assessments, consisting of questions about hypertension management; (c) risks associated with potential loss of confidentiality; and (d) risks of worsening mental or emotional state.

Participants will be told that they are not permitted to use the phones while driving. If study staff become aware of mobile phone use while driving, they will do what is necessary to eliminate the risk (e.g. let the person know they should not use the phone while driving). Data for all participants will be kept strictly confidential except as mandated by law. All research files are kept on secure, password protected departmental and medical school servers. All data collected via the Lark HPCP and the Omron applications will be transmitted using a secure file transfer protocol (FTP) All electronic data will be stored on secure servers behind firewalls. Any paper documentation will be kept in locked file cabinets or a locked file room. All data presentation will be of aggregate-level data; participants are never individually named.

Any risks associated with antihypertensive medications are beyond the scope of this study because we are examining hypertension self-management, not medications. Participants will be prescribed antihypertensive medications by their physician as part of their conventional medical care. Participants can add, change or discontinue their medications at any time as they would do if they were not in the study. Study staff will encourage regular contact with their physicians to facilitate optimal treatment decision-making.

3. If applicable, describe risks to others who are not participants.
There are no risks to others who are not participants.

4. Withdrawal of Participants
There are no specific criteria for removal of a patient from the study or termination of the trial. A patient will be removed if continued participation is determined to constitute a danger to the patient's health or well-being by the PI based on input from the evaluators. Clinical evaluators are required to

inform the PI and study coordinator if they suspect deterioration or adverse effects in the patient. The PI and study coordinators will perform all necessary evaluations. If the PI determines the patient must be removed from the study immediately, the patient will be removed and all appropriate referrals will be made. The IRB will be informed.

Participants may discontinue their antihypertensive medication at any time and still continue in the study by completing assessments. Participants may withdraw from the study at any time.

11.0 Potential Benefits to Participants:

1. Describe the potential benefits that individual participants may experience from taking part in the research. Describe also the probability, magnitude, and duration of the potential benefits.

Participants may directly benefit from their participation. Use of the HPCP application (Lark HTN Pro) during the study may improve blood pressure level, hypertension control, adherence to antihypertensive medications, build better medication-taking behavior, and improve lifestyle behaviors (i.e. diet, physical activity, sleep duration, and weight maintenance), all of which are associated with improved health outcomes. The control group will receive a HBMD (commercially available without a prescription) that may assist them in the self-management of their hypertension.

2. Indicate if there is no direct benefit to participants. Do not include benefits to society or others.

Not applicable.

12.0 Financial Compensation:

1. Describe any financial compensation that will be provided to participants. Include how much money or what gifts will be provided and for what activities.

Participants attending a screening visit who are not eligible or who choose not to participate will receive $10. Participants who are enrolled in the study will be given $25 and a commercially-available HBMD manufactured by Omron. Participants who complete the follow up visit will receive $50.

2. Include whether compensation will be prorated if there are multiple research activities or if a participant withdraws from the study before finishing.

See above

3. Describe any costs that participants may be responsible for because of participation in the research.

Participants will not be provided with iPhones or phone service. Participants who lose their iPhone or phone service during the course of the study will not be excluded. Participants will be compensated for public transit, taxi (up to $25) or be provided with a parking voucher for study visits.

13.0 Provisions to Protect the Privacy Interests of Participants:

1. Describe the steps that will be taken to protect participants' privacy interests throughout the research activities.

Participants will be assigned a unique identification number; the research database will be password protected and accessible only to the research team and the Institutional Review Board. Information linking patients with their unique identifier will be kept on a password and firewall protected FSM network server. Once the study is complete, the linking file containing identifiers will be permanently deleted. Northwestern will retain a completely de-identified data file for analysis. These methods are compliant with the "Standards for Privacy of Individual Identifiable Health Information" under the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy Rule.

