ClinicalTrials.gov Study Protocol

Study Title:

Improving Hypertension Medication Adherence for Older Adults

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THE UNIVERSITY OF ARIZONA Research Innovation & Impact

IRB Protocol for Human Subjects Research

Basic Information	
Title of Study:	Improving Hypertension Medication Adherence for Older Adults
Short Title:	Improving Hypertension Medication Adherence for Older Adults
Principal Investigator Name:	Jeannie K. Lee
Principal Investigator's Department/Unit:	Pharmacy Practice & Science

1.0 Background (Limit 1,000 words):

Provide the scientific or scholarly background for the proposed Human Research. Discuss relevant prior experience or preliminary data (e.g., existing literature).

Blood pressure (BP) medications are remarkably effective in reducing adverse outcomes of uncontrolled hypertension. Proper adherence to BP medications yields major reductions in heart failure (>50%), stroke (40–50%), and myocardial infarction (20–25%), and preserves cognitive function. Hypertension is especially common in older adults (~67% in persons over 60), with a high prevalence of negative consequences of uncontrolled hypertension, including damage to the heart, kidneys, retina, and brain. The benefits of BP medications are often unrealized in older adults, as nonadherence is alarmingly common (~50%), leading to decreased quality of life and high healthcare costs ($290 billion/year in the US).

Older adults experiencing cognitive changes that influence medication adherence are an increasing proportion of the population, requiring a disproportionate share of healthcare resources. We developed and tested the theory-based Multifaceted Prospective Memory Intervention (MPMI), which significantly improved older adults' BP medication adherence, but benefits were not maintained over time when the intervention ended. Sustainable interventions depend on self-motivation. According to self-determination theory, people are more likely to adopt and maintain healthcare management behaviors when basic psychological needs (e.g., competence, autonomy) are satisfied. Hence, we developed Medication Education, Decision Support, Reminding, and Monitoring System (MEDSReM), which translates MPMI strategies to a mobile application (App). MEDSReM changes medication taking from an onerous process dependent on executive functions and cognitive processes that decline with age (e.g., working memory), to customized, cue-driven associative processes that are mostly preserved with age. MEDSReM also provides relevant education and decision support (what to do after a missed dose), promoting competence and autonomy to motivate individuals to engage in the intervention, thereby sustaining its effectiveness over time. However, enhancement is required to fulfill user competence and autonomy—BP self-monitoring via the App and end-user set-up of the App.

Capitalizing on technology developments, we will advance MEDSReM to integrate electronic BP monitoring and provide feedback on the relationship between medication adherence and BP. Specific feedback about outcomes can increase competence and autonomy and improve adherence. MEDSReM will use optical capture via the smartphone camera to enable an easy set-up when older adults are entering medications and personalizing their reminder schedule. MEDSReM will also increase decision support for missed BP medications by expanding the medication database and associated algorithms for safe dosing**.**

2.0 Lay Summary:

Provide a brief description of the proposed research using terms that someone who is not familiar with the science or discipline can understand.

Blood pressure (BP) medications are very good at reducing negative results of uncontrolled hypertension, and optimal use reduces heart failure, stroke, and heart attack, and maintains brain function. Hypertension is especially common in older adults (~67%), but BP mediation benefits are not realized for many older adults, as nonadherence is ~50%, leading to decreased quality of life and high health care costs ($290 billion/year in US). We developed the theory-based Multifaceted Prospective Memory Intervention (MPMI), which significantly improved older adults' adherence to BP medications, but benefits did not last. So, we developed the Medication Education, Decision Support, Reminding, and Monitoring System (MEDSReM) mobile application (App), which changes medication taking from a complex process dependent on brain functions and processes that decline with age, to customized, cue-driven simple processes that are mostly preserved with age. MEDSReM will have more technological advances to integrate additional functions to MEDSReM including electronic BP monitoring and provide feedback about the relationship between medication adherence and BP. We will have older adults (≥ 65 years), who take at least one hypertension medication, use the improved MEDSReM system to see how easy it is to use and if it improves medication taking and blood pressure for older adults.

3.0 Purpose:

Describe the purpose, specific aims, objectives, questions to be answered, hypotheses, and/or primary and secondary study endpoints of the Human Research.

Aim 1, to advance the design of the Medication Education, Decision Support, Reminding, and Monitoring (MEDSReM) system, was completed during years 1-2 of this research project. Aim 2 will be completed in years 3-5.

The purpose of this study is to examine the potential benefit of the MEDSReM system, to improve medication taking and blood pressure for older adults

Aim 2: The MEDSReM system will be tested for efficacy and scalability.

Aim 2a: Efficacy will be assessed through a multi-site, 6-month randomized clinical trial (RCT). We will screen 448 older adults with hypertension, identify 224 nonadherent to hypertension medication, and randomize to 6-month intervention. Primary outcome: improved adherence after 6 months of MEDSReM system engagement (n=112) vs. education comparison (n=112). Secondary outcomes: 6-month improvement in mean seated systolic blood pressure (SBP), perceived competence and autonomy, and mobile device proficiency.

Aim 2b: Examine adherence change over time for individual participants and individual difference moderators of sustainability of the intervention (e.g., cognitive ability, baseline adherence, age, sex).

Scaling up and tailoring to individuals is the next step after a successful RCT. We will assess whether MEDSReM is more or less effective in yielding improved outcomes for different individuals, with the goal of identifying potential challenges to successful replication of the intervention and the circumstances and activities that contribute to successful adoption of the intervention on a larger scale. At the group level, we expect the MEDSReM intervention group to show better adherence relative to the Education comparison group. However, individual differences are likely to moderate intervention effects, as we observed with the original MPMI, wherein the intervention effect was moderated by executive function. Hence, we will explore moderators such as cognitive function (executive function and working memory), health literacy, propensity to embrace technologies, hypertension knowledge, baseline adherence, age and sex, comorbidities, and polypharmacy, which affect sustained hypertension medication adherence over 6 months.

