PROTOCOL

Digital Self-management System to Support Blood Pressure Medication Adherence

21 Feb 2024

IRB Protocol for Human Subjects Research

Basic Information	
Title of Study:	Digital Self-management System to Support Blood Pressure Medication Adherence
Short Title:	Digital Technology to Support Adherence to Hypertension Medication
Principal Investigator Name:	Kathleen C. Insel
Principal Investigator's Department/Unit:	College of Nursing/Biobehavioral Health 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).

The prevalence of hypertension is estimated at 74.1%[1] for people ≥ 60 years, and uncontrolled hypertension is known to be a risk factor for cognitive decline.[2,3-5] Medication adherence decreases the potential effects of hypertension on cognition. Medication adherence is defined as using medications as prescribed based on a regimen agreed upon between a patient and their provider and is crucial to medication benefit. People with mild cognitive impairment (PwMCI) are at risk of medication non-adherence.

Mild Cognitive Impairment (MCI) refers to impairment in one or more cognitive domains without fulfilling the diagnostic criteria for dementia. It is estimated that approximately 16–20% of people aged 65 or older have MCI and are known to be at risk of developing dementia.[6,7] Given that the Food and Drug Administration (FDA) approved treatment of MCI is limited to intravenous infusion therapy, controlling co-morbid health conditions in PwMCI is critical to slow and possibly prevent progression to dementia. One of the strategies recommended by the World Health Organization (WHO) Global Action Plan on the public health response to dementia 2017– 2025 (WHO, 2017a)[8] is to improve the management of hypertension, a common co-morbid condition in PwMCI. If it were possible to control vascular risk factors by adhering to prescribed hypertension medications, cognitive decline could be potentially prevented or modified in PwMCI.[9]

Although PwMCI are unimpaired in basic activities of daily living (ADLs) they experience functional impairment in complex instrumental activities of daily living (IADLs) such as medication self-management.[10-13] Given that hypertension is asymptomatic and not associated with identifiable cues such as pain, it is easy for PwMCI to forget to take medications without regular reminders. The asymptomatic nature of hypertension also undermines the ability to sustain adherence because it is difficult to sense the improvement in health over time, and cues (e.g., pain) are not available to serve as reminders to take medications.[14] Thus, an innovative intervention approach is needed to effectively support hypertension medication adherence.

An appropriate strategy for improving hypertension management for PwMCI is to leverage the advances in mobile health (mHealth) technology to foster medication self-management by tapping into preserved skill learning and procedural memory[15-17] abilities. In terms of health monitoring technology, mobile applications (Apps) on smartphones hold strong potential for supporting self-management in older adults.[18] The number of older adults using smartphones is rising and is currently 81% for adults aged 60-69 years[19,20] making this a viable option for healthcare support. However, none to our knowledge have attempted to examine the use of health monitoring technology for medication adherence in PwMCI specifically tapping into preserved cognitive abilities such as skill learning and procedural memory.[21-23]

In our previous work, we developed and tested the theory-based Multifaceted Prospective Memory Intervention (MPMI) aimed at improving hypertension medication adherence.[24] The MPMI is the only medication adherence intervention that has used prospective memory theory and research to guide the intervention development.[25,26] The central goal of MPMI is to change medication-taking from an effortful process dependent on prospective memory to one more dependent on associative processes that are relatively preserved with aging. The MPMI was compared to an education-attention group among older adults aged ≥65 years. The MPMI resulted in a 35% increase in adherence to hypertension medications.[27] Our group has developed a mHealth technology called the Medication Education, Decision Support, Reminding, and Monitoring System (MEDSReM) to replicate the critical components of the MPMI. MEDSReM contains additional functions such as visualizations of adherence patterns over time and decision support specifically designed to meet the needs of older adults. Supported by an NIH grant, we have further refined the system to meet the needs of PwMCI through needs assessments, cognitive walk-throughs, heuristic evaluations, and iterative usability testing. This optimized system is called Medication Education, Decision Support, Reminding, and Monitoring System-Memory (MEDSReM-M)

MEDSReM-M system provides medication reminders consistent with the person's routines and prescribed frequency and is tailored to an activity (e.g., breakfast). Encouraging immediate action when reminded to take the prescribed medication at the correct time is a central component of MEDSReM-M as even a delay in the execution of a prospective memory intention as short as 5 seconds has been shown to lead to forgetting to do the intended task.[28] Monitoring is another critical component of prospective memory strategies, that is, creating the ability to check whether medications were taken as intended. PwMCI will be able to check and monitor whether they are taking their medication as intended using the MEDSReM-M system. Adherence is monitored over time, and users can see graphical representations of their adherence success. This type of feedback is motivating and can improve adherence in the long term.[29] The decision support tool improves proper adherence and reduces risk by responding to questions about whether to take a medication early. The system also offers education about hypertension and health management. The goal of the current study is to test the efficacy of MEDSReM-M system for PwMCI in a randomized controlled trial (RCT).

References

1. Stierman B, Afful J, Carroll MD, Chen TC, Davy O, Fink S, et al. National Health and Nutrition Examination Survey 2017–March 2020 prepandemic data files—Development of files and prevalence estimates for selected health outcomes. National Health Statistics Reports; no 158. Hyattsville, MD: National Center for Health Statistics. 2021. DOI: https://dx.doi. org/10.15620/cdc:106273. (accessed 6/13/2023).
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7. Roberts RO, Geda YE, Knopman DS, et al. The incidence of MCI differs by subtype and is higher in men: the Mayo Clinic Study of Aging. Neurology 2012; 78(5): 342-51.
8. Organization WH. Risk reduction of cognitive decline and dementia: WHO guidelines. Geneva: World Health Organization; 2019.
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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.