Data collected from participants using the Lark app or the Omron app will be collected by these companies using the same approaches and securities they employ for regular consumers (see attached privacy documents, available at these websites: https://omronhealthcare.com/privacy/ AND http://lark.com/hipaa-privacy-policy/). Data collected by these apps will be stored at Lark or Omron, respectively, along with personal identifiers that are used by the participant to register for the app. However, when this data is used for research purposes or transmitted between research partners (namely between Northwestern, Omron, and/or Lark) these files will not contain personal identifiers other than an anonymous study code. Northwestern investigators will provide these codes to participants at the time of enrollment and have them enter these codes into the applications. Northwestern study staff will use these study codes to merge data collected from the Lark and Omron applications with data collected at Northwestern. Merged data will only be stored with the participant's unique Subject ID (different from the study code used in the app) and not with any other personal identifiers. Omron and Lark agree to make no attempt to re-identify individuals from these research data sets.

2. Indicate who on the research team and how the research team is permitted to access any sources of information about the participants.

At Northwestern, only authorized research staff who are included on the IRB approved protocol will have access to participant data. Data collected by Northwestern will be shared with Omron the sponsor only with study ID identifiers.

14.0 Confidentiality and Data Management:

1. Describe how data (and if applicable, biological specimens) will be handled study-wide including:

a. **What information will be included as data (or associated with the specimens)? "Data" includes all information collected in the conduct of the research, such as but not limited to: consents, surveys, interview notes, audio or video recordings, photographs, notes of observations, field notes, etc.**
b. **Where and how will data (or specimens) be stored? How will data be transported from the point of collection to where they will be stored? Note: electronic storage of data in both domestic and international research must be secured using adequate protections.**
c. **How long will the data or specimens be stored? (Note: IRB policy is 7 years after the completion of the study. However, there are circumstance when other time frames may apply.)**
d. **Who will have access to the stored data or specimens?**
e. **Who is responsible for receipt or transmission of the data or specimens?**

Data handling study-wide

Information furnished to the investigator shall be maintained in confidence, and such information will be divulged to the institutional review board, ethics committee (IRB/EC) or similar committee; affiliated institution and employees, under appropriate understanding of confidentiality with such committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

The Research data collected by Northwestern shall be anonymized and files sent back to our associates (Omron, and Lark) will not include identifying data other than. Specifically, anonymized data include only a unique Subject ID as identifier of an individual subject. Study staff and doctors will connect the identity of the individual patient with the Subject ID through maintenance of a Subject ID Log. The Subject ID Log and other documents containing identifying information are required to be kept in locked storage.

The associates (or associates representative), IRB/EC, or regulatory authority representatives may consult and/or copy trial documents in order to verify source document/case report form data. In this way, these individuals will have access to a patient's identifying information. By signing the consent form, patients agree to this process. If trial documents will be photocopied during the process of verifying source document/case report form information, the patient will be identified by the unique Subject ID only; full names will be masked prior to transmission to the associates.

2. Describe the steps that will be taken secure the data (e.g., training, authorization of access, password protection, encryption, physical controls, certificates of confidentiality, and separation of identifiers and data) during storage, use, and transmission.

- Training: All personnel involved in study will complete human subjects protections training and register within eIRB+, and be added to authorized personnel list. Dr. Karmali and or Dr. Persell will regularly evaluate the workflows and procedures of project coordinators and IT personnel interacting with participants and their data.
- Authorization of access: All Northwestern staff on the study will be on the authorized personnel list. We will work with the 'minimum necessary' framework to grant access to secure study folders on secure division drives based on an individual's need to see data. Analysts and investigators working on data analysis will have a restricted access folder. Project coordinators will only have access to what they need to do their job and will not interact with patient data unless as required by their role.
- Password protection and Encryption: All study files with identified data will be kept password protected. This includes recruitment tracking files, survey files, and chart abstraction data. The laptops study staff use will be encrypted and will require log-in and password.
- Separation of Identifiers: All subjects will be assigned a unique identification number (Subject ID). Information linking participants' names and contact information with their unique identifier will be kept in a separate password protected file on FSM servers. Similarly, we will generate study codes to provide to participants that are distinct from the Subject ID that we will have participants enter into Omron and Lark apps. These codes will allow Omron and Lark to securely send us files that do not contain other personal identifiers.
- These methods are compliant with the "Standards for Privacy of Individual Identifiable Health Information" under the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy Rule.
- Once study enrollment and data analysis are complete, the file linking patients with their unique identifier will be permanently deleted.

