Protocol

rSTAND: Remote Digital Health Intervention to Improve Balance and Reduce Fall Risk

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Remote Digital Health Intervention to Improve Balance and Fall Risk (rSTAND)

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Posit Science Corporation

INVESTIGATOR

NAME:_____
Signature:_____
DATE: _____

By signing here, the investigator acknowledges that he or she has reviewed and understands the protocol referenced above and agrees to comply with it. Additionally, the Principal Investigator's signature indicates that his/her site has not been the recipient of prior FDA 483 reports or other detailed audit findings. Any and all prior FDA 483 reports or regulatory warnings have been submitted to Posit Science Corporation prior to the commencement of this clinical trial.

Title

Remote Digital Health Intervention to Improve Balance and Reduce Fall Risk (rSTAND)

Principal Investigators and Key Staff

The trial is sponsored by Posit Science Corporation (PSC) and is funded exclusively by the National Institute of Health. PSC will assist with posting flyers and ads online and serve as the coordinating and data management center. Key staff may be found below:

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Overview

This study called rSTAND (*Remote Digital Health Intervention to Improve Balance an Reduce Fall Risk*) is a validation study to evaluate efficacy of a computerized training program (rSTAND) to extend older adults' functional independence and reduce fall risk. Both the study and the training program being investigated meet the criteria of **Non-Significant Risk**.

This study is registered in an online database for clinical trials that is run by the federal government. The purpose of this database is to serve as a resource with easily accessible information about publicly and privately funded research studies that are being done or have been done. This database will not include information that can identify participants that partake in the study. This listing is available to the public at http://clinicaltrials.gov.

Specific Aims

The primary objective of this study is to establish feasibility of the software-based cognitive training program built on the principles of brain plasticity with demonstrated efficacy and real-world effectiveness in healthy aging populations, and preliminary evidence of efficacy in fall risk, for deployment as a fully-remote intervention with several novel features.

Background

Approximately one third of community dwelling senior over age 65 are at risk of suffering at least one fall annually, resulting in fractures or other major injuries in over 10% of cases[1]. Fall risk increases quickly with advancing age, with risk doubling from age 65 to 75 to affect over 60% of older adults[2-4]. Although numerous fall prevention interventions have been developed, the prevalence of falls is increasing[3,4]. A recent analysis of longitudinal Health and Retirement Study data found that the prevalence of falls increased more than 8% between 1998 and 2010[4]. Collectively, falls and their consequences may result in disability, institutionalization[1], and even mortality[5]. Falls that ultimately resulted in a fatality were estimated in 2015 to cost $637.2 million, and the treatment of non-fatal fall injuries was estimated to cost $31.3 billion[6,7]. Thus, prevention of falls in older adults is critically important to ensure sustained functional independence later in life, prevent disability due to fractures or worse (premature mortality) and maintain the viability of our limited health care resources[6,7].

Interventions that target fall risk are classified as targeting intrinsic and/or extrinsic factors[8,9]. Intrinsic risk factors, predictive of future fall risk include advanced age, female gender, white race, poor balance and gait, vestibular dysfunction, poor lower extremity strength, low vision, cardiovascular disease, depression, dementia, and cognitive decline. Extrinsic risk factors include, polypharmacy, home environment (e.g., poor lighting, loose rugs) and type of footwear. *Single component* interventions that have been developed to prevent falls include exercise, targeted drugs and medication review, education, use of assistive-technology, home safety, psychological and surgical interventions [10]. Fall prevention interventions that involve combinations of two or more different types of intervention (e.g. exercise and home safety) are considered multifactorial or *multiple component* interventions. A recent Cochrane review (2018)[11] examined 62 randomized controlled trials involving multiple component interventions in healthy older people (ages ranging from 62 to 85 years, median of 77 years) living in the community (a total of 19,935 participants). Most interventions included the application of supervised or unsupervised targeted exercises, modification of the person's living environment, medication review, or the use of assistive technologies to aid mobility, communication and/or personal care. All of the interventions, except one, included a physical exercise as the main active component. As control interventions, trials included attention control, socio-educational interventions, a specific exercise targeting gait or balance or waitlist /inactive control. The main outcomes were the rate of falls (number of falls per person-years), the risk of falling (number of people with one or more falls) and the risk of recurrent falls (two or more falls in a specified time period). Secondary

outcomes were the presence of fall-related fractures, the need for medical attention or hospital admission due to falls, health-related quality of life (HRQoL) and adverse effects of the intervention. The authors found that 17 multiple component interventions with exercise as a main part of the program, seemed to be effective in reducing the rate of falls and the risk of falling (moderate quality of evidence) with slight improvement in the quality of life; however, only when compared with inactive controls. When compared with exercise interventions (i.e., well-matched control conditions) only one intervention study met the review criteria and demonstrated "very low-quality evidence" for change in rate of falls or risk of falling.

Strikingly, no intervention approach reviewed in the Cochrane review directly addressed the declining cognitive operations inherent in healthy aging. Especially considering that the integrity of the executive functions are correlated with balance, gait, and risk of falls[12-14]. Similarly, in a 2015 CDC report, in which 41 fall prevention interventions were reviewed[15], only two of the intervention approaches screened for cognitive decline (without intervening) and only one engaged participants in a cognitive challenge (walking an obstacle course while listening to a story) as part of the intervention. To date, although many programs and resources have been allocated toward fall prevention, little, or no attention has been paid to cognitive factors; despite the fact that older adults exhibit consistent declines in speed of processing and executive functions.

A growing body of literature supports the positive impacts of cognitive training on executive functions and mobility among healthy older adults, with preliminary evidence presented here that indicates that benefits also translate to balance, gait and body sway; effectively reducing fall risk. This is important, presently, as there is a growing need to apply interventions that improve balance as protection against the deleterious effects of memory *decline*. The transition to memory *problems* in older adults can dramatically increase the rate of falls. Notably, dementia, including Alzheimer's disease, which is generally associated with executive dysfunction, contributes to greater instability in gait and balance than healthy adults[46]. In fact, individuals with Alzheimer's disease are 2-3 time more likely to fall compared to healthy older adults[47]. Poor balance, mobility and depression can also diminish health-related quality of life and accelerate cognitive decline. Interestingly, in addition to improvements in balance, body sway and gait speed, cognitive training may also improve depressive symptoms and bolster health-related quality of life among older adults[38-41]. The intervention, therefore, may provide an effective, low-risk intervention to improve and sustain

good balance, as well as executive functions and information processing speed, to reduce fall risk and improve health-related quality of life.