Uncontrolled hypertension is known to be a risk factor for accelerated cognitive decline in older adults. It is well established that PwMCI with vascular risk factors including hypertension convert to dementia at a faster rate compared to peers with no vascular risks. Although blood pressure (BP) medications are good at reducing the negative results of uncontrolled hypertension, the benefits of BP medications may not be realized due to non-adherence (not taking medications as prescribed). An underlying deficit in prospective memory contributes to such medication nonadherence issues in PwMCI. We have developed a digital medication self-management system called Medication Education, Decision Support, Reminding, and Monitoring-Memory (MEDSReM-M) system based on the unique needs and preferences of PwMCI. This system is designed based on the theory-based Multifaceted Prospective Memory Intervention (MPMI), which significantly improved older adults' adherence to BP medications in a previous study. MEDSReM-M changes medication taking from a complex process of holding information in mind over time to a

customized, cue-driven simple process that is mostly preserved in PwMCI. The current project aims to test the benefits of using the MEDSReM-M system relative to a standardized educational intervention to support medication self-management in PwMCI.

3.0 Purpose:

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

The purpose of this study is to examine the benefits of MEDSReM-M to support medication self-management in PwMCI.

Specific Aim: To determine the efficacy and identify predictors for the adoption of MEDSReM-M for PwMCI through a 4-month RCT relative to a standardized educational intervention.

Objective: To conduct a 4-month RCT to assess improvement in adherence, blood pressure (SBP), and technology acceptance in the MEDSReM-M group (N=50) relative to the standardized educational intervention group (N=50).

Hypothesis: We hypothesize that advances in technology can be leveraged in PwMCI to improve adherence by harnessing retained cognitive ability for skill learning and procedural memory.

Outcome: Completed RCT with identification of variables that inform improved adherence.

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. eIRB tip: For externally funded projects, the institutional proposal or award number provided must be linked in the "Study Funding Sources" section 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/NIH
	Institutional Proposal or Award Number: 019618-00001
	eDoc # (for multi-site projects):
☐ **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 multisite study involves the University of Arizona and the University of Illinois Urbana-Champaign. Potential participants for the proposed research will be identified through multiple avenues.

Available resources for potential recruitment: Recruitment will occur at varying sites in Arizona and Illinois with established partnerships with a variety of medical and community-based organizations. Participants will be recruited from neighborhood centers, senior living communities, area senior centers, and meal sites, which provide access to a diverse population of older adults in terms of age, sex, ethnicity, religion, education, and economic status. Dr. Insel gives talks at health-focused events, such as a public lecture series offered at area hospitals and community health fairs, and these events 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 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 through the encounter form (located in the appendix). The research staff will follow up with the potential participants ideally the next day, for formal recruitment into the study. Additionally, we will identify potential participants through local geriatric, cardiovascular, and primary care providers caring for older adults with hypertension who agree to display our recruitment brochures in their clinics (please see an example flyer for the language that will be used in flyers advertising the study). An ad in local newspapers will be used to reach older people not associated with sites or events using the same language as in the flyer. The print materials will contain both email and phone contacts of the project team so that participants may use either method with which they are most comfortable.

At Arizona, Banner University Medical Center, El Rio, Tucson Medical Center are potential recruitment options for this study. We will use the same language from the flyer and the emails found in the appendices to recruit prospective participants for this research study.

We will also use email to existing registries of people who have agreed to be contacted for potential participation in research studies. For example, Dr. Matt Grilli has an ongoing registry among the older adult community in southern Arizona.

We will seek site permission prior to recruitment activities.

At Illinois, participants will be recruited through Dr. Mudar's laboratory registry of PwMCI; Carle Neuroscience Institute, a recruitment site; and independent living seniors supported by CJE Senior Life in Chicago. Dr. Mudar has a registry of PwMCI who are interested in participating in research studies. The MCI registry was developed by Dr. Mudar's research affiliation and ongoing MCI studies with the Carle

Neuroscience Institute, which sees approximately 100 MCI patients per year. Also, participants will be recruited in partnership with community partners including CJE Senior Life, which supports about 20,000 older adults, including PwMCI, who live in independent living communities. 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), 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. None of these recruitment sites will be directly involved in conducting research activities.

The Site PI will ensure that recruitment, consent, and implementation of study protocol will be conducted by study personnel who have completed required human subjects training, Good Clinical Practice (GCP) certification, and Conflict of Interest (COI) review. Study staff will also adhere to standardized training in the study protocol. With participants' consent, audio and video (of the Zoom screening) recordings will be made of visits with participants and reviewed by the Site PI and project coordinator to ensure fidelity to protocol.

We are contracting with Ephibian, a local computer science and electrical engineering company. Ephibian serves as a technical resource to the research team linked to the MEDSReM-M system and will not directly interact with participants. Ephibian builds high-performance software solutions and for more than 25 years has served multiple audiences including the aging population; in particular, the Patient Reported Outcomes Consortia (http://c-path.org/programs/pro/). Ephibian helped develop the first version of MEDSReM and the advanced design of our MEDSReM-M system. They specifically built the system to protect the smartphone's local device information with encryption, protect all data transmissions, require pin entry for application access for additional user security, remove any data on user request or application uninstallation, and meet HIPAA security requirements.

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: PwMCI have only mild problems with cognition. They can make independent decisions without needing assistance and are capable of providing informed consent.
☐ 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.

PwMCI will meet the following general inclusion criteria: i) 60 years or older, ii) community-dwelling, iii) fluent in English, iv) have adequate self-reported visual and hearing ability to interact with others and with the smartphone, v) self-reported memory problems, (vi) the Modified Telephone Interview for Cognitive Status (TICS-M)[1] score between 27-37, vii) self-managing at least one antihypertension medication, viii) no diagnosis of dementia or other neurological disorders such as stroke, traumatic brain injury (TBI), and Parkinson's disease, ix) no major history of depression or other mental health diagnoses, and x) use a smartphone. Participants who do not meet these general inclusion criteria will be excluded.