3. Describe any procedures that will be used for quality control of collected data. If conducting online research, specify if you will be using any attention check measures. If yes, you need to indicate what you will be doing and what happens if a participant fails the attention checks.

Quality control of collected data

The HBMD provided by Omron (Omron BP761N) is an FDA approved model. The integrity of collected blood pressure data is secured with automated data transfer from device to server. The study will be conducted and data will be generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable local regulations. Dr. Persell and or Dr. Karmali will work with data programmer and other study staff members to ensure validity of collected data.

4. Describe the data analysis plan, including any statistical procedures is applicable.

Data analysis plan, including any statistical procedures

We will perform analysis to address each primary and secondary aim using SAS v9.4 (SAS Institute, Carey, NC). We will use a 5% level to signify statistical significance and calculate 95% confidence intervals. All analyses will assume intention-to-treat principles.

The proposed study is a simple randomized controlled trial where the unit of randomization is the participant. Anticipating a follow-up rate of 85% at 6 months, we aim to recruit 350 participants in total who will be allocated in a 1:1 fashion to the HPCP+HBMD group or the HBMD alone group. This will provide at least 300 total participants who will contribute to the primary data analysis at follow-up. If time and resources permit, we may expand recruitment efforts to 400 participants in total in case follow-up rates are lower (i.e. 75%).

Statistical analyses

Before conducting formal analyses, we will perform descriptive statistics to compare the two treatment groups to ensure adequate balance of potential confounders. These characteristics include: socio-demographic characteristics, comorbidities, baseline blood pressure values, and number of antihypertensive medications used.

For the primary analysis plan, we will compare the differences in systolic blood pressure at 6 months of follow-up between the two treatment groups using a linear regression model, adjusting for baseline age (years), sex (male or female), and baseline systolic blood pressure (mmHg). We will perform similar analyses for the secondary outcomes of continuous variables (diastolic blood pressure, weight, diet score, and physical activity), adjusting for age, sex, and baseline variable. We will assess model assumptions and explore residual diagnostics. As appropriate, transformations of variables and/or nonparametrics may be employed.

For the binary outcome of blood pressure control (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg), we will use a logistic regression model adjusting for age, sex, and baseline systolic blood pressure level. For the secondary outcomes that are not measured at baseline, we will adjust only for age and sex in regression models.

We will also compare the effects of treatment group in stratified analyses by weight (BMI >=25 and BMI <25) and SBP >=150 or <150.

Power Calculation

Without much prior knowledge regarding the overall variance in outcome that may be accounted for by the planned covariates, we can conservatively estimate power based on the independent two-sample t-test. With the planned analytic sample size of 300 (150 per arm), we have 80% power to detect a small to moderate (0.3 standard deviations) effect size across the two arms at the 5% level of significance. Thus, if the observed standard deviation is 15mmHg, we have adequate power to detect a 5mmHg difference in mean six-month SBP across the two arms. Since we have pre-specified adjustment for baseline SBP, sex, and age, we anticipate increased precision in analysis of primary outcome, allowing for more than 80% power to detect the same effect size via our planned primary outcome analyses. If we estimate between 0% - 25% of the variation (R-squared) to be explained by the planned covariates, the analytic approach will allow for 80% power to detect a 5mmHg mean difference in six-month SBP across the two arms if the standard deviation is no larger than 17mmHg (i.e., a slightly smaller [0.29] effect size).