Aim 2c: Evaluate MEDSReM use patterns over time to identify functions used most (e.g., education, reminders, decision support) and evaluate factors related to adherence and BP management.

We will assess patterns of the MEDSReM system use to evaluate factors related to medication adherence and BP management. System use is related to individual differences—in one of our previous study, we found that long-term use of the system was predicted by earlier use of the system, executive functioning, and computer efficacy. Understanding personal characteristics that relate to more or less use over time is also valuable. In an another RCT, we investigated the effects of personal characteristics on the number of days people used an online lifestyle diary with a personal computer assistant and found that cognitive abilities and motivation to perform self-care were important determinants of attrition. We expect our self-determination measures (competence and autonomy) to be indexed to these groups.

These data will provide insights about where community-based interventions might need additional support with respect to underuse or lack of sustained use of the tool and the importance of identifying personal motivators that result in a focus on different aspects of the MEDSReM system.

4.0 Funding Information:

Indicate all sources of funding for the project, including gift funds, departmental funds, or other internal funding. For each funder, list the name of the funder, and the institutional proposal number or award number you received from Sponsored Projects. For externally funded projects, the information below should match the Study Funding Sources in eIRB.

☐ **No Funding**	
☒ **Federal Funding**, including flow-through federal funding (i.e., NIH, NSF, DoD, etc.)	Name of funding source: National Institute of Nursing Research
	Institutional Proposal or Award Number: R01NR018469.
	eDoc # (for multi-site projects): 20273038
☐ **Industry Funding**	Name of funding source:
	Institutional Proposal or Award Number:
	eDoc #:
☐ **Foundation Funding**	Name of funding source:
	Institutional Proposal or Award Number:
☐ **Department Funding**	Name of funding source:
☐ **Gift Funding**	Name of funding source:
☐ **Other**	Name of funding source:

5.0 Resources Available to Conduct the Human Research:

Describe the resources (facilities, time, emergency resources, etc.) available to recruit, consent, conduct study procedures, and analyze data.

This project will have access to resources from the University of Arizona (UA), UA Health Sciences, UA Colleges of Pharmacy, Medicine, and Nursing, and UA Health Sciences Library. We have well-established relationships in the Arizona Center on Aging, Pima Council on Aging, Sarver Heart Center, Tucson Medical Center Senior Services, and many other organizations around Southern Arizona to support recruitment of older adult participants.

In addition, this project will have access to resources from the University of Illinois Urbana-Champaign, the College of Applied Health Sciences, the Human Factors and Aging Laboratory, the Beckman Institute, the CHART Apartment at Clark-Lindsey Village, and the LIFE Home. We have a participant registry for recruiting participants and established relationships in the community to support recruitment of senior adults.

We are contracting with Ephibian a local computer science and electrical engineering firm. Ephibian helped develop the first version and the advanced design of our MEDSReM system. They specifically built the MEDSReM system to: 1. protect the local device information with encryption; 2. protect all data transmissions; 3. require pin entry for application access for additional user security; 4. remove any data on user request or application uninstallation; and 5. meet HIPAA security requirements.

Ephibian has been building high-volume, high-performance solutions for more than 25 years. Their software development services include mobile, web, client-server applications and data solutions, including application development, user experience, data integration, along with security and cloud solutions to support these applications. They have been successful creating solutions for clients across the globe including AOL, Intuit, Honda, AT&T and IBM to name a few. Ephibian designed and developed the first fully integrated enterprise management solution used to manage networks and systems across the Army nationwide, which is now the U.S. Army Network Enterprise Command's Continental United States Theater Network Operations and Security Center (CTNOSC). They delivered on more than 400 projects and none have failed (see http://ephibian.com/). Ephibian built the 10 Fifty Safety mobile application targeting older adults that are mobile, active, and independent. This application is easy to use, offers patented, multi-protocol technology that moves seamlessly between cell service, blue tooth and WiFi to get a call for help completed without traditional technology barriers. Ephibian built the data platform that enables The Critical Path Institute, to bridge the gap between scientific research and medical product development under a collaborative agreement with the FDA. They serve multiple audiences to include the aging population in our work with the Patient Reported Outcomes Consortia (http://c-path.org/programs/pro/) as well as serving Alzheimer's and Parkinson's diseases, polycystic kidney disease, and tuberculosis.

Ephibian built a personalized vitamin recommendation and medication health check mobile responsive application that serves over 1.5 million users each month, many of

whom are an aging population. This application integrates directly with manufacturing, nutritionist support and subscription-based services with an emphasis on usability, content management, product feedback and search engine optimization (https://www.weilvitaminadvisor.com).

6.0 Study Population:

6.1 Select all the categories of participants included in the research:

☐ Healthy adults	☐ Non-English-speaking subjects
☒ Non-healthy adults	☐ UA staff/faculty
☐ Children (under 18 years old) *	☐ UA students
☐ Pregnant women, neonates, and/or fetuses*	☐ Banner employees
☐ Prisoners*	☐ Refugees
☐ Native Americans, Alaskan Native, and Indigenous Populations*	☐ Other – please explain: Click or tap here to enter text.
☐ Adults unable to consent (i.e., cognitively impaired adults) *	

6.2 For each of the above selected categories, describe the inclusion and exclusion criteria. Indicate age range, gender, and ethnicity.

The inclusion criteria for study participants are: 1) age 65 years or older, 2) self-manage at least one hypertension medication, 3) able to read and speak English, 4) willing to participate in the study for six months, 5) currently have and use an Apple iPhone, and 6) have hypertension medication adherence ≤ 90% in the last 2 weeks of the 4-week baseline monitoring period using an AARDEX MEMS® cap. No minimum adherence is set for inclusion as the intervention may be more beneficial to those with very low baseline adherence.

Participants will be excluded if they: 1) have inadequate visual acuity (> 20/50 corrected near vision on Snellen test); 2) experience severe depression (> 11 on Geriatric Depression Scale Short Form, GDS-15); 3) are at risk for cognitive impairment (< 23 on Montreal Cognitive Assessment, MoCA); or 4) been instructed by their healthcare provider to withhold their blood pressure medication.