Participants who meet general eligibility criteria and express interest in enrolling will be scheduled for a video screening. Electronic informed consent will be obtained from all participants using REDCap. After providing informed consent, participants will complete a background questionnaire. The Montreal Cognitive Assessment (MoCA)[2] will be administered to assess global cognition. The Geriatric Depression Scale (GDS)[3] will be administered to screen for elevated depressive symptoms. Participants with MoCA cut-off scores between 20 to 26 will be invited to participate in the study. If they agree to participate, they will be scheduled for in-person consenting for the RCT and baseline assessment. If a participant does not qualify or prefers not to participate despite being eligible, they will be thanked for their participation. The session will last approximately 45 minutes. All participants regardless of eligibility will be paid $15 for the video screening session.

Participants will not be excluded based on gender or ethnicity. Both women and men will be included, and both groups will be equally targeted for recruitment into the RCT. This project will include all potential participants regardless of their racial/ethnic background, limited only by the available population.

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2. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. Journal of the American Geriatrics Society 2005; 53(4): 695-9.
3. Yesavage JA, et al. Development and validation of a Geriatric Depression Screening Scale: A preliminary report. Journal of Psychiatric Research 1982; 17(1): 37-49.

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

A total of 100 PwMCI will be recruited. There will be two treatment arms: N=50 in the MEDSReM-M intervention group, which will be henceforth referred to as MEDManage-S, and N=50 in the standardized educational group, which will be henceforth referred to as the MEDManage-P. This is a multi-site project, and our local (University of Arizona) enrollment goal is n=60 participants. The research team at the University of Illinois Urbana-Champaign aims to enroll n=40 participants.

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 will use our well-established multi-pronged recruitment strategies, which include word-of-mouth, email, and telephone scripts to members of established registries; flyers and brochures shared by community organizations and partners; advertisements in newspapers and newsletters; potential opportunities on the radio and television and personal visits to community events. All recruitment materials will be pre-approved by the IRB.

- Emails will be used to contact people who have expressed an interest in participating in research studies and are in an existing registry (as in the appendix).
- The same language used in the flyer will be used in flyers (as in the appendix), bookmarks, and brochures. We will work on the graphics to provide these additional means of advertising the study, but the language will not vary from what is shown on the flyer in the appendix.
- If a participant leaves a phone contact, we will call them and share information about the study.
- We will share information about the study at talks given for community centers. We will use the encounter forms if people are interested in learning more about the study.
- Social media: using the same language as in the flyer, we will publicize the study on social media, television and print.

At Illinois, participants will be recruited through Dr. Mudar's (Co-PI) laboratory registry of PwMCI, Dr. Rogers's (Co-investigator) 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 these registries will be contacted about the study and inclusion criteria. These individuals will be emailed (see email drafts of the 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. Additionally, participants will be recruited from Carle Neuroscience Institute in collaboration with Dr. Daniel Llano (co-investigator), Staff Neurologist at Carle Hospital, and other local providers. Participants will also be recruited through community partners such as CJE Senior Life. CJE Senior Life supports about 20,000 older adults, including PwMCI, who live in independent living communities.

Phone Screening: Potential participants will undergo an initial phone screening to determine eligibility for the next step (the video screening). During this call, the research staff will gather information using the phone screening questionnaire and provide information about the study. The research staff will ask for the potential participant's verbal consent to retain information collected during the screening. If potential participants decline verbal consent, the research staff will not retain data from this call. TICS-M will be administered to screen for global cognition. Participants who score between 27-37 on TICS-M and meet the eligibility criteria will be invited to participate in a video screening. The research staff will clearly explain the time commitment, expectations for participation, and answer any questions the participant asks. If eligible individuals express interest in enrolling, the team will schedule an appointment for the video screening.

Video Screening: Electronic informed consent will be obtained from all participants using REDCap prior to conducting video screening. PwMCI will have no deficits in global cognitive functioning, as determined by TICS-M. Subtle cognitive changes observed in these individuals do not impact their ability to provide informed consent; therefore, no proxy consent will be required. After obtaining online informed consent, participants will complete a background questionnaire. The Montreal Cognitive Assessment (MoCA) will be administered to assess global cognition. The Geriatric Depression Scale (GDS) will be administered to screen for elevated depressive symptoms. Researchers will review and determine final eligibility for participation. Those who meet eligibility including a MoCA cut-off score between 20 to 26 will be invited to participate in the study. If they agree to participate, they will be scheduled for in-person consenting for the RCT and baseline assessment. If a participant does not qualify or prefers not to participate despite being eligible, they will be thanked for their participation. The session will last approximately 45 minutes. All participants regardless of eligibility will be paid $15 for the video screening session.

8.0 Diversity, Equity, and Inclusion

8.1 Explain how the research plan (recruitment, study population, data collection, etc.) is equitable and represents the demographic makeup for the location in which the research will be conducted.

There will be no discrimination based on sex/gender or racial/ethnic status.

Both women and men will be included. The proposed RCT is focused on examining the efficacy of MEDSReM-M with female and male older adults (≥ 60 years). Therefore, both groups will be equally targeted for recruitment into the RCT. We consider sex as a biological variable and will examine through point biserial correlations with adherence and BP.

This project will include all potential participants regardless of their racial/ethnic background, limited only by the available population. Racial/ethnically, Arizona is approximately 4.9% Black or African American, 30.9% Hispanic or Latino (primarily of Mexican American heritage), 55.5% Non-Hispanic White, 3.4% Asian, 5.4% American Indian and Alaska Native, and 2.8% more than one race. Illinois is approximately 14.7% Black or African American, 17% Hispanic or Latino, 61.7% Non-Hispanic White, 5.5% Asian, 0.6% American Indian and Alaska Native, and 1.9% more than one race. Since over 30% of the community is of Hispanic heritage in Arizona, specific efforts will be made to enroll members of this community including using staff familiar with the culture and community. The neighborhood centers, senior centers, and meal sites used for recruitment provide services for a significant number of older adults who reflect such an ethnic ratio because these sites are in various locations in the community serving ethnically diverse

populations. Furthermore, the study will be advertised using widely reaching methods including partnerships at community centers serving senior citizens throughout the community.