General Study Design

We will employ a single arm study open label usability/feasibility study comprised of a computerized training program that targets core executive functions (working memory, inhibition), speed of processing and sustained attention, and is grounded on design principles that drive adaptive brain plasticity to improve cognitive function and bolster functional abilities in older adults with an elevated fall risk.

This project will recruit 30 participants, 65 years of age or older in this single-arm study, in an effort to obtain 24 completers. All study activities will be performed remotely. Potential participants will be recruited by Posit Science and will complete a remote informed consent. After consent, participants will complete the *Screening* (V0) to determine full eligibility. Those who are deemed eligible will complete the *Baseline* (V1) assessments. Following the baseline assessment, participants will be asked to wear a fall monitoring device (an Apple Watch) for the duration of the intervention period. During the *Intervention period,* participants will be monitored and supported as they engage in 50 sessions of *rSTAND training* program over 10 weeks. Study personnel will conduct check-ins with participants, as needed, to ensure no specific issues arise and to answer any questions. After completing 50 sessions of training, participants will then stop using the training program and will complete a *Post-intervention* (V2) assessment.

The protocol will be conducted in accordance with the protocol submitted to and approved by the Institutional Review Board prior to implementation.

Study Population

The study population is comprised of adults, aged 65 years or older, with at least one self-reported fall within the last 1 year or a self-reported mobility limitation. This study is open to all races, ethnicities, and genders.

Inclusion/Exclusion Criteria

Following informed consent, participants will be screened for the following inclusion/exclusion criteria.

Inclusion Criteria

1) Potential participant must be 65 years or older at the time of study screening.
2) Potential participant must be a US resident.
3) Potential participant must have at least one self-reported fall within the last year or difficulty walking one half a mile (5-6 blocks) or difficulty climbing one flight of stairs (10 steps). For example, must slow down, take a break or rely on handrail to complete task.
4) Potential participant must be fluent English speakers from the age of 12, per self-report, to ensure reasonable neuropsychological results on key assessments.
5) Potential participant must have adequate sensorimotor capacity to perform the program, including motor capacity adequate to control a computer mouse or a tablet.

Exclusion criteria:

1) Potential participant has had joint replacement surgery or significant joint/leg injury less than one year prior to the screening visit.
2) Potential participant has a joint replacement surgery scheduled within the next 6 months.
3) Potential participant uses a walker or wheelchair on a regular basis (use of cane is OK only if used as needed).
4) Potential participant has a diagnosis of benign paroxysmal positional vertigo (BPPV), labyrinthitis or suffers migraines that result in chronic vertigo.
5) Potential participant self-reports vision or hearing difficulties that would interfere with the ability to complete the study tasks.
6) Potential participant has untreated psychiatric conditions, including substance abuse/dependence disorders, recent hospitalization, ongoing chemotherapy or other cancer treatment.
7) Potential participant has medical illnesses, injuries or conditions predisposing to imminent functional and/or cognitive decline (e.g. multiple sclerosis, stroke, traumatic brain injury, dementia, etc.)
8) Potential participant is enrolled in a concurrent clinical trial involving an investigational pharmaceutical, nutraceutical, medical device, or behavioral treatment that could affect the outcome of this study. However, participation in standard treatments (e.g., occupational therapy) or use of prescribed medications (e.g., anti-depressants) is allowable.
9) Potential participant is using computer-based cognitive training programs or has used it within a month of the consent date.

10) Potential participants answers 'yes' to
Question 4 (Active Suicidal Ideation with Intent) or Question 5 (Active Suicidal Ideation with Specific Plan and Intent) on the Columbia-Suicide Severity Rating Scale (C-SSRS) or 'yes' to any of the suicide-related behaviors (actual attempt, interrupted attempt, aborted attempt, preparatory act or behavior) on the C-SSRS "Suicidal Behavior" *if the ideation or behavior occurred within 2 months from Participant's date of consent* (as recommended by the FDA for treatment trails.)

Recruitment

Study participants will be recruited through pools of patients already identified with fall risk at the Osher Lifelong Learning Institute at University of Massachusetts Boston, as well as the University of California San Francisco Memory & Aging Center. In addition, we will recruit through the Internet. Following IRB approval, study flyers and ads that include information about the study aims and procedures may be posted through Google, Facebook, Craigslist, Reddit, Nextdoor app, television, radio, the study website, as well as other web-based recruitment sites; in addition, efforts will be made to recruit participants through retirement and community centers. Participants may also contact the Posit Science team directly via the phone or the internet (email, website, social media, etc.). This approach is equivalent to a convenience sample approach, which is universal in controlled clinical trial recruitment.

Study recruitment materials will describe the opportunity to volunteer for a clinical trial to advance the science and improvement of fall risk. Participation in this study is completely remote, no in-person visits are required. The emphasis of the benefit will be on advancing science to assist others with elevated fall risk. Compensation will be described in appropriate terms that are not overemphasized relative to the remainder of the text. No indication of "free medical treatment" will be communicated.

All materials used for advertising or recruitment will have received IRB approval prior to implementation. If interested, they will be remotely screened and electronically consented using REDCap Cloud. The study personnel will manage these efforts and contact individuals that express interest.

PSC study personnel are required to follow Good Clinical Practices and institutional best practices in the identification and recruitment of research participants. PSC will directly manage and support this study in San Francisco, using standard and established methods.

Description of Informed Consent Process

Prospective participants who express interest in the study will be able to follow prompts to initiate the pre-screening process through a link sent to their email address to assess for general eligibility. Those who are deemed eligible will be invited to complete the consent process. Participants will read through the consent form as presented through REDCap Cloud. Participants will be prompted to call or email the study personnel who will review the consent form over the phone or via Zoom, and be available for any questions or comments, if they so choose. Participants will be provided a copy of the IRB-approved consent form detailing the general purposes and procedures of the study. The consent form will include the purpose of the study is to evaluate the effectiveness of a cognitive training program for improving fall risk, along with the potential risks and benefits. It will also be emphasized that there is no established health-related benefit acquired through participation and that no medical benefits will be lost if they choose not to participate or drop out of the project at any time. A member of the study staff will also sign the consent form. No study activities will take place prior to completion of the consenting process.