6.3 Describe the total number of subjects to be enrolled locally. If obtaining specimens, specify the maximum number of specimens needed for this project.

Approximately 448 will complete the first 4 weeks and 224 persons will be asked to participate in the additional 6 months of the study. Locally, 65% of the total number of participants will be enrolled so 291 for the first four weeks and 146 for the 6 month portion of the study. The additional 35% will be recruited at the UIUC site.

7.0 Recruitment Methods:

7.1 Select the methods used to recruit individuals.

☒ Email	☐ Screening of the Electronic Medical Record (EMR)
☒ Face to face	☐ Social media
☒ Flyers	☐ SONA System
☒ In person presentations	☒ TV, Radio, Print
☐ Online advertisements	☒ Other – please explain: research registries
☒ Phone calls	

7.2 Explain the recruitment process. Describe how potential subjects will be identified, where recruitment will take place, when recruitment will occur, and the methods that will be used to recruit individuals.

We have already established partnerships with community-based organizations including neighborhood centers, senior living communities, area senior centers, and meal sites in Arizona and Illinois, which provides access to individuals of diverse age, sex, ethnicity, religion, education, and economic status. We have a support letter for this research from Clark-Lindsey in Urbana, a non-profit Life Plan Community in Illinois. Area centers on aging (e.g., Pima Council on Aging), university-affiliated programs (e.g., Osher Lifelong Learning Institute), and cultural centers (e.g., Tucson Chinese Cultural Center) frequently hold programs for older audiences, which provide valuable recruitment opportunities. Health-focused events, such as a public lecture series offered at an area hospital or a community health fair, have proven to be valuable sources of potential participants. As in previous recruitment successes, the research team will be present in person at these sites and events to offer blood pressure screenings. The team can offer blood pressure screenings as a way to meet potential participants and identify those who may be eligible for participation. People who are interested in hearing about the study will be asked for contact information. Additionally, we will identify potential participants through local, geriatric, cardiovascular and primary care providers caring for older adults with hypertension throughout the communities in Arizona and Illinois. The

Co-PIs and Co-investigators will network with area providers who agree to display our recruitment brochures/study flyers in their clinics. An ad (copy of brochure/study flyer) in local newspapers, magazines, and newsletters may be used to reach older people not associated with aforementioned sites or events. We will also promote our research project through our university's relevant health websites (e.g., The University of Arizona Health Sciences Innovations in Healthy Aging). Our study flyer will be shared on these websites and will contain both email and phone contacts of the project coordinator so that participants may use either method with which they are most comfortable.

Additionally, participants will also be recruited through various participant registries including The Technologies to Support Aging-in-Place for People with Long-Term Disabilities (TechSAge) Participant registry (UIUC IRB #20662), the Illinois Health and Engagement through the Lifespan Project Registry (I-HELP) research registry (UIUC IRB #08524), and The Disability and Education Services (DRES) Research Registry (UIUC IRB #13731). Individuals have signed up for these registries because they have expressed an interest in being contacted to participate in research studies. Participants who are enrolled in this registry will be contacted about the study and inclusion criteria. These individuals will be emailed (see email drafts of short announcement and study introduction in our recruitment materials) about the study and asked to contact our staff if interested in learning more about the study.

The research staff will follow up with the potential participants ideally the next day for formal recruitment into the study. The team will document all attempts to contact potential participants and will vary day and time of contact attempts if the person is not reachable on the first attempt. While general information about the study will be given face-to-face in community settings, formal recruitment will be completed via phone to ensure privacy and individual service. The research team will complete encounter forms for all potential participants. During the recruitment call, the research staff will follow a script to gather information about eligibility status and give information about the study. The research staff will clearly explain the time commitment, expectations for participation, and answer any questions the participant asks. If the person expresses interest in enrolling, the team will schedule an in-person appointment to review the consent (visit 1).

8.0 Consenting Process:

8.1 Indicate the informed consent process(es) and/or document(s) for the study. Check all that apply.

Written Consent
☒ Informed Consent (ICF) – written or electronically signed form
☐ Parental Permission – written or electronically signed form
☐ Assent (participants under 18) – written or electronically signed form

☐ Combined ICF/PHI Authorization – written or electronically signed form
☐ Protected Health Information (PHI) Authorization – written or electronically signed
☐ Translated Consent/Assent – written or electronically signed form(s)
☐ Short Consent Form – written or electronically signed form (see guidance on **Short Form process**)
☐ Debriefing Script or Form – document used to properly inform subjects of the study's purpose when intentionally deceived

Oral/Online/Unsigned Consent (Appendix for Alteration/Waiver of Consent or PHI is Required)
☐ Informed Consent – oral script/online/unsigned
☐ Parental Permission – oral script/online/unsigned
☐ Assent – oral script/online/unsigned
☐ Translated Consent/Assent – oral script/online/unsigned

Waivers of Informed Consent and/or PHI Authorization
☐ Waiver of Consent
☐ Full Waiver of PHI Authorization
☐ Partial Waiver of PHI for Screening Purposes

8.2 Describe in detail the consent processes checked above, including any waiting period for subjects to sign the consent, steps to minimize the possibility of coercion or undue influence, and the language used by those obtaining consent.

If potential participants are interested and meet the general inclusion criteria we will set up a meeting at a convenient time and location (at their home, the university, or another private location of their choice). Prior to the meeting, we will email the time details to the potential participant and attach a copy of the Informed Consent Form (ICF) so they will have time to read it and prepare any questions for the meeting. We have found it helpful working with older adults to give them an opportunity to review the consent form in their home and ask family/significant others to review it. In this way they know what is involved and are not trying to understand the procedures in a potentially stressful situation. At the appointment, we will use REDCap to review the ICF with the potential participant and answer any questions. Individuals who decide to join the study will be asked to add their electronic signature to the ICF in REDCap. In the event REDCap is not available during the study visit (e.g. power outage or computer issue) we will have backup printed copies of the ICF) available. The participant will be given one copy and the research staff will use another copy to guide the participant through the consent information. We will read the consent while the participant reads the consent form. The research staff will ask if the participant has any questions. No data will be collected unless the participant elects to sign the consent form. If the

individual needs more time to make a decision, we will schedule a subsequent meeting to obtain the signature on the consent form and start the data collection. The participant will be provided a copy of the consent form to refer back to at any time.