Prior experience and the establishment of social relations will improve participation. In fact, several investigations found that people of Hispanic heritage were more likely to participate than those of other racial/ethnic backgrounds and attributed the cooperation to cultural factors such as the simpatica social script that promotes positive social relations.[1] Prior relationships, clear elucidation of goals and procedures, the establishment of legitimacy, and familiarity of staff with the community, will each work in positive ways to encourage participation from diverse locations in the community.

1. Marin, G., & Marin, B. V. (1991). *Research With Hispanic Populations*. Newbury Park, California: Sage Publications.

8.2 Describe whether non-English speaking subjects will be included in the study. If yes, please explain how your research team is prepared to meet the needs of the population. If not, please explain why non-English speakers will be excluded from the study population.

Non-English speakers will be excluded from the study population because study materials (MEDSReM-M app and portal, screening tools, etc.) and standardized measures are in English. Future projects will seek funding to translate study materials and protocols into other languages, including Spanish.

8.3 What methods will you use to collect demographic information from participants? If you will not collect demographic information, please explain why not.

During the initial phone screening, verbal consent will be obtained, and limited demographic information to determine general eligibility (e.g., age, sex, education, race/ethnicity, living situation, comorbidities, and medications) will be collected from participants. Following the phone screening, the research staff will obtain informed consent from individuals who qualify for the video screening. During the video screening, the research staff will administer a background questionnaire.

9.0 Consenting Process:

9.1 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
☒ 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

9.2 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.

The consent process and forms will be presented to participants in English, as all individuals recruited for the study will speak, read, and understand English.

Verbal Consent for Phone Screening: At the beginning of the phone screening, we will obtain verbal consent from potential participants to retain the limited data collected during this brief conversation. The research staff will explain that declining consent to retain information obtained during screening will not have any influence on the eligibility assessment for the study. If potential participants decline verbal consent, the research staff will not retain data from this call. During phone screening, the research staff will clearly explain the time commitment, expectations for participation, and answer any questions the participant asks. If the person meets general eligibility criteria and expresses interest in enrolling, the team will schedule an appointment for conducting a video screening.

Informed Consent for Video Screening: Electronic informed consent will be obtained from all participants using REDCap to participate in a screening session over Zoom. Participants will provide a digital signature on a unique link sent to them. PwMCI will have no deficits in global cognitive functioning, as determined by TICS-M. Subtle cognitive changes observed in these individuals do not impact their ability to provide informed consent; therefore, no proxy consent will be required. Those who meet eligibility as determined by the video screening will be invited to enroll in the RCT. If a participant does not qualify or prefers not to participate despite being eligible, they will be thanked for their participation. All participants regardless of eligibility will be paid $15 for the video screening session.

Informed Consent for RCT: Following the video screening, if eligible individuals remain interested and meet the general inclusion criteria, study staff will set up an initial in-person meeting and baseline assessment at a convenient time and location for participants (at their home, the university, or another location of their choice, e.g., community center with site permission). Prior to this meeting, we will call and mail or email the time details to potential participants and attach a copy of the Informed Consent Form 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 when under what may be perceived as time constraints.

The consent form will include: 1) The purpose of the study; 2) Who will be asked to participate; 3) How many people are involved; 4) Study procedures to be used; 5) The length of the study; 6) The benefits and potential risks; 7) How confidentiality will be assured using a code number rather than names on documents; 8) Planned destruction of the link associating the subject's name to the unique code number; 9) The participant's right to withdraw from the study at any time; 10) Encouragement of participant to notify the primary care provider if they experience symptoms that they feel are in any way associated with their illness or medications; and 11) Access to the data by representatives of the sponsor that support the research study and representatives of regulatory agencies (e.g., The University of Arizona Human Subjects Protection Program).

Informed consent will be completed in-person in a private space with potential participants by research staff who are trained in Human Subjects Protection. The participant will be given a copy, and the research staff will use another copy to guide the participant through the consent information. Each section of the consent will be reviewed. Participants will be encouraged to ask questions and the research team will respond to the questions. Individuals who decide to join the study will be asked to sign the consent. A copy of the consent will be provided to the participant.

No data will be collected unless consent is obtained from the participant. If the individual needs more time to make a decision about whether to participate or not, we will schedule a subsequent meeting to obtain the signature before beginning data collection. The participant will be provided with a copy of the consent form. Phone numbers for the Site PI, study team, and the IRB will be provided on the consent form if participants have questions or would like to discuss the study or any concerns.

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

The original signed consent documents will be stored in the locked MEDSReM-M Research Team office at the University of Arizona College of Nursing building Rm 418E, and a scanned version will be placed in Box (folder). At the University of Illinois Urbana-Champaign site, the team will follow the same storage procedures and will store original signed consent documents in a locked office in the Speech and Hearing Science Building (Rm 209) and a scanned version will be placed the in Box.

9.4 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.