Participants will engage with the rSTAND training program in their place of residence. Their participation will include 50 sessions of computerized training over the course of a 10-week period, and include wearing a fall monitoring device (an Apple Watch) for the entire duration of the intervention period. The Apple Watch will be configured to contact emergency services in the event of a fall. Participants can choose to override this function in the event of a minor slip or loss of balance, or minor fall without injury. When a fall is detected, the Apple Watch will present two options: Emergency Services or “I’m OK”. If no response is made within a minute after a fall, emergency services will automatically be contacted.

Assessments will be completed at baseline and post-training. The training sessions and assessments will be scheduled at their convenience within the prescribed timeframes, and they may choose to discontinue their participation in the research at any time, for any reason.

To participate in this study, an individual must be judged capable of understanding the nature of the research and the risks and potential benefits. Special care will be taken to ensure that participants understand each aspect of the informed consent clearly. Within the consent form are six questions that will assess the participant's understanding of the study procedures and participation expectations. Participants that fail to correctly answer all six questions will not be able to complete the consent form without speaking directly with the study personnel via phone or Zoom. The qualified study personnel authorized by the Principal Investigator (PI) will review the consent form with the participant and ask the potential participant to explain their understanding of the study and what their involvement in the study would entail. The designated study personnel will discuss the nature of the trial, the purpose of the research, the trial procedures, the possible risks and benefits of participation, confidentiality and the voluntary nature of participation in the trial (emphasizing the participant's right to withdraw from the study at any time). In addition to allowing time for participants to read the consent form, specific contents of the consent form will be discussed with each participant, and any questions will be answered.

Participants may invite a friend or family member to be present during the call or Zoom to further discuss their decision to enroll in the study. In addition, participants will be provided the option to defer their decision to discuss their decision with friends or family members, and continue the consent process at a later time. At the participant's request, the study personnel may place them on 'hold' to provide privacy for such discussions. The consent form will include telephone and email contact information for the study personnel and the PI. At any point during or after completion of the study, the participant may contact the study personnel, PI or the reviewing Institutional Review Board to obtain additional information regarding his/her rights as a participant. No study activities will take place prior to completion of the consenting process. When the participant signs the consent form electronically, a copy of the informed consent will be provided directly to the participant and a second will be retained in a secure manner by the sponsor and be available for inspection upon the request of representatives of the reviewing Institutional Review Board or other relevant regulatory agencies.

The consenting study team member will inform participants about compensation for their participation in the study. Specifically, we will provide $10 USD for completing the *Consent/Screening Visit,* $20 USD for completing the *Baseline Assessment*, $125 USD for 50 training sessions completed during the *Intervention Period*, and $30 USD for completing the *Post-Intervention Assessment.* Participants who complete the study in its entirety will be earn $185 USD. In the event that a participant must repeat an assessment visit due to administrative assessment or study staff errors, participants may be provided additional compensation for that session. If, for any reason, e.g. technical or vendor issues prevent the Study personnel from issuing the reloadable debit card, adding funds to the reloadable debit card, or making any other changes to the debit card, participants will be compensated through a gift card (e.g. Amazon eGift Card, Visa Gift Card, or similar vendor). If the participant does not complete the study or withdraws early for any reason, the participant will only be compensated for the study visits and/or training sessions they have completed.

Participants that consent and complete the 10-week program/intervention (n=30 enrolled; 24 completers)	
Visit	**Compensation**
Consent/Screening (V0)	$10
Baseline assessment (V1)	$20
Program participation (a total of 50 sessions)	$125
Immediate Post-program assessment (V2)	$30
Total Participant Compensation	$185

Participation in this study requires the use of an Apple Watch and iPhone which will be loaned to all study participants. If a participant does not have a device to complete the training program, an iPad may be loaned to them for the study duration.

Participants who screen failed will receive compensation for the Consent/Screening Visit (V0) after the end of the visit. Eligible participants will

receive compensation for all study activities completed from V0 through V2, including the program participation, after the participant returns the study loaned device(s) to the Site Study personnel after V2. Participants will be sent a pre-paid label and box (if necessary) to return the device(s) at no cost to them. Participants who withdraw from the study will be compensated for all study visits they have completed once the loaned device(s) has been returned to the Site Study personnel. For participants who do not return the device(s), all forms of appropriate means and communication (e.g. phone contact, email, mailed letters) will be used in an effort to retrieve the study device(s).
Study device(s) loaned to participants will have a mobile device management (MDM) platform installed that will enable the Posit Science Property Management team to remotely deactivate the device(s) so that it is unusable, and/or erase the contents of the device(s). Only when a device has been reported lost or stolen, the Posit Science Property Management team may access the geolocation of said device through this MDM platform to lock, erase, or restart the device, ensuring participant data is protected and inaccessible. Participants will not face any legal or financial retribution for failure to return the device(s).

During the consenting process, participants will also be requested to fill out an emergency contact form. This form will detail primary and secondary emergency contact information. If the participant agrees to fill this form out, the participant authorizes the Site Study personnel to contact the primary or secondary emergency contact in case of an emergency. Participants will be notified before Site Study personnel contacts their emergency contacts for any reason.

Individuals with altered mental capacity who are otherwise not capable of providing independent consent, or who require a Legally Authorized Representative (LAR) to consent, are not eligible for to enroll in the study. The informed consent form will be changed if increased risk or other adverse events, which will influence a person's willingness to participate or increase their risk of participation, are noted. In such cases, IRB review and approval will be obtained for the revised consent form and active participants will be re-consented.