8.3 Where will the original signed consent and PHI authorization documents be stored?

The MEDSReM Research Team office at the University of Arizona College of Pharmacy Skaggs building Rm 108 and our Box Health folder.

8.4 Acknowledgement of consent form storage.

☒ I will store original signed consent and/or PHI authorization documents for at least 6 years past the time the study is concluded.
☐ For studies involving minors, I will store original signed consent and/or PHI authorization documents for at least 6 years after the youngest participant turns 18.
☐ Not applicable – I am not collecting signed documents.

9.0 Research and Data Collection Procedures:

9.1 Select the methods of data collection that will be used in this study (select all that apply):

☐ Anthropometric measures (e.g., height, weight, waist circumference, etc.)	☒ Participant observation
☒ Audio/video recording	☒ Screening data
☐ Benign interventions	☐ Self-health monitoring (e.g., pedometers, food diaries, etc.)
☐ Biological specimens – blood draws	☐ Surveys – paper
☐ Biological specimens – clinically discarded blood or specimens	☒ Surveys – internet (including online and email-based data collection)
☐ Biological specimens (urine/feces, tissue, saliva, skin, hair, nails, nasal swab)	☒ Surveys – telephone
☐ Clinical Data Warehouse (CDW)	☒ Randomization with control and experimental groups
☒ Cognitive or behavioral measures, including daily diaries	☐ Records – billing

☒ Data collected using other communication/electronic devices (e.g., cell phones, pagers, and texting devices)	☐ Records – educational
☐ Data previously collected for research purposes	☐ Records – employee
☐ Deception	☐ Records – lab, pathology and/or radiology results
☒ Instrumentation, equipment, or software not approved by the FDA	☐ Records – mental health
☐ Interviews – focus groups	☐ Records – substance abuse
☐ Interviews – in person	☐ Research imaging protocols
☐ Interviews – virtual/online	☐ Recombinant DNA
☐ Medical records review	☐ Social networking sites
☐ MRI/ultrasound with contrast	☐ Stem cells
☐ MRI/ultrasound without contrast	☐ Radiation Scans (X-Ray, CT Scans, etc.)
☐ Non-invasive instruments (e.g., external sensors applied to the body)	☒ Other activities or interventions – describe: use a blood pressure digital therapeutic

9.2 Description of research procedures.

Telephone Screening: The research staff will follow up with interested potential participants who shared their contact information ideally the next day for formal recruitment into the study. The team will document all attempts to contact potential participants and will vary day and time of contact attempts if the person is not reachable on the first attempt. While general information about the study will be given face-to-face in community settings, formal recruitment will be completed via phone to ensure privacy and individual service. The research team will complete the pre-screen encounter sheet for all potential participants. During the recruitment call, the research staff will follow a script to gather information about eligibility status and give information about the study. The research staff will clearly explain the time commitment, expectations for participation, and answer any questions the participant asks. If the person expresses interest in enrolling, the team will schedule an in-person appointment to review the consent (visit 1).

Screening (visit 1) and Run-in (4 weeks): A private room will be reserved for all study visits. Frailty or travel fear will not limit participation as we will examine the effect of the intervention on the spectrum of older adults. All study visits will take place at a location

preferred by the participant (e.g., University, home, senior center). Through a formal consent procedure, the study will be described to potential participants. They will be informed that if eligible, they will be randomly assigned to either the MEDSReM or Education group. Participants will complete screening [Geriatric Depression Scale (GDS-15), Snellen chart, Montreal Cognitive Assessment (MoCA), Beliefs about Medications Questionnaire (BMQ), Technology Readiness Index (TRI 2.0), Newest Vital Sign (NVS) and Chew et al. health literacy questions, Hypertension Knowledge Level Scale (HKLS), Trail Making Test (Trails A & B), Reverse Digit Span] and demographic questionnaires online via RedCap. Two BP readings will be obtained with the participant sitting and standing.

One randomly selected hypertension medication will be monitored via MEMS® cap (AARDEX Group, Liège, Belgium) for 4 weeks for each participant. Potent loop diuretics (e.g., furosemide) will be excluded as people vary use and time of dosing to prevent frequent urination. The names of all other hypertension medications taken by each participant will be placed in an opaque envelope, and one drawn for MEMS® monitoring. The selected medication will be transferred to a MEMS® container by the participant. Participants will be given a blank adhesive label and asked to write their name, medication name, dosage, and administration instructions from their original hypertension medication bottle. They will be asked to place the completed label onto the MEMS® container. The newly labeled MEMS® bottle will be checked against the original medication bottle label by the research staff to ensure accuracy of the transcribed information. Our study can use IBM Micromedex® Drug ID to check on actual medications/pills that are inside the bottle, but we will provide this only if the participant asks. Participants will also be asked to place future refills in the same container. If medicines change, participants will be asked to call the study staff to obtain a new MEMS® container. The participant will be asked to record medication changes, life events (e.g., new diagnosis, vacation without MEMS® bottle), and any adverse event experiences on a medication log sheet. If any participant is currently using a medication organizer, the organizational strategy will be preserved using a box with seven compartments, each the size of the MEMS® container, for the monitored medication. The seven compartments will be labeled with the days of the week (SMTWTFS), which will allow the participant to move the MEMS® container to the next day after the medication has been taken. If the monitored medication is prescribed more than 1 time per day, a second box will be provided. In this way, the MEMS® cap can be used for all participants without interfering with their organizational strategies. This MEMS® cap protocol was successfully used by the study investigators during previous R01 and R21 studies. An appointment will be scheduled for the adherence assessment and MEDSReM intervention or Education comparison visit (visit 2) at the participant's preferred location.