10.0 Research and Data Collection Procedures:

10.1 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.): arm circumference for selection of appropriate blood pressure cuff size	☐ Participant observation
☒ Audio/video recording	☒ Screening data
☐ Benign interventions	☒ Self-health monitoring (e.g., pedometers, food diaries, etc.): medication log sheet and blood pressure monitoring for those in the intervention group
☐ 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): MEDSReM-M system	☐ 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 of a blood pressure device

10.2 Description of research procedures.

To test the MEDSReM-M intervention efficacy, we will conduct a RCT. This is a multi-site study led by MPIs Dr. Kathleen Insel and Dr. Raksha Mudar and includes research staff at the University of Arizona (UofA) and the University of Illinois Urbana-Champaign (UIUC). Throughout the study, research personnel at both UofA and UIUC will adhere to the same study procedures as listed chronologically below:

Phone Screening: Phone screening will not be recorded. Formal recruitment will be completed via phone to ensure privacy and individual attention. The research staff will follow up with interested potential participants who have shared their telephone contact information, ideally the next day for recruitment into the study. The team will document all attempts to contact potential participants and will vary the day and time of contact attempts if the person is not reachable on the first attempt. During the screening call, verbal consent will first be obtained prior to asking questions to determine eligibility. The research staff will confirm that participants meet the following criteria: i) 60 years or older, ii) community-dwelling (that is not in an assisted living situation) iii) able to speak and read English, iv) have adequate self-reported visual and hearing ability to interact with others and the smartphone, v) self-reported memory problems, vi) managing at least one hypertension medication, vii) no self-reported diagnosis of dementia or other neurological disorder such as stroke, TBI, and Parkinson's disease, viii) no major history of depression or other mental health diagnoses, and ix) experience using a smartphone. If participants are eligible, they will complete the Modified Telephone Interview for Cognitive Status (TICS-m); eligible participants will score between 27-37. 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 and is eligible, the participant will be scheduled for a video screening. The phone screening will span approximately 5-15 minutes.

Video Screening: After providing electronic informed consent, participants will complete video screening. The video screening will be recorded. Video screening will include the Montreal Cognitive Assessment (MoCA), and Geriatric Depression Scale (GDS). Participants will also complete questionnaires on demographic information (age, gender, education, race/ethnicity, income, living situation, comorbidities, and medications), nature of support received by a caregiver, and health status. Responses to these items can be entered by the data collector directly into an electronic file. Participants with MoCA cut-off scores between 20 to 26 will be invited to participate in the study and complete an in-person baseline assessment. If they agree to participate, they will be scheduled for in-person consent for the RCT and baseline assessment. If a participant does not qualify or prefers not to participate despite being eligible, they will be thanked for their participation. The video session will last approximately 45 minutes. All participants regardless of eligibility will be paid $15 for the video screening session.

Visit 1 Baseline Assessment: The baseline assessment will be scheduled within three months of the video screening. Informed consent will be completed in-person for the RCT in a private space by research staff who are trained in Human Subjects Protection before study procedures are administered. Upper arm circumference will be measured to determine the appropriate-sized blood pressure monitor cuff. To obtain blood pressure readings (BP), the research staff will use the Omron 3 Series Upper Arm Blood Pressure Monitor (FDA approval: https://fda.report/GUDID/00073796100315) or the A&D UA-789 (FDA approval: https://fda.report/PMN/K062027), if participants require an XL BP cuff. Utilizing the 2017 American College of Cardiology/American Heart Association's guidelines for home blood pressure measurement (HBPM), BP readings will be obtained both standing and sitting. If a problem is detected

during the visit, for example an elevated BP (>180 mm Hg systolic or 110 mm Hg diastolic), or an unusually low BP reading (<90 systolic), or BP that drops more than 20 mmHg when standing, the research staff will encourage participants to contact their primary care provider.

The research staff will administer a background questionnaire (Modified TechSAge Background Questionnaire (TBSQ) (REDCap Version for PwMCI) and hypertension knowledge questionnaire (Hypertension Knowledge-Level Scale (HK-LS) [1]. Measures to characterize cognitive abilities and intervention outcomes will be administered, including the: Rey Auditory Verbal Learning Test (RAVLT verbal)[2]; Benson Complex Figure Copy Test and recall (BCFT) (Visual)[3]; Trail Making Test (TMT): A &B[4]; Multilingual Naming Test (MINT)[5]; Craft Story 21[6]; Medication Adherence Report Scale (MARS-5)[7]; Mobile Device Proficiency Questionnaire (MDPQ-16)[8]; Delis Kaplan Executive Function System (D-KEFS) Verbal Fluency and Color-Word Interference[9]; National Alzheimer's Coordinating Center (NACC) Number Span Text, [10]; and Prospective and Retrospective Memory questionnaire (PRMQ)[11].

Participants will be given a MEMS® medication bottle and cap (AARDEX Group, Liège, Belgium) that will track hypertension medication-taking to establish baseline adherence. Participants will be given a handout on MEMS® medication bottle and cap. If the participant takes more than one hypertension medication, one randomly selected hypertension medication will be monitored via MEMS® cap for 4 weeks for each participant. The names of all hypertension medications will be individually written on a slip of paper of the same size, and all placed in an opaque envelope. One randomly drawn paper will be used to determine the medicine that will be monitored using the MEMS®. The selected medication will be transferred to a MEMS® container by the participant. Participants will be given an 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. 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® cap and container.

The participant will be asked to record any time in which the participant could not use the container (hospitalizations, vacations, etc., or if they intentionally chose not to take the medication) on a medication log sheet. If a 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 one 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 ability to maintain the participant's organizational structure was successfully used by the study investigators during previous MPMI and MEDSReM studies.

Visit 1 will be recorded and will take approximately 90-120 minutes. At the completion of the assessment visit, enrolled participants will be compensated ($30). Research staff will schedule an appointment with participants for Visit 2, four weeks later.

Visit 2 – Intervention (will be audio recorded to ensure fidelity): Visit 2 will involve collecting adherence data and introducing participants to the intervention groups. Adherence data by MEMS® monitoring will be downloaded to a study laptop from all participants' MEMS® caps via a USB connected MEMS® cap reader/communicator. The research staff will review the participant's medication log sheet. The research staff will take both standing and seated BP. If elevated BP (>180 mm Hg systolic or >110 mm Hg diastolic) or unusually low BP reading (<90 systolic) or BP drops more than 20 mmHg between sitting and standing measurements, the research staff will encourage participants to contact their primary care provider. After these measures are obtained, staff will determine the participant's group assignment (MEDManage-S or MEDManage-P) based on randomization.