Screening Procedures

Following informed consent, potential participants will go through a set of structured interviews, short neuropsychological assessments, self-report questionnaires, and provide basic demographic information, medical and medication history to evaluate their suitability for the study given the

inclusion/exclusion criteria. The following measures will be administered to participants at screening:

- Demographics, Medical History and Medications: A structured clinical interview will be used to collect key demographic (e.g. year of birth, age and education) and medical history information, including medical diagnoses or conditions that may be grounds for exclusion (e.g., neurocognitive disorders, chemotherapy treatment, current therapies (including enrollment in other clinical trials that may be grounds for exclusion), and current medications.
- Participants will be asked to complete the Columbia-Suicide Severity Rating Scale (C-SSRS); potential participants that answer 'yes' to Question 4 (Active Suicidal Ideation with Intent) or Question 5 (Active Suicidal Ideation with Specific Plan and Intent) or, any of the suicide-related behaviors (actual attempt, interrupted attempt, aborted attempt, preparatory act or behavior) on the "Suicidal Behavior" portion will be excluded from the study *if the ideation or behavior occurred within two months from Participant's date of consent* (as recommended by the FDA for treatment trials.) Participants excluded for this reason will be referred to a physician for appropriate treatment. Further, participants meeting these criteria at any time throughout the study will be asked to complete a final assessment, if appropriate, then withdrawn from the study and referred for appropriate treatment.

Study Flow and Procedures

Study Procedures: Participants will flow through the study in the following manner:

1. *Consent and Screening Visit* (V0)*:* Study staff will discuss study goals, activities, and requirements with the potential participant; complete the informed consent discussion, and if/when appropriate the potential participant will consent to join the study. Study staff will perform required inclusion/exclusion assessments. This visit will last approximately 1 hour.

2. *Baseline Visit (V1):* Participants will complete a set of cognitive and functional assessments, and questionnaires prior to training to establish baseline performance.

3. *Program Orientation*: The participant will attend a program orientation session so that study staff may orient them to the training program remotely. The participant will also receive detailed written information on how to perform the training program over the next several weeks. During this period, study staff will conduct weekly check-ins to answer questions and troubleshoot any issues.

4. *Intervention Period:* The participant will engage in assigned program for ~30 minutes per session, 5 sessions per week, for 10 weeks.

5. *Post-Intervention Visit* (V2): Repeat all assessments performed at baseline to assess changes in performance following program use. In addition, participants will be asked to fill out an online exit survey to rate enjoyment, usability, perceived benefits, and ease of fit into schedule. The participant will be informed that they will no longer have access to the intervention after this visit.

Retention

We will use a variety of proven retention strategies as detailed by Robinson et al. (2015)[166] such as a clear study identity, consistent contact study staff for scheduling, flexible appointment times and reminders, and financial incentives. In the consent process, we will stress that enrolling in the study involves a commitment to complete the required online assessments and questionnaires, and 25 hours of exercises to be completed on a computer, tablet, or mobile device, and involve wearing an Apple Watch. Participants will each be provided with a flow chart of the study visits. Staff will arrange assessment visits for each participant and participants will be reminded that their goal is to complete 25 hours of training. The study staff will establish a positive rapport with participants by mailing greeting cards, newsletters, and or email appointment reminders. Telephone support and or reminders will be made at the participant's request. The study staff will provide the orientation, support and troubleshooting issues for participants using any of the study devices. When possible, every effort will be made to accommodate participants' schedules. To promote rigor, we will encourage participants to complete the minimum required number of training sessions to allow them to return for their post-training online assessments and questionnaires. We will indicate for each participant the best manner (e.g., email or phone) and times to contact them to facilitate communication. We will also ascertain information for a secondary

contact person for each study participant to facilitate follow-up. If we lose contact for 15 days or more, we will reach out to the participant's secondary contact. All participants will be paid at the completion of each study visit.

All procedures will be overseen by Project PI, Dr. Thomas Van Vleet. Given our patient populations, prior experience, and resources, we are confident we can meet or exceed our recruitment and retention goals.

Assessments. We will use neuropsychological and functional assessments from those moderately distal from program use (e.g., standardized neuropsychological assessments of untrained cognitive functions) to those very distal from program use (e.g., assessment of functional abilities). This structure will allow the investigators to determine the degree of transfer of benefit to untrained modalities, including the extent to which improvements generalize to untrained functional ability and real-world experience (e.g., quality of life).

The complete cognitive assessment battery will be performed at the *Baseline Visit* (V1) and the *Post-Intervention Visit* (V2). For a full list of all assessments and administration times, please direct your attention to *Appendix I* and/or the *Description of Assessments*. All assessments will be administered to all participants, alternate forms of the assessments will be used when available to mitigate test-retest effects. Performance on all measures will be scored, submitted into the study database, and monitored for accuracy and integrity by the PSC Data Monitor(s). Any discrepancies in scoring will be resolved by referring to the raw data collected during the assessment visit(s).

Description of Assessments

Self-Reported Mood Assessment
The Geriatric Depression Scale (GDS) will be used to assess mood. This assessment is a 7-minute 30-item self-report questionnaire to assess depression in older adults.[153,154]

Suicidality Assessment
The Columbia Suicide Severity Rating Scale (C-SSRS) will be used to screen for and assess suicidal ideation. Those that do not meet inclusion criteria for this assessment will not be enrolled in the study. The C-SSRS will be repeated at every assessment visit to screen for any changes in suicidal ideation over the course of the study.

Self-Reported Balance Confidence Assessment
The Activities and Balance Confidence scale (ABC) will be used to assess confidence in performing various activities without losing balance or experiencing a sense of unsteadiness. This assessment is a 16-item self-report questionnaire.

Gait Assessment
A measure of stride time variability and stability will be collected via actigraphy (accelerometer measured acceleration forces from three dimensions in units of gravitational force (g-force, approximately 9.81 m/s^2). Actigraphy metrics inform a model approach to derive stride time variability and stability of the individual. This assessment uses an iPhone.

Self-reported Pain Assessment
The Brief Pain Inventory (BPI) will be used to assess the severity of pain (predictor of fall risk)[73] and its impact on functioning. This assessment is a 11-item self-report questionnaire comprised of self-reported current pain intensity and degree that pain interferes with daily life on a 10-point scale.

Self-reported Physical Activity Assessment
The Physical Activity Scale for the Elderly (PASE) will be used to assess the physical activity levels in the community dwelling older adults. This assessment is a 12-item self-report questionnaire comprised of self-reported occupational, household and leisure activities over a one-week period. It can be used to distinguish between different physical activity levels and several environmental factors that may affect level of mobility.