Enrollment with Randomization to MEDSReM or Education (visit 2): At this visit, the percentage of correct inter-dose intervals will be calculated for the last 2 weeks (of the

4-week monitoring period) as baseline because initial electronic monitoring has been shown to change behavior in the first 2 weeks, but adherence behavior returns to baseline in the last 2 weeks. If adherence is ≤ 90%, participants will be invited to take part in the 6-month intervention trial. Participants will also complete the additional primary and secondary outcome measurements [Medication Adherence Report Scale (MARS-5), BP (sitting and standing), Mobile Device Proficiency Questionnaire (MDPQ), and Treatment Self-Regulation Questionnaire + Perceived Competence Scale (TSRQ+PCS)] during visit 2. The participant's medication log sheet will also be reviewed.

Using a random number sequence, eligible participants will be randomized to MEDSReM or Education group. The participant is the unit of randomization, and the allocation ratio is 1:1. Older adults are likely to take multiple medications and have comorbid conditions, but we expect person-level randomization to distribute the effects of polypharmacy and comorbidities across the groups. Because comorbidities and polypharmacy could impact both adherence and BP outcomes, they will be included as covariates and evaluated in relation to outcomes.

Older adults in the MEDSReM group will be provided the MEDSReM App on their iPhone and access to the full online portal. The study staff will walk the participant through the process of downloading the app to their phone and accessing the online portal. MEDSReM system will provide education, decision support, and reminders and monitor all hypertension medications and BP. The interventionist will teach the participant how to use the MEDSReM system. For participants randomized to the Education group, information on how to use the MEDSReM online portal to access education about hypertension and medications will be provided by the study staff. Visit 2 will be voice recorded to track fidelity to the intervention protocol and to identify how the set-up components were tailored. Intervention quality checks will be conducted by the project coordinator, under the direction of Dr. Lee, who will monitor fidelity to the intervention. At the completion of visit 2, participants will be offered $50 regardless of their enrollment or group assignment.

Teach Back (visit 3): A 1-hour follow-up visit will be scheduled 1 week after visit 2 to assess, reinforce, and/or reteach the MEDSReM system or education-only portal to ensure solid understanding and use capability. Participants will be asked to demonstrate and observed using the blood pressure system. Visit 3 will be voice recorded and checked for consistency. If drift from the initial intervention protocol is detected, the project coordinator will meet with the interventionist to review the audio recording, discuss areas in which the intervention strayed from the protocol, and conduct retraining. Sitting and standing BP will be measured and the medication log sheet will be reviewed.

Study Follow Up (visit 4 and visit 5): Adherence by MEMS® monitoring for MEDSReM and Education participants will be downloaded to a study laptop from the participant's MEMS® cap via a USB connected MEMS® cap reader/communicator at 3 and 6 months (visits 4 and 5) after the two intervention or education visits, respectively. Subjective adherence (MARS-5), competence and autonomy (TSRQ+PCS), and mobile device proficiency (MDPQ) will also be measured at those visits. Additionally at visit 5, we will administer the Hypertension Knowledge Level Scale (HKLS) again and complete the Blood Pressure Study Opinion Questionnaire. To ensure we capture all of the participant feedback and opinions the responses to this questionnaire will be audio recorded. During all study visits, sitting and standing BP will be taken twice and the medication log sheet will be reviewed. If a problem is detected during a visit (e.g., adverse reaction to medication), the participant's primary care provider will be notified. If elevated BP (>180 mm Hg systolic or 110 mm Hg diastolic) is detected, the participant will be referred to their healthcare provider. If the BP reading is unusually low (<90 systolic) or drops more than 20 mmHg when standing, participants will be informed and instructed to call their providers. The PI or program coordinator will contact the health care provider as well to ensure safety. Participants in both groups will be instructed to call the program coordinator if their hypertension medications change, or if they have problems or questions after the two intervention or education visits. MEDSReM intervention does not change the participants' medications.

A research staff blinded to the group assignments will conduct visits 4 and 5. Along with the primary and secondary outcome measures, cognitive function (MoCA), and hypertension knowledge (HKLS) will be measured at visit 5. At the completion of visit 4, participants will be offered $50. At visit 5, the MEMS® cap will be retrieved, and the participants will receive $50.

9.3 Specify the total estimated time commitment for subject participation, and the estimated time commitment for each activity.

The study will initially take 4 weeks, and if the participant is eligible, an additional 6 months. During the full 6 months of the study, the participants will be asked to attend 5 visits. Each visit will range between 60-90 minutes for a total of 6 hours.

9.4 If any biological specimens (blood, urine, tissue, etc.) are being collected for research, state the amount, method, frequency, and type of specimen to be collected and what the specimen will be used for.

NA

10.0 Potential Benefits to Subjects:

10.1 Describe the anticipated benefits of this study to society, academic knowledge, or both.

If we find the MEDSReM system effective, then we will be able to market the first theory and evidence-based adherence system, specifically designed for and tested among older adults with hypertension. MEDSReM has the potential to improve hypertension medication adherence, which can improve blood pressure, prevent complications, and improve quality of life of the older users. Participants will provide expert advice on how technology might be used to help older adults self-manage medications. This view is collaborative and respectful and older adult participants appear to enjoy engaging with the research staff in prior studies.

10.2 Describe any benefits that individuals may reasonably expect from participation (not including compensation, which cannot be considered a benefit of participation).

If the participant is eligible for the 6-month study, they will receive information on hypertension and medications. The participant may also improve their medication taking.

11.0 Risks to Subjects:

11.1 Describe all physical, psychological, social, legal, and/or economic risk that could be associated with participation in this research.