Randomization Process: The randomization process is designed to achieve the appropriate generation of the random allocation sequence and concealment of the allocation sequence. A researcher who is not involved in phone screening, video screening, or informed consent will generate the randomization list prior to the screening of the first person for the randomized, controlled trial. The randomization list will use computer-generated random numbers and will use block randomization. The block size will vary randomly between 4 and 6. Research personnel who perform phone screening, video screening, informed consent, or assessments will not be able to access the randomization list.

For participants randomized into the MEDManage-S intervention arm (MEDSReM-M app + Standardized Education via the portal; n=50), research staff will walk participants in this group, through the process of downloading the MEDSReM-M app to their phones and accessing the portal. The portal has standardized information on hypertension and medications and links to vetted resources (e.g., the American Heart Association, National Heart, Lung and Blood Institute pages) for laypersons on their phones. Participants in the MEDManage-P control arm (Standardized Education Group without the MEDSReM-M app; n=50) will receive education on hypertension and antihypertensive medications and the link to the participant portal that has the standardized information on hypertension and medications websites resources that have been vetted (e.g., the American Heart Association, National Heart, Lung and Blood Institute pages) for laypersons. The research staff will walk them through the process of accessing the portal on their phones. Participants in both groups will be recorded and checked for consistency. If drift from the initial intervention protocol is detected, the project coordinator will make a note of the session in the participant file on REDCap. The coordinator will meet with the study staff to review the audio recording, discuss areas in which the intervention strayed from the protocol, and conduct retraining. Please see screenshots of the app added to the appendix.

Visit 2 will take approximately 90-120 minutes, and all participants will receive $30 in compensation through checks, cash, e-codes, or gift cards based on participant preference. During this visit, participants in both intervention arms will be provided a blood pressure monitor to enable regular monitoring at home. The study staff will provide instruction on the 2017 American College of Cardiology/American Heart Association's guidelines for home blood pressure.

Online/Phone Session: Within a week of Visit 2, a telephone or Zoom visit will be held to assess, reinforce, and/or re-teach the use of the app and/or portal for MEDManage-S group to ensure solid understanding and use capability. Participants assigned to the MEDManage-P group will be asked how they are using the portal to ensure that the participant is comfortable using the portal for educational resources. This remote session will take approximately 15-20 minutes.

Visit 3 Post-Intervention Assessment (will be recorded): Four weeks after Visit 2, both MEDManage-S and MEDManage-P groups will complete an outcome assessment visit during which all outcome measures (adherence, BP, technology acceptance) including structured interviews will be administered. The interview will be audio-recorded for analysis. Along with the outcome measures, hypertension knowledge (HKLS) will be measured. Research staff will collect medication adherence data via the MEMS® tracking caps. Participants in both arms of the trial will continue to use the MEMS® medication cap and bottle that track hypertension medication adherence. During all the study visits, sitting and standing BP will be taken, and the medication log sheet will be reviewed. If there is elevated BP (>180 mm Hg systolic or >110 mm Hg diastolic) or unusually low BP reading (<90 systolic) or BP drops more than 20 mmHg between sitting and standing measurements, the research staff will encourage participants to contact their primary care provider. Visit 3 will take approximately 90-120 minutes and participants will be compensated $30 through checks, cash (for in-person visit), e-codes, or gift cards based on participant preference.

Visit 4 Follow-Up (will be recorded): Eight weeks after Visit 3, the research staff will conduct the final visit. Data will be collected regarding adherence and BP. Research staff will collect medication adherence data via the MEMS® and will collect the MEMS®cap and pillbox. Seated and standing BP will be measured and the medication log sheet collected. This close-out visit will take approximately 30-45 minutes and participants will be compensated $30.

If participants are unable to meet for Visit 4, the research staff will provide a postage-paid envelope and ask participants to return the MEMS® cap to the study office. The participants will be compensated ($30) for study completion through checks, cash (for in-person visit), e-codes, or gift cards based on participant preference. The research staff will offer an optional meeting remotely via Zoom to do the wrap up.

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2. Rey, A. (1958). Memorisation d'une serie de 15 mots en 5 repetitions. In A. Rey (Ed.), L'examen clinique en psychologie. Paris : Presses Universitaires de France.
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6. Craft, S., Newcomer, J., Kanne, S., Dagogo-Jack, S., Cryer, P., Sheline, Y., Luby, J., Dagogo-Jack, A. and Alderson, A., 1996. Memory improvement following induced hyperinsulinemia in Alzheimer's disease. *Neurobiology of aging*, *17*(1), pp.123-130.
7. Chan AHY, Vervloet M, Lycett H, Brabers A, van Dijk L, Horne R. Development and validation of a self-report measure of practical barriers to medication adherence - the Medication Practical barriers to Adherence Questionnaire (MPRAQ). Br J Clin Pharmacol 2021.
8. Roque NA, Boot WR. A new tool for assessing mobile device proficiency in older adults: The Mobile Device Proficiency Questionnaire. Journal of Applied Gerontology, 2016; 26.

9. Delis DC, Kaplan E, Kramer JH. Delis-Kaplan Executive Function System (D–KEFS): APA PsycTests; 2001.
10. Wechsler D. Wechsler Adult Intelligence Scale--Fourth Edition (WAIS-IV): Pearson Assessment, 2008.
11. Crawford, J., Smith, G., Maylor, E., Della Sala, S., & Logie, R. (2003). The Prospective and Retrospective Memory Questionnaire (PRMQ): Normative data and latent structure in a large non-clinical sample. *Memory*, *11*(3), 261-275.