Self-reported Mobility Assessment
The Activity Measure for Post-Acute Care (AM-PAC ®) will be used to assess aspects of an individual's ability to perform everyday activities in three different areas of function: basic mobility, daily activity, and applied cognitive functions. The AM-PAC Generic Outpatient Basic Mobility Short Form is an 18-item self-report questionnaire to assess the level of difficulty experienced doing an activity.

Description of Protocol Device (Software Program)

This study employs a computerized intervention comprised of executive function, speed of processing and attention training. Participants will be asked to engage in the assigned training exercises for approximately 30 minutes per session, 5 sessions per week, over 10 weeks. To address factors that contribute to non-compliance we have incorporated several elements of flexibility in the training schedule to accommodate the challenges that older adults may encounter. These risks and associated accommodations will also be discussed with the participant.

- *Location of Use:* Both assessment visits and rSTAND training program are web-based, allowing participants to access and complete the study activities remotely, at different locations, as convenient.
- *Fatigue:* Participants may report symptoms of fatigue, and we expect that some participants may not be able to complete a full session (~30 minutes) in one sitting. To accommodate this issue, participants may choose to break the time into shorter segments, such as 15 min in the morning and 15 min later in the day. Participants can pause the sessions to take a break at any time and continue where they left off. The participant may discuss this with the study staff, who will work out a schedule that is feasible, given the participant's experience.
- *Extra Time*: Participants who complete fewer than 50 sessions in the 10-week schedule because of their commitments to non-study activities or because of health issues may be allowed to continue program use for 4 more weeks (for a total of 14 weeks in the program use period). To ensure a time-bounded study commitment, after 14 weeks such participants will perform their post-training assessments given that participants have met the minimum number of training sessions required to complete these assessments. However, participants who do complete at least 10 sessions during the first 3 weeks of the Research Use period will be deemed as non-compliant and will be exited from the study, and will be asked to return all study devices.
- *Variable Number of Total Sessions:* We expect that some participants will not be able to complete the minimum number of training sessions per week, every week. To accommodate this, we will explain to participants that the study will benefit from them doing as much program use as their schedule permits. However, if they need to reduce the number of sessions

per week, the study staff will work with them to generate a feasible training schedule.

- *Cessation of Program Use While Continuing Participation in the Study:* In some cases, a participant may wish to stop or minimize use of the program going forward, while remaining in the study. Potential reasons for this decision might include a change in work circumstances, a change in residence health/psychiatric issues, family/personal issues, or a lack of interest in program activities. However, the participant may want to meet their personal commitment to the basic scientific research of the study. In such cases, after discussion with the study personnel, the participant will be permitted to cease using the program, and be scheduled for post-training assessments at the appropriate time relative to the baseline assessments, given that the participant has met the minimum number of training sessions required to complete these assessments.
- *Emergency*: All participants will be told how to contact study personnel in the case of an emergency.

Several of these options in aggregate are likely to lead to variation with regard to the total number of sessions completed. Although this is not ideal, we believe that this is the correct approach given that such flexibility will allow more participants to join the study (compared to no program use flexibility) and may produce less drop-out. In addition, this approach has the value of more closely mimicking real-world use of the program, increasing the prospective validity of the study.

Each study participant will be remotely supervised by the study staff. They will have phone contact up to three times in the first week to ensure a smooth start, and at least once per week for the following weeks. Contact with participants may be adjusted depending on each participant's needs. Based on our previous experiences with in-residence trials, we have developed protocols and training that will allow the study staff to establish rapport with participants, identify and tend to any barriers to program use or compliance (such as establishing reminders to train or reducing distracters in the environment), and to provide feedback and support around performance.

rSTAND Intervention

This program combines a speed of processing and attention exercise (TAPAT), along with visual processing, perception and attention exercises delivered over a

10-week period (approximately 30 minutes per session, 5 sessions per week, for a total of 50 sessions).

TAPAT. The goals of TAPAT are to amplify the response power of modulatory control machinery controlling attention to improve the individual's intrinsic regulation of alertness, executive control, mood, and learning rate. TAPAT was first invented by Department of Veteran affairs neuroscientists and co-inventors Dr. Thomas Van Vleet and Dr. Joseph DeGutis (U.S. Patent 13/068,850; VA Ref: 08-0156). The training approach is specifically designed to elicit two well-characterized, intrinsic properties of the attention- and alertness-control machinery of the brain: *tonic* and *phasic* alertness. Tonic alertness refers to the ongoing state of intrinsic readiness that fluctuates on the order of minutes to hours, and is intimately involved with sustaining attention and also provides the cognitive tone necessary for performing more complicated functions such as working memory and executive control.[122,123] Poorly sustained attention is characterized by low amplitude, noisy tonic responses in locus coeruleus (LC) neurons.[93] In contrast, phasic alertness is the rapid modulation in alertness due to any briefly engaging event, and is vital for operations such as orienting and selective attention.[122] Normal aging is marked by a progressive declines in tonic alertness and in both tonic and phasic responses in both LC neurons and acetylcholine-expressing neurons in the nucleus basalis (NB) in this exercise task setting. With their 'exercise' by intensive, repeated engagement, there is an up-regulation of trophic factors (primarily EGF) that result in a strong increase in the functional status of LC, NB and the VTA.

TAPAT is an innovative variation of a continuous performance training strategy that targets sustained attention by requiring users to remain alert and engaged while responding to stimuli and ignoring foils. Users must remember a target image presented at the start of the trial after which a continuous stream of images (target or foil of unequal presentation probability) are interleaved with variable ISIs to promote vigilance (see Figure 1B). The task is to press the response button for all non-targets ("GO") and withhold responses for all targets ("NO-GO"). The primary *adaptive dimension* is the duration of the inter stimulus presentation (determined by 80% criterion accuracy on an image-by-image basis); an adaptation to induce greater response control. There are 40 unique levels of TAPAT that vary in the discriminability between targets and foils, the ratios of targets and non-targets, the categorical nature of the stimuli presented, and the attractive powers of distractors. With this design, participants must sustain attention over long periods of time, respond to successively presented stimuli in a consistent manner (i.e., low RT variability), and inhibit the proponent

motor response when an anticipated target is presented (i.e., high target accuracy). These conditions, again, very strongly engage both LC and NB neuronal populations.