The largest risk posed by participation in the study is unintentional loss of confidentiality of one's health-related information. To avoid breaches of confidentiality, we will be using computer-based data collection procedures. This reduces the number of people who view the data, and increases protection of the data. All data will be stored and managed in a central location at the College of Pharmacy on a secure server. Participant names will not be kept with the data. All data files will be assigned a code number identifier.

There is some risk of fatigue. For participants who currently use a pillbox or organizer the use of the medication bottle with the special cap may interfere with their existing strategies to remind them to take their medications. To mitigate this interference, those who use a pillbox or organizer will be supplied a box that allows them to move the MEMS® container from one day to the next. The box will be labeled with day of the week, consistent with pill organizers. If the participant reports feeling faint or lightheaded or a high blood pressure reading (over 140 mm Hg systolic or over 90 mm Hg diastolic) is measured they will be asked to contact their health care provider. Similarly, if their blood pressure reading is unusually low (below 100 systolic) or drops

significantly (more than 20 mm Hg) when their blood pressure is measured while standing they will be instructed to call your health care provider.

11.2 Discuss what steps will be taken to minimize risks to subjects/data.

To protect subject privacy, no names will be used or any identifying information in reports or study discussions. Each participant will have a code number and the link between the code and the name will be destroyed after 2 years post study completion.

To protect data confidentiality, transcriptions from the audio recordings will not be identifiable and will be destroyed within 6 years of study completion. The audio recordings themselves will be erased once transcribed.

12.0 Costs, Compensation, and Injury:

12.1 Describe any costs, monetary and non-monetary, that subjects may incur. This includes time.

There are no costs involved with participating in the study. The study will initially take 4 weeks and if the participant is eligible, an additional 6 months. During the full 6 months of the study, the participants will be asked to attend 5 visits. Each visit will range between 60-90 minutes for a total of 6 hours.

Discuss the amount of compensation (monetary and/or non-monetary) subjects may receive. Describe if compensation will be prorated.
The compensation is structured as follows: 1) $20.00 Amazon gift card after visit 1. 2) $30.00 Amazon gift card following the first 4 weeks in the study (visit 2). 3) $50.00 Amazon gift card for data collection 3 months post-intervention (visit 4); and 4) $50.00 Amazon gift card for data collection 6 months post-intervention and study closeout (visit 5).

13.0 Privacy of Subjects and Confidentiality of Data:

13.1 Describe steps, if any, to protect the privacy of the subjects throughout their participation (e.g., during the recruitment process, consent process, and/or research procedures).

No names will be used or any identifying information. A participant will be assigned a code number and the link between the code and the name will be destroyed after 2 years post study completion.

Only de-identified data will be stored in REDCap and a secure Box Health file with study ID for tracking purposes. The master list that links the participants' personal information with the de-identified data will be kept under password protection on a secure university server separately from the data at all times. Hard copy data will be kept in a locked cabinet inside a locked office.

13.2 Describe if data or specimens will be kept for future research, including unspecified future research and genetics. If data or specimens will be stored in a repository, indicate who holds the repository and what information will be sent to the repository. Ensure this information is reflected in the subject's informed consent form.

NA

13.3 Discuss how study results will be shared with subjects, families, and/or the institution, both immediately and long-term.

Participants will be thanked for their involvement with the study and provided feedback on their blood pressure.

13.4 Indicate if the research team will be accessing any of the following records.

☐ Substance abuse records (HIPAA and 42 CFR Part 2)
☐ Medical records (HIPAA)
☐ Educational records (FERPA)*
☐ Employee records (ABOR Policy 6-912)*
☐ Other, specify: Click or tap here to enter text.

NA

13.5 For each record source selected above, summarize the data elements to be accessed, who will access them, and how the information will be obtained.

NA

13.6 Indicate where data will be stored:

☐ Box@UA	☐ OnCore
☒ Box@UA Health	☐ PACS medical imaging software
☐ Clinical Data Warehouse (CDW)	☐ Password Protected Drive
☒ Cloud Server	☒ REDCap
☐ Department Drive	☒ Transmitting/receiving subject data to/from an outside group
☒ Department Office	☐ UA Records Management & Archives
☐ Encrypted Drive	☐ Banner Server/Platform, specify:
☒ External Drive (hard drive, USB, disk)	☐ Other, specify: Click or tap here to enter text.
☐ Google Suite for Education	

13.7 For EACH of the storage locations checked above, discuss the type of data to be stored, including if the data is identifiable, coded, or de-identified upon storage. Discuss who may have access to the data and how long the data will be kept.

We will be using computer-based data collection procedures via REDCap. Information about this research study will remain confidential. All participants will be assigned a participant code that is not related to their personal information in any way. This participant code will be used for all in-person data collection. There will be one master sheet linking participant name and device user names to the participant code. This sheet will be electronically stored on Box Health with restricted access to the research team. The master sheet will be destroyed at the end of the project period. Any electronic copies of the data will be stored by participant code in Box Health that only research team has access to, including the interview recordings. Once recording files are uploaded to the Box Health, these files will be deleted from the initial recording device. Strict security will be maintained to access the Box Health. No identifying information will be mentioned in any presentations or publication.

All hard copies of the consent forms will be kept in locked files at the University of Arizona College of Pharmacy Skaggs building Rm 108 for 6 years after the completion of the study.

Ephibian, our contracted MEDSReM (iOS app and website) developer, uses Microsoft's Azure cloud services platform to host and support the necessary MEDSReM servers and corresponding operating systems and software. MEDSReM's required servers include database, web, and Application Programming Interface (API) servers. Azure supports HIPAA compliance and incorporates all the necessary safeguards to ensure HIPAA requirements can be satisfied. Microsoft provides a secure VPN and web portal to connect to Azure, so any data uploaded to or downloaded from Azure is encrypted and all data stored in its cloud instances are encrypted. HIPAA requires access controls to be implemented to limit who can access PHI. Azure offers these controls and uses Active Directory to allow permissions to be set. Azure includes detailed logging, so administrators can see who accessed, or attempted to access PHI. The MEDSReM system records a username, an email address associated with the provided username, reported medication taking event times, and downloaded or manually entered BP readings from the Withings BPM Connect device (an FDA approved device since May 2011). The username, medication taking event times, and blood pressure readings will be uploaded to Box Health. These data will be stripped of the username, relabeled with the participant code, and merged with the data collected during the in-person visits.