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

Research Activity	Participant Estimated Time Commitment
Phone Screening	5-15 minutes
Video Screening	45 minutes
Visit 1 Baseline Assessment	90-120 minutes
*Eligible PwMCI who agree to participate in the study will be enrolled for **approximately 4 months** after randomization.*	
Visit 2 Training	90-120 minutes
Remote Teach-back Session	15-20 minutes
Visit 3 Post-Intervention Assessment	90-120 minutes
Visit 4	30-45 minutes
TOTAL	**365-485 minutes (6-8 hours)**

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

N/A. No biological specimens will be collected for this research.

10.5 If the study is a clinical trial, confirm registration with https://clinicaltrials.gov/ has been completed:

This study is not a clinical trial: ☐
Registration complete: ☐
Registration pending: ☒

11.0 Potential Benefits to Subjects:

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

If we find the MEDSReM-M system (app + portal) effective, then we will be able to offer the first theory and evidence-based adherence system, specifically designed for and tested among older adults with hypertension and MCI to the larger population of PwMCI. MEDSReM-M has the potential to improve hypertension medication adherence, which can improve blood pressure, prevent complications, and improve the quality of life of the users.

11.2 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 study, they will receive information on hypertension and medications. Participants may also improve their medication taking.

12.0 Risks to Subjects:

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

The primary risks of the evaluations and observations are fatigue and frustration due to the difficulty of some tasks. We will provide encouragement, scheduled breaks, and a supportive environment to make participation an interesting and beneficial experience.

There is a risk related to inadvertent loss of confidentiality of one's health-related information. Potential participants will be informed of the risks inherent in participating in this project and of the procedures to minimize any of these risks from occurring. The topic of the proposed research is not deemed to be particularly sensitive or emotionally charged. MEDSReM-M does not change the participants' medications. Although this study includes a technology designed to improve medication adherence and standardized educational intervention for the comparison group, we do not anticipate any health risks resulting from participation in the MEDSReM-M intervention or Standardized Education control group.

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. All participants in the MEDSReM-M intervention will be provided with a pillbox and encouraged to use it. The box will be labeled with the day of the week, consistent with pill organizers.

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

We will provide encouragement, scheduled breaks, and a supportive environment to make participation an interesting and beneficial experience and minimize fatigue during assessments.

To protect against loss of confidentiality, no participant names will be used on any forms for data collection, only project identification numbers. Only the Site PIs and the research coordinators will have access to the Master List that links personal and project identification numbers. All hard copy data files will be kept in locked files in the data storage area at the respective sites, while all electronic files will be stored in Box. Audio recordings and transcriptions obtained to assess fidelity will be stored in Box. All electronic communication between project staff in Illinois and Arizona will use project identification numbers that contain no personal information about participants. The information on specific individuals collected in this project will be used for research purposes only. In reference to such information in publications, presentations, or reports (i.e., individual case studies), no personal identifiers will be used.

Reports will only use aggregated data. No report of individual data will be provided. The Co-PIs and Co-Investigators will be responsible for monitoring data to ensure the safety of participants. A Data Safety Monitoring Committee will monitor any safety concerns and adverse events related to the RCT following the protocol. The DSMB will be established prior to IRB approval and subject recruitment.

13.0 Costs, Compensation, and Injury:

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

There are no costs involved with participating in the study, apart from the participants' time:

Research Activity	Participant Estimated Time Commitment
Phone Screening	5-15 minutes
Video Screening	45 minutes
Visit 1 Baseline Assessment	90-120 minutes
*Eligible PwMCI who agree to participate in the study will be enrolled for **approximately 4 months** after randomization.*	
Visit 2 Training	90-120 minutes
Remote Teach-back Session	15-20 minutes
Visit 3 Post-Intervention Assessment	90-120 minutes
Visit 4	30-45 minutes
TOTAL	**365-485 minutes (6-8 hours)**

Discuss the amount of compensation (monetary and/or non-monetary) subjects may receive. Describe if compensation will be prorated.

To promote the highest retention rate possible, participants will receive incentives at each data collection session for their time and participation in the study. The incentives vary in amount depending on the portion of the study and the amount of data collected during the session. Based on participants' preference, compensation will be rendered via checks, cash, e-codes or gift cards. Participants can withdraw at any time and will be paid a prorated rate of $15/hour for the hours spent in direct contact with the research team as part of the assessments or training.

Research Activity	Participant Compensation
Video Screening	$15
Visit 1 Baseline Assessment	$30
Visit 2 Training	$30
Visit 3 Post-Intervention Assessment	$30
Visit 4	$30
TOTAL	**$135**

14.0 Privacy of Subjects and Confidentiality of Data:

14.1 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).

To protect against loss of confidentiality, participants' names will be replaced by project identification numbers. Only the site PIs and the research coordinators will possess the Master List that links personal and project identification numbers. All hard copy data files will be kept in locked files in the data storage area at the respective sites, while all electronic files will be stored in Box. Audio recordings and transcriptions obtained to assess fidelity will be stored in Box. All electronic communication between project staff in Illinois and Arizona will use project identification numbers that contain no personal information about participants. The information on specific individuals collected in this project will be used for research purposes only. In reference to such information in publications, presentations, or reports (i.e., individual case studies), no personal identifiers will be used.

14.2 Will data be kept for future research, including unspecified future research and genetics? Yes ☒ No☐

14.3 If yes to the above question, describe future use plans here including any storage in a repository (if applicable), and what data will be retained/reused.

Within the Informed Consent document, there is a section that asks participants if the study staff may contact them in the future for other unspecified research participation opportunities. If the participants check "no," the study staff will not retain their contact information for future research. For those participants who provided permission by checking "yes," their contact information (name, phone number, email address) will be kept in a secured electronic file in Box. No data associated with this study will be stored with the contact information.