Daily Diary

Participants will be asked to complete a daily questionnaire of reported falls and indicate the duration of time the Apple Watch and iPhone were worn and inform the research team of any circumstances that may affect the fidelity of remotely collected metrics (e.g., participant is ill and stays in bed resulting in a reduction in normal activity that is unrelated to the intervention).

Apple HealthKit Data

We will analyze Apple HealthKit data (such as steps, distance traveled, stride length, gait speed, and double support time) collected through the study loaned devices, the Apple Watch and iPhone, to evaluate if the experimental software program results in a reduction of falls and changes in your quality of life and general health. The data will be exported in a de-identified manner, such that your personal identifying information (name, phone number, account information etc.) will not be associated with the exported data.

Laboratory Specimens

There are no laboratory specimens collected for this study.

Sample Size Justification

Because this is a usability/feasibility pilot study, sample size is not determined from statistical tests of outcome measures. Sample size justification is based on a balance of having a sufficient number of participants to ensure diversity of participant experience against having a number that exceeds the ability of a user-experience designer to effectively debrief participants and synthesize their diverse experiences into actionable guidance for a next round of product improvements. In our experience, usability/feasibility trials are most effective with at least 6 and no more than 30 participants. We specify 24 participants for this usability/feasibility trial as the center of this range.

Data Management

All study-related data will be recorded into a secure, web-based electronic case report form (eCRF) through REDCap Cloud. This system meets all relevant privacy and security standards for electronic clinical trial data entry and storage, as well as the Health Insurance Portability and Accountability Act (HIPAA) standards for confidentiality and privacy.

Following consent, each participant will be assigned a standardized Participant Identification Number (PIDN) composed of three digits to identify the site and 3 digits to identify the participant. The digits will begin with "xxx001" for the first consented participant and ascend thereafter. All eCRF data entry will use the PIDN only and not the participant name; Posit Science will be expected to maintain secure documentation that links the participant name and PIDN link.

Posit Science will be a single recruitment and enrollment site. Data collected by Posit Science will be captured in eCRFs in REDCap Cloud. Authorized personnel will be granted access to REDCap Cloud and enter eCRFs directly into the study database. Study personnel will also transcribe and upload de-identified data and de-identified source documentation, if any, into the study database for data monitoring. Periodic analysis of each data field (across all cases) will be performed by the PSC Clinical Data Monitor in order to examine the expected distributions of data, and to identify outliers for possible data mistakes. Particular attention will be paid to the following:

- *Data Cleaning:* All eCRFs are automatically subjected to initial checks for omitted data and data inconsistencies. These deficiencies are required to be resolved at the point of data entry to prevent errors from entering the system.
- *Data Editing:* Each data record is evaluated on a regular interval. Any discovered error is then referred to the Investigator Designee by email, telephone, or secure communication through the Electronic Data Capture system via the Data Monitor. The Investigator Designee will review the queries and make the corrections through the eCRF system. All such changes are automatically logged to allow a complete audit trail and recovery to any point in the change log if required.
- *Data Update:* The cycle of data edit will be ongoing until all the data are clean. If further data entry or source documentation errors are discovered, corrections will be made at that time through the eCRF system.

- *Data Back-up*: The eCRF system employs an automatic continuous replication system to ensure that all data including change logs and access logs are replicated to two independent remote servers. At any point, the system can emit the entire store of eCRFs as paper CRFs for offsite storage or auditing if required.

We will take all standard and appropriate steps to protect the privacy and confidentiality of participants in this trial. At enrollment, participants will be assigned a PIDN as described above, and all study data collection derived from that participant will be coded by PIDN. All eCRF pages, including those with demographic as well as assessment data, will have the PIDN on them rather than the participant's name. The eCRF system runs on remote servers not physically accessible to any study staff; all electronic access to the eCRF system is logged and regularly reviewed for any inappropriate access. All study related paper materials will be stored in locked file cabinets inside of locked rooms when not in use. The study program will not collect or store any personally identifiable information on the laptop, mobile devices, or on PSC servers. For the fall monitoring data from the Apple Watch, only de-identified data will be used data interpretation and analysis.

This protocol includes the administration of the Columbia-Suicide Severity Rating Scale which may result in the collection of sensitive information that requires reporting to state or local authorities. If study staff become aware of specific issues outside of the ordinary data collection procedures (e.g., spousal abuse), they will follow established procedures already in place and contact their local jurisdiction to report such knowledge.

Confidentiality

Participation in research may involve a potential loss of privacy. All records and documents pertaining to participation in this study will be handled as confidentially as possible. However, absolute confidentiality cannot be guaranteed.

All information, if collected on paper, will be kept in areas of limited access available to approved study staff only. Data keys will be stored separately and securely. Electronic data will be password protected and securely stored.

Representatives of the Sponsor, the reviewing Institutional Review Board, and the NIH will be permitted to audit study-related data and related materials. Personally identifiable information will not be used in any study reports or publications; data contained in these will only be presented or published in aggregate form.

The program will not capture, collect, transmit or store personally identifiable data, except for dates that training exercises are completed. De-identified data will be encrypted and will not reside on the device but will be transferred immediately with no personal identifiers, except for dates. Data collected through the computerized program does not include geographic location data. IP address data is stored only in memory and in request logs, and is used for technical support and troubleshooting, but not persisted with the participant's data. Data are uploaded using SSL over encrypted channels to secure servers every 30 seconds. Therefore, security of electronic data is ensured at the level of the server, the user, and the database.

Disposition of Data

The following study records will be retained by the study site for a minimum of two years following the conclusion of the study:

1. Signed participant informed consent forms
2. Patient medical/psychiatric records, including all significant diagnostic reports
3. Supporting documentation of all adverse events
4. Completed eCRFs
5. Study related correspondence and study reports

The sources of the research material will be data collected remotely strictly for research purposes. Participants will be carefully screened for contraindications prior to participation. All data are coded so as not to identify any given participant. Data will be recorded in REDCap Cloud, a secure, web-based software application designed to support data capture for research studies. REDCap Cloud is designed to comply with GCP and HIPAA-regulations, including Title 21 CFR Part 11. Data files will be retained for a minimum of two years after the study's completion. A list of names, email addresses and telephone numbers of all participants will be stored electronically on password protected computers with access limited to authorized study personnel for purposes of contacting the individual participants. The types of data collected

will be: data concerning medical and fall history, behavioral data from neuropsychological assessments, self-reported questionnaires and objective fall monitoring data.