The Withings BPM Connect device reads and stores participant BP data. The BP data is uploaded from the BPM device to the Withings servers with a unique username and an email address associated with the provided unique username. Withings notifies Ephibian when new BP data are available and the MEDSReM system downloads the new BP data from the Withings server. Withings follows all the GDPR rules to protect the data and all data sent from their blood pressure monitor device to their server is encrypted.

The MEMS® cap records and stores the date and time when the participant opens the study bottle. During the study visits a MEMS® USB NFC (Near Field Communication) reader will be used to transfer the

time-stamped medication taking events from the MEMS® cap to a password protected laptop only accessed by study staff. These data will be uploaded and stored in Box Health.

13.8 Describe what security controls (e.g., administrative, physical, technical) are in place to make sure data/specimens are secure.

All data will be stored de-identified and in the secure Box Health file with only the research team having password-protected access.

13.9 Indicate how data/specimens will be shared with collaborating entities:

☐ Data and/or specimens will not be shared between UA and any outside group or collaborating entity.
☐ Data/or specimens will be transmitted and/or disclosed to an outside group or a collaborating entity.
☒ Data and/or specimens will be received from an outside group or a collaborating entity.
☐ PHI will be transmitted to or received from an outside group or a collaborating entity. *
☐ A Limited Data Set will be transmitted or received from an outside group or a collaborating entity. *
☐ Data/specimens will be sold to pharmaceutical companies.

Data from the MEDSReM system will be uploaded to Box Health, stripped of the username, and relabeled with the participant code.

13.10 Describe what information will be shared, who it will be shared with, and how it will be shared (e.g., secure file transfer, REDCap, etc.):

The MEDSReM system records a username, an email address associated with the provided username, reported medication taking event times, and downloaded or manually entered BP readings from the Withings BPM Connect device. These data will be uploaded to Box Health, stripped of the username, and relabeled with the participant code.

14.0 Additional Questions (complete as applicable):

14.1 <u>Subject Injury</u>: If the research involves more than minimal risk to subjects, describe the provisions for medical care and available compensation in the event of research related injury. If the Human Research has a clinical trial agreement, this language should reflect what is stated in the agreement.

There is no risk for injury to participants in this study. The participants' medications will not be changed by the intervention. If, during the process of checking blood pressure a high (over 140 mm Hg systolic) or

(over 90 mm Hg diastolic) is found, the participant will be encouraged to contact their health care provider. If the person feels faint or lightheaded, they will be asked to contact their health care provider.

14.2 Withdrawal of Subjects: Discuss how, when, and why subjects may be removed from the study. If abrupt withdrawal is necessary, discuss how subjects will be withdrawn so that they are not put at increased risk. Discuss what happens if a subject is withdrawn from one part of the study but asked to continue with other parts, such as ongoing follow-up.

Participants can withdraw at any time from the study without creating hard feelings or interfering with any care or service. We will retain data from any participants who withdraw since we plan to use intention to treat analysis.

14.3 Monitoring for Subject Safety: Provide a brief lay discussion of your plan to monitor for subject safety. Describe what safety information will be collected, including serious adverse events, how safety information will be collected, and the frequency of collection including a timeline of when the data and review(s) will occur, who will review the information, and the plan for reporting findings.

If there will not be a way to monitor for subject safety, please explain.

We will follow a MEDSReM Safety Monitoring Schedule as the quality assurance process to verify data integrity and validation. Prior to the onset of the RCT, the Safety Monitoring Committee (SMC), including a geriatrician and biostatistician, will review the full study protocol including data collection process and forms. Any recommendations for adjustment will be discussed with the MPI and program coordinators. The SMC will continue to review the research protocol, progress on trial, data integrity, recruitment/enrollment/retention, participant risk vs benefit, and safety factors as needed throughout the study. Each month, the program coordinator will be responsible for auditing 10% of participant records for compliance with the IRB and informed consent requirements, verification of source documents, and integrity of data collected to ensure adherence to the study protocol. A summary of the audits will be presented to the MPI and SMC at bi-yearly meetings or as needed and any adjustment to the study protocol will be discussed.

We will identify, review, and report any adverse events and unanticipated problems to the University of Arizona IRB, NINR and FDA (if adverse drug event). Although this is a clinical trial, minimal adverse events are anticipated as the participant's hypertension medication regimen is not altered by the intervention.

We will use the FDA definition of adverse event, "any untoward medical occurrence that may present itself during treatment or administration with a pharmaceutical product, and which may or may not have a causal relationship with the treatment" (http://www.fda.gov/cder/guidance/iche3.pdf). Though we will neither administer study medications nor change the participant's usual prescribed regimen, we will report any adverse incidents observed during the study that result from their medical conditions or treatment according to the NIH Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-Supported Multicenter Clinical Trials (http://grants1.nih.gov/grants/guide/notice-files/not99-107.html). All study personnel will be trained to identify and accurately document any participant reports of study-related adverse events and report them to the program coordinator and MPI, Dr. Lee, who will help determine if such report requires an adverse drug event report to the FDA. Being a clinical

pharmacist with an active geriatrics practice, Dr. Lee is intimately familiar with monitoring and reporting adverse drug events to the FDA.

Since adherence may increase during the study, reducing BP further, BP will be taken during each study visit for both the MEDSReM system and education groups. BP will be measured twice, both sitting and standing. Sitting BP will be measured first while the participant is seated with his/her arm extended at the heart level. The participant will then be asked to stand for 1 minute prior to the standing BP measurement. The BP measures will be obtained after the participant has been seated for at least 15 minutes using a digital BP monitoring device (Withings BPM Connect, Issy-les-Moulineaux, Paris, France). Two sitting and standing BP measures will be taken 5 minutes apart following the procedures outlined in the 2017 ACC/AHA High Blood Pressure Clinical Practice Guideline, and averaged to obtain mean BP. If elevated blood pressure (greater than 180 mm Hg systolic or 110mm Hg diastolic) is detected, the participant will be instructed to call their primary care provider and/or the prescribing provider (if the primary care provider and prescriber differ) for prompt treatment.