14.4 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. Participants may also benefit from improved knowledge about health technology mobile applications for older adults but will also help us to further develop this system to support older adults in successfully managing their antihypertensive medications. It has been our practice to send a summary of the study findings to all study participants once the data has been collected and analyzed along with the thank you for participating in the study from the Site PI.

14.5 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.

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

N/A. We will not be accessing any records listed in 14.5.

14.7 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)	☐Soteria
☐ Google Suite for Education	
☐HIPAA Research Computing Service	☐ Other, specify: Click or tap here to enter text.

14.8 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, and who may have access to the data.

We will be using computer-based data collection procedures for assessment 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 names and device usernames to the participant code. This sheet will be electronically stored on Box with restricted access to the research team. Any electronic copies of the data including audio files will be stored by participant code that only the research team has access to, including the interview recordings. Once recording files are uploaded to Box, these files will be deleted from the initial recording device. Strict security will be maintained to access Box. No identifying information will be mentioned in any presentations or publications.

Ephibian, our contracted MEDSReM (iOS app and portal) 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 Box. 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 Box.

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.

14.9 Storage of research records (research records should be maintained for whichever of the following time periods is the longest, select one):

☒ I will store research records for at least 6 years past the time the study is concluded.
☐ For studies involving minors, I will store research records for at least 6 years after the youngest participant turns 18.
☐ I will store research records for the length of time required by law or study sponsor, please specify: Click or tap here to enter text.

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

To protect against loss of confidentiality, participants' names will be replaced by project identification numbers. Only the Site PI and the research coordinators will possess the Master List that links personal and project identification numbers. All hard copy data files will be kept in locked files in the data storage area at the respective sites, while all electronic files will be stored in secured university Box.

14.11 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.

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.). Also include information about future use sharing and repositories Specify if the shared data will be identifiable, coded, a limited data set, or de-identified.

The MEDSReM-M system records a username, an email address associated with the provided username, and reported medication taking event times. These data will be uploaded to Box, stripped of the username, and relabeled with the participant code. All electronic communication between project staff in Illinois and Arizona will use project identification numbers that contain no personal information about participants. The information on specific individuals collected in this project will be used for research

purposes only. In reference to such information in publications, presentations, or reports (i.e., individual case studies), no personal identifiers will be used. All hard copies of the consent forms will be kept in locked files. Data from the MEDSReM system will be uploaded to Box, stripped of the username, and relabeled with the participant code.

15.0 Additional Questions (complete as applicable):

15.1 Subject Injury: 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 of injury to participants in this study. The participants' medications will not be changed by the intervention. The research staff will not alter the participants' standard of care in any way. If a problem is detected during a visit with participants, such as elevated BP (>180 mm Hg systolic or 110 mm Hg diastolic), an unusually low BP reading (<90 systolic) or BP that drops more than 20 mmHg when standing, the research staff will encourage participants to contact their primary care provider. At the participant's request, the research staff will assist with contacting the participant's healthcare provider, but the research staff is not altering the participant's standard of care in any way.

15.2 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 any 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. Participants will be paid a prorated rate of $15/hour for the hours spent in direct contact with the research team as part of the assessments or training.

15.3 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-M Safety Monitoring Schedule as the quality assurance process to verify data integrity and validation. Before the start of the RCT, the Safety Monitoring Committee (SMC), including a geriatrician and biostatistician, will review the full study protocol. Any recommendations for adjustment will be discussed with the Site PI 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 MPIs Drs. Kathie Insel and Raksha Mudar 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 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 Site PI.

Since adherence may increase during the study, reducing BP further. BP will be taken during each study visit for both 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 (Omron 3 Series Upper Arm Blood Pressure Monitor, FDA approval: https://fda.report/GUDID/00073796100315; or A&D UA-789 Blood Pressure Monitor, FDA approval: https://fda.report/PMN/K062027). The 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. If elevated BP (>180 mm Hg systolic or >110 mm Hg diastolic) or unusually low BP reading (<90 systolic) or BP drops more than 20 mmHg between sitting and standing measurements, the research staff will encourage participants to contact their primary care provider. 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). No serious adverse events have occurred in the research team's prior studies of older people with hypertension.

All study personnel will be trained to identify and accurately document any participant accounts of unanticipated problems and report them to the program coordinator, who will be responsible for reporting the event to the Site PI. Participants will be instructed to call the research team if any medication changes 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 MPIs, Drs. Kathleen Insel and Raksha Mudar, 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 National Institute of Nursing Research (NINR) Program Officer within 24 hours of the report of incident. The Site PIs will present unanticipated problems to the SMC during quarterly meetings. The SMC will determine if changes to the research protocol are 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 PI, Dr. Insel. The summary will also be included in the project's annual report to the University of Arizona IRB and NINR, submitted by Dr. Insel.

15.4 Data Management Plan: Please discuss the data management plan, if required by your funder. For additional resources, reference the HSPP Data Management webpage. If your sponsor/funding agency requires a Data Management Plan, please upload the approved copy in eIRB. This section and the informed consent form should contain all pertinent information including:

- **What data/metadata will be shared (imaging, survey; raw data or derived; protocol, data form; etc.)**
- **What repository will be used (if known)**
- **How will data be stored (in a de-identified or identifiable format)**

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. Resources will be shared among the team members through online collaboration tools. Both the 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) 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.

15.5 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.

N/A. We will not conduct any research outside of the United States.

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 CV or bio sketch
- Advisor approval (if the PI is a student or medical resident)
- Department/Center/Section Review approval
- Scientific/Scholarly review approval
- Responsible physician approval and CV (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, 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 for each site
    - Documentation of reliance
    - CV and medical license (if applicable) of site PI
    - Human Subject Training Verification for site PI and site staff
- Sponsor protocol and MOPs that are used in the study (if applicable)