Study staff will comply with the requirements (i.e., the enrolling institution) data storage and disposition policies at the conclusion of the record retention period.

Sharing Research Results

We will share the overall study results with all participants who enrolled in the study when such results are completed and accepted for publication. We will create a lay-person oriented summary of study results to be emailed to each participant at the end of the trial. At enrollment, two pieces of information are collected that, if appropriate, we will share with the participant to ensure they are receiving appropriate health care, including depression status and suicidal intent. Any participant screening positive for any of these medical issues will be referred to ensure they are receiving appropriate treatment. We do not intend to share individual assessment data with participants, as the assessment battery is not intended to be the type of comprehensive battery a rehabilitation psychologist would use to guide treatment. Any participant interested in such comprehensive assessment will be referred to an appropriate clinician.

Foreseeable Risks, Risk Management & Emergency Response

The following foreseeable risks are described in the consent form, as will the following measures taken to minimize such risks:

- *Diagnostic assessments and self-report measures*. Participants may feel uncomfortable or embarrassed due to sensitive questioning about their condition and medical history on screening assessments and self-report measures. Participants will be reminded that their participation in the study is voluntary and that as such, they may skip individual questions or assessments or withdraw from the study entirely.
- *Discomfort During Assessments and Training*. Computerized assessments and training may be fatiguing or frustrating for some individuals. To minimize this potential discomfort, breaks are encouraged and scheduled within the session. If a participant appears to be under undue strain, testing sessions are discontinued.
- *Lack of Assessment Feedback*. Participation in this study does not include feedback to participants on their individual assessment results, as the

assessment battery is not intended to be the type of comprehensive battery that would be used to guide treatment. Though participants are informed of this policy during consent, some participants may find the lack of feedback to be frustrating. Any participant interested in such comprehensive assessment will be referred to their Primary Care Physician.

- *Risks of Email Communication*. This study will rely on the use of email communication between study staff and research participants as part of their participation in the clinical trial. Study staff are expected to email participants about their upcoming visits, provide weekly updates on program usage, or communicate other important study information, including the instructions for completing study activities remotely. Participants may also ask questions of study staff using email. There are risks associated with email communication, and these risks increase when emails are sent without an encryption service. Risks of sending or receiving unencrypted emails include, but are not limited to:
    - Others can intercept messages
    - If messages are sent or received on an employer-owned device, the employer may have the right to save and read the messages. The internet or cell-phone provider may also have the right to save and read email messages
    - A copy of the message may be saved on a device or computer system, even if it is deleted
    - If an email address is not typed correctly, it can be sent to the wrong person
    - Emails can spread computer viruses
    - Others may be able to access messages on devices that were lost, stolen, or thrown away
    - If a user changes emails without notifying study staff, they may miss communications.
- *Loss of Privacy*. The most significant risks to the participants are those that would follow a breach of confidentiality and the disclosure of clinical information. Participation in any research study, including this one, may involve a loss of privacy, and absolute confidentiality cannot be guaranteed. Procedures designed to maintain data confidentiality include (1) formal protocol training sessions for all study team members emphasizing the importance of confidentiality, (2) adherence to specific procedures developed to protect participants' confidentiality, and (3) formal mechanisms limiting access to information that can link data to

individual participants. One reason for breaching confidentiality is that, under certain jurisdictions, study staff are required by law to report cases of physical or sexual abuse to local law authorities; and another is that despite all procedures, an error may occur. To mitigate this risk, all data collected on paper will be kept in locked file cabinets and accessible only to authorized study staff. Only the unique ID number, assigned by the study staff, will represent participants during participation in the study. To facilitate tracking, a document securely stored in a locked filing cabinet or a password-protected computer file will be maintained containing the identity of participants, their ID numbers, and contact information. Electronic data will be password protected and stored on a secure network. All data keys will be stored separately and securely. Only study staff will have access to the study data. No participant names will be used in study reports or publications.

PSC does not provide compensation for research-related injuries and will not reimburse or pay medical expenses for the treatment of research-related injuries.

Participants will be encouraged to report any adverse effects occurring during the duration of the study to the point of contact within study staff. Although there is little chance for a study-related emergency, study staff are required to follow institutional standard operating procedures for obtaining emergency care or treatment for adverse effects requiring such. All participants will be told how to contact study staff in the case of an emergency.

Potential Benefits

The following benefit will be described to participants:

Benefit to Science: Results from this study will provide important scientific knowledge about the potential of a computerized training program (rSTAND) to reduce fall risk.

Sponsor Staff

PSC will serve as the recruitment and enrollment site, data management and coordinating center for this clinical trial.

Key staff at PSC include:

- Principal Investigator (Thomas Van Vleet) is responsible for the overall design of the study protocol and data analysis plan as well as

the eventual publication of the result (with input and authorship from all investigators). He is also responsible for the execution of the study protocol, including coordinating activities from all staff participating in the trial.

- Co-Investigator (Dr. Mahncke) will provide feedback and supervision of study activities, as well as direction of the software engineering and study design.
- Co- Investigator (Dr. Ogawa) will contribute to the design and development of the intervention; development of the implementation plan; and feedback and guidance regarding data collection and outcomes for pilot programs.
- Clinical Trials Manager (Sarah-Jane Grant) will provide oversight, advise on regulatory procedures, and support the research coordinator with their responsibilities, as needed.
- Study Coordinator (Kathy Wannaviroj) is responsible for assisting the PI with the execution of the study protocol and for data management. She will also be responsible for monitoring all submitted data for consistency and integrity, discussing qualifying criteria with participants, leading consent visits with potential participants, administering assessments as needed. She will be responsible for calling participants who are currently training for weekly check-ins and is responsible for assisting the PI with the execution of the study protocol, overseeing data management, and ensuring IRB compliance.

Dr. Van Vleet, Dr. Mahncke, Ms. Grant and Ms. Wannaviroj disclose a conflict of interest: all are paid employees of PSC and shareholders and could benefit if this training program is shown to be an effective treatment in this trial.