Similarly, if the blood pressure reading is unusually low (below 100 systolic) or drops more than 20 mmHg when standing, participants will be informed and instructed to call their providers. In addition, the MPI or program coordinator will contact the participant's health care provider(s) to ensure safety. The participants in both groups will be instructed to call the program coordinator if their hypertension medications change. If participants experience problems such as symptoms of lightheadedness, dizziness, or syncope (fainting), they will be instructed to contact their primary care provider and/or the prescribing provider (if the primary care provider and prescriber differ). The MPI or program coordinator will also contact the research participant's providers to assure that they have been informed. No serious adverse events have occurred in the research team's prior studies of older people with hypertension.

If an adverse reaction to a medication is detected during a study visit, the participant's primary care provider will be notified by the program coordinator. If there is an adverse event, research personnel will contact the primary care provider on the same day to receive instructions for the transfer of the participant for treatment and follow up of the adverse event. Per the University of Arizona Research's Reportable New Information protocol, unanticipated adverse device effect (UADEs) are "any serious effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects." Any UADEs will be reported to the University of Arizona IRB within 24 hours of the report occurrence. The NINR Program Officer, and other federal agencies as indicated, will also be notified. The program coordinator will present summary of adverse events to the SMC and MPI during as needed monthly SMC meetings. These reports will also be included in the project's annual report to the IRB and NINR, submitted by Dr. Lee.

All study personnel will be trained to identify and accurately document any participant accounts of unanticipated problems and report them to the program coordinator. Participants will be instructed to call the research coordinator if any medication changes or adverse events occur. They also will be asked to record medication changes, life events (e.g., new diagnosis, vacation without MEMS® bottle), and adverse event experiences on their medication log sheet.

The program coordinator will report the incident to the MPI, Drs. Lee and Rogers to determine if the incident is truly unanticipated or study-related. Any severe unanticipated problem will be reported to the University of Arizona IRB and NINR Program Officer within 24 hours of the report of incident. The program coordinator will present unanticipated problems to the SMC during monthly meetings. The SMC will determine if changes to the research protocol is warranted to mitigate risks, such as modification of inclusion or exclusion criteria, addition of procedures for monitoring subjects, suspension of enrollment and/or research procedures, modification of informed consent, and provision of additional information regarding recognized risks. The summary of the unanticipated problems will be sent to the University of Arizona IRB and NINR post-SMC meeting by the MPI, Dr. Lee. The summary will also be included in the project's annual report to the University of Arizona IRB and NINR, submitted by Dr. Lee.

14.4 Data Management Plan: Please discuss the data management plan if required by your funding agency. For additional resources, reference the HSPP Data Management webpage.

The investigators will comply with the letter and spirit of policies on data sharing, and on sharing of unique research and product resources in connection with the proposal that do not harm the intellectual property position of either party. Both the University of Arizona and the University of Illinois commit to complying with the Bayh-Dole Act and will rely on NIH (National Institutes of Health) policies in this regard; specifically with the NIH policies on Data Sharing and Sharing of Research Resources.

Data coordination among team members occurs in several ways. First, resources will be shared among the team members through MEDSReM, in terms of system usage via a researcher portal developed by Ephibian. We can also use online collaboration tools, such as BlackBoard Collaborate and RedCap, which are part of the technology assets that the University of Illinois Office of Information, Security and Technology will make available to the project team members. Third, both universities use Box and we have already set up a sharing system for files related to the project. These are complementary elements to guarantee proper interaction and data sharing among the members of the project.

Data and resources generated during the performance of the project will be shared with the research community primarily via conference presentations, journal articles, and summary reports made available on laboratory and company websites. Technical manuals created during the project may be made publicly available via websites geared towards sharing resources in the research community or licensed, as appropriate, and after University review. Completely de-identified final data will be shared with existing and new collaborators of the laboratories participating in this project, using HIPAA-compliant file transfer methods (i.e., Box Health) once the investigators complete a data-sharing agreement. The data-sharing agreement will ensure that privacy,

confidentiality standards, and data security will be maintained at the recipient site and will prohibit manipulation of data.

International Research: Describe site-specific regulations or customs affecting the research, local scientific and/or ethical review structures that differ, and if community advisory boards are involved. If so, describe their composition and involvement. For research being conducted outside of the US, please explain any local laws, regulations, or customs the IRB needs to be aware of.

NA

Additional items needed for review:

- Word Versions of applicable subject materials: Consents, PHI Authorization Form(s), Recruitment Materials, Data Collection Materials, additional Participant Materials
- Current PI/Co-PI CVs or biosketch
- Advisor approval (if the PI is a student or medical resident)
- Department/Center/Section Review approval
- Scientific/Scholarly review approval
- Responsible physician approval (if the PI is conducting medical procedures for which he/she is not clinically certified to perform)
- Additional approvals, as needed (e.g., RIA/Banner feasibility, Export Control, Radiation, COI, UA travel registry, CATS, SRC, school district approval, tribal approval, etc.)

Other items as applicable:

- HSPP Appendices
- Data Monitoring Charter and Plan
- Drug/Device information
    - Applicable drug or device appendix
    - Investigator's Brochure, drug product sheet, device manual, user's manual, instructions for use, package insert, IND/IDE documentation, FDA 1572 form, 510k indication, FDA exemption, sponsor determination of device risk, etc.
- Multi-site information (for sites engaged in research where the UA is the IRB of record)
    - Appendix for Multi-site Research
    - Documentation of reliance
    - Copy of the site's human subjects training policy
    - CV and medical license (if applicable) of site PI
- Sponsor protocol, if separate from this form