15.0 Data Monitoring Plan to Ensure the Safety of Participants:

1. Describe the plan to periodically evaluate the information collected regarding risks or harms to determine whether participants remain safe. For example, if you are collecting depression or suicidality data, what is your plan for monitoring severity? Note: the plan might include establishing a data monitoring committee and a plan for reporting their findings to the IRB and the sponsor. It also could include referral to an appropriate resource. Include the following:

a. What information / data are reviewed, including safety data, untoward events, and efficacy data.

b. How the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls with participants).
c. The frequency of data collection, including when safety data collection starts.
d. Who will review the data.
e. The frequency or periodicity of review of cumulative data.
f. The statistical tests for analyzing the safety data to determine whether harm is occurring.
g. Describe any conditions where the research team may intervene and what the plan is for intervening. (For example, if a participant identifies harm to self or others.)
h. Describe any conditions that might trigger an immediate suspension of the research.

This is a minimal risk study because participants are only subject to an app that promotes the standard of care for individuals with hypertension and the use of a commercially available home blood pressure monitor (currently available without a prescription for self-monitoring of blood pressure). We will convene a data and safety monitoring committee for this study consisting of 4 clinical researchers (of which one is a statistician) for data and safety monitoring. Meetings will be organized every 6 months. At these meetings, the study protocol, procedures, and any issues of concern related to research integrity will be discussed. Email correspondence, or teleconference meetings may be arranged for issues that require immediate attention.

We will set thresholds for blood pressure readings taken as part of the study visit that require a clinical response. All study participants will receive a notification of their average blood pressure taken on the study visit day. Lower threshold: If the average systolic blood pressure is < 80 mmHg or the average diastolic blood pressure is <50 mmHg, study staff will alert the patient to speak with their clinician that day. Upper threshold: If the average systolic blood pressure is >180 mmHg or the average diastolic blood pressure is >110 mmHg, study staff will alert the patient to speak with their clinician that day.

16.0 Data and if applicable, Specimen Banking:

Not applicable for this study.

17.0 Qualifications to Conduct Research and Resources Available:

1. For international research or research with vulnerable populations, describe the qualifications (e.g., training, experience, oversight) of you and your staff as required to conduct the research. When applicable describe the knowledge of the local study sites, culture, and society. Provide enough information so the IRB knows that you have qualified staff for the proposed research.
Note: If you specify a person by name, a change to that person will require prior approval by the IRB. If you specify people by role (e.g., coordinator, research assistant, co-investigator, or pharmacist), a change to that person will not require prior approval by the IRB, provided that person meets the qualifications described above to fulfill their roles.

Not applicable. Not conducting international research or research with vulnerable populations.

2. Describe other resources available to conduct the research: For example, as appropriate:
a. Describe your facilities or other physical resources needed for the conduct of the research.

This study will take place in General Internal Medicine (GIM) outpatient clinics - The GIM clinic of Northwestern Medical Group has 40 doctors who practice full or part time in the clinic. The clinic has 39 exam rooms and approximately 250 to 300 patient visits per day. All physicians use an electronic medical record (Epic; Epic Systems Corporation; Verona, Wisconsin) for all clinical encounters (in-person and telephone). The GIM clinic has three private rooms in the clinic dedicated for research. The Division also has a Clinical Research Center with 4 examination rooms in the same building as

the clinic. Additional private rooms that may be used are located in the General Internal Medicine and Geriatrics academic offices on the 10th floor of 750 N Lake Shore Drive.

b. Describe the availability of social, emotional or psychological resources that participants might need as a result of an anticipated consequences of the human research.

Because this is a minimal risk study, we do not expect that participation will result in significant changes in the needs for social, emotional or psychological resources. Physician investigators (who are practicing physicians at Northwestern) will be available by phone or pager to help participants and research staff plan appropriate responses to unanticipated social or emotional problems that might occur and to help participants access appropriate care if needed.

c. Describe your process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions.

Research staff will have adequate time devoted to this study in order to conduct recruitment activities and answer any questions that participants have about using the HPCP application. A project coordinator and data analyst are familiar with this protocol and have estimated the time needed to successfully meet objectives. Within the division of General Internal Medicine & Geriatrics, our study team work together frequently on studies similar to this protocol. We have adequate computer (both hardware and statistical software) resources and server storage capacity. The study team will meet quarterly to ensure all authorized personnel are informed about protocol. Drs. Persell and Karmali will be working closely with study staff to ensure the study protocol is followed and all duties are being appropriately carried out.

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