This conflict will be mitigated by ensuring that the complete investigator team, including Dr. Van Vleet, Dr. Mahncke, Ms. Grant, and Ms. Wannaviroj and other study staff, have joint and overlapping responsibility for the design of the protocol, the execution of the protocol, the *a priori* design of the data analysis plan, the execution of the data analysis plan, the interpretation of the study results, and the authorship of publications emerging from the study. In addition, this conflict of interest will be disclosed to all study participants, and through standard mechanisms for all publications.

Withdrawal from the Protocol

Study participants may withdraw from the study at any time, for any reason, or for no stated reason. We anticipate that a common reason for study withdrawal will be the time required to use the program. For participants seeking to withdraw for that reason, we will offer the alternative of discontinuing use of the program and, if appropriate, scheduling and completing the follow-up visit(s). The data analysis plan is structured so that their data will be valuable even if they do not complete the intended number of sessions. Participants who still wish to withdraw following that option will withdraw. Across all reasons for withdrawal, we will ensure an orderly end to the participant's involvement in the study by arranging for team members to conduct an informational interview with the participant to understand the reasons for study withdrawal and identify any issues with study conduct or adverse events that are relevant and arrange study compensation for sessions that the participant completed.

In rare cases, an investigator may decide to prematurely discontinue a participant's involvement in the study for any of the following reasons:

a) Safety,
b) Participant non-compliance,
c) A change in circumstance that would prevent completion of protocol-required assessments or intervention activities,
d) Participant relocation to an area that, due to great distance, would prohibit a participant from receiving follow-up at the study site,
e) Participant displays inappropriate behavior toward study staff members,
f) Loss of funding, or;
g) A clinical determination, by the investigator, that continuation in the study is not in the participant's best interests.

Across all reasons for withdrawal, we will ensure an orderly end to the participant's involvement in the study by arranging for the study staff to recover the Apple Watch, conducting an informational interview with the participant to understand the reasons for study withdrawal and identify any issues with study conduct or adverse events that are relevant, and arrange study compensation for sessions that the participant completed.

Modifications to the Protocol

Any significant changes to the protocol, including changes to inclusion/exclusion criteria, changes to assessments, changes to recommended levels of program use, changes that could potentially increase risk to study participants, and additions

or removals of study site(s) will have to be approved by the grant recipients/PI (Thomas Van Vleet), any such changes will also be discussed with and approved by the Institutional Review Board in the form of a protocol amendment prior to implementation.

Protocol Deviations

Protocol deviations will be noted and recorded by study staff if they detect the deviation. All protocol deviations will be reviewed monthly and signed off by the PI (Thomas Van Vleet); any such deviations suggesting systematic problems with the protocol procedures as implemented by the study site will be reviewed and corrective action determined and implemented by the study site.

Reporting of Unanticipated Adverse Device Effects & Problems

This is a minimal risk protocol. There is no significant risk to using the program in this study, beyond the minor discomfort and tedium risks of using computerized software.

An event that is serious must be recorded on the case record and requires expeditious handling to comply with regulatory requirements. If a participant becomes ill or injured as a direct result of participation in the project, necessary medical care will be made available. Any adverse events attributable to the study activities and/or program use will be reported to the reviewing IRB in a timely manner, if applicable. The NIH Project Officer will be informed of any actions taken by the IRB as a result of such adverse events. In the unlikely case of study-related serious adverse events, an interim analysis will be performed to determine whether a change in the risk/benefit ratio has occurred. If so, this change will be brought to the attention of the reviewing IRBs for review, current and future participants will be notified of this change and stopping rules will be considered.

We will also conservatively follow guidelines for medical devices (i.e., computerized cognitive training) in the reporting of adverse events in this trial, which defines unanticipated adverse device effects (UADEs) in The Code of Federal Regulations in 21 CFR 812.3(s) as any serious adverse effect on health or safety associated with, a device. Furthermore, an effect is classified as an UADE if it is judged by the investigator to be a serious problem associated with a device that related to the rights, safety, or welfare of participants. We will operationalize this definition of a serious problem as one that result in any of the following outcomes: death, life-threatening situation, inpatient hospitalization atypical of the participant's diseases condition, persistent or significant disability/incapacity; or any other adverse event that, based upon appropriate medical judgment, may jeopardize the participant's health or the health and well-being of all participants enrolled in the study. The study team will ask about any UADEs during each contact with participants and will be alert to any volunteered UADEs. All UADEs will be documented and will be classified by the investigator to their degree of seriousness and their relationship to the study software. All UADEs, whether or not we believe them to be related to the protocol, will be reported to the IRB as soon as possible, but in all cases within 3 working days of the event.

Safety Officer

We will employ a Safety Officer, Dr. James Muir, to monitor participant safety, review all unanticipated problems involving risk to participants, serious adverse effects, and any participant deaths associated with the protocol, and provide an unbiased written report of the event within ten calendar days. The Safety Officer will be notified of serious adverse effects within 24 hours of the PI being informed. The Safety Officer will comment on the outcomes of the adverse event and relationship of the event to the protocol. The Safety Officer will also indicate whether they concur with the details of the report provided by the PI. Reports for events determined by either the PI or Safety Officer to be possibly or directly related to participation, and reports of events resulting in death will be promptly forwarded to the IRB. Meetings will be scheduled with the Safety Officer approximately every 6 months through the end of the project.

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Appendix I. Table of Assessments

	Consent and Screening Visit (V0)	Baseline Visit (V1)	Program Orientation and Intervention Period for 10 Weeks	Post-Intervention Visit (V2)
Informed Consent	X			
Inclusion and Exclusion Criteria	X			
Demographics	X			
Medical History	X			
Medications	X			
C-SSRS, Screening	X			
Activities and Balance Confidence Scale (ABC)		X		X
Physical Activity Scale for The Elderly (PASE)		X		X
Gait Speed Analysis		X		X
Brief Pain Inventory (BPI)		X		X
Geriatric Depression Scale (GDS)		X		X
Activity Measure for Post-Acute Care (AM-PAC)		X		X
C-SSRS, Since Last Visit		X		X
Medications, Since Last Visit		X		X
Adverse Effects		X		X
Program Orientation			X	
Computer Training/Daily Diary			X	
Weekly Phone Check-In			X	
UADE				X
Study Exit				X