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Improving Balance and Mobility (MMBI)

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Study protocol and analysis plan

Every 5 seconds an older American falls, yielding annual costs over $30 billion for fall-related injuries.[6] Beyond financial concerns, for adults over the age of 65, falls are the leading cause of injurious death, non-fatal injuries, and hospital admissions for trauma.[6] With more than 60% of current veterans over the age of 55, preventing falls and fall related injuries has become a major concern for the VA health system. Despite a wide variety of research into fall prevention, the state of the art fall prevention programs reduce falls by only 30%, suggesting more research is required.[7] Falls are multifactorial in origin with a failure to negotiate environmental hazards, muscle weakness, impaired postural control, and gait and balance deficits being among the top contributors to falls in older adults.[8-12] The multifactorial origins of falls requires a multimodality approach to effectively reduce falls. Derivations of t'ai chi ch'uan (Tai Chi) have become popular in western society as low-impact balance and fitness programs suitable for older adults, and Tai Chi is the only modality specifically recommended by the CDC for fall prevention.[13] However, while previous research has demonstrated that Tai Chi may be effective at improving balance and general lower body strength, there are questions concerning its actual effectiveness to prevent falls.[14] Some Tai Chi program also have low adherence rates resulting in a decreased effectiveness. The slow choreographic weight shifts central to Tai Chi may improve some aspects of balance and may provide a general lower body strengthening but do little to improve gait, negotiation of environmental hazards, nor dynamic balance recovery following perturbation. Targeted interventions focused on improving stepping and walking ability may be even more effective at improving balance and mobility.[5] Preliminary studies demonstrate that our novel progressive group multimodal balance intervention (MMBI), focusing on lateral movements, lower extremity strengthening and dynamic obstacle negotiation, can improve balance, gait and strength in older adults at high risk for falls. It is our overall hypothesis that both MMBI and Tai Chi interventions will improve muscle strength and balance, but we hypothesize that MMBI will result in larger improvements in gait, balance and lower extremity strength in older veterans at high risk for falls and thereby result in fewer falls and lower fall rates in the MMBI group.

To test our hypotheses, we propose to conduct a pilot randomized clinical trail with the following specific aims:

Specific Aim 1: To compare the effectiveness and adherence to 6 months of a novel Multi Modal Balance Intervention (MMBI) program versus Tai Chi exercise training to improving balance [Four-Square Step Test (FSST) and Functional Gait Assessment Tests (FGA)], gait (spatio-temporal gait parameters), lower extremity isometric strength (Biodex) and mobility fitness (distance covered during a 6 minute walk) pre and post intervention in older veterans at increased risk for falling.
H1: MMBI will result in larger improvements than Tai Chi in balance, gait, lower extremity strength, and mobility fitness.
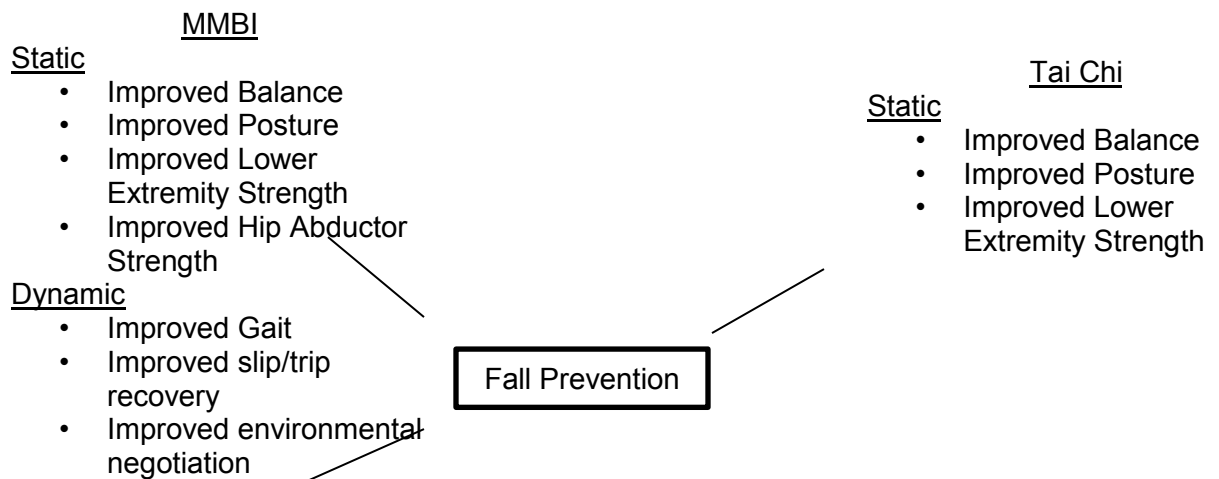H2: MMBI will have a higher adherence rate than a Tai Chi exercise program

Specific Aim 2 (exploratory): To determine and compare the effectiveness of 6 months of MMBI versus Tai Chi exercise training to prevent falls and reduce the number of serious falls in older veterans at increased risk for falling.
H1: MMBI will result in greater decreases in serious falls than Tai Chi and this will be maintained for 6 months following the completion of the exercise program.

<u>Background and Significance:</u>

Falls are complex and multi-factorial in origin with numerous deficits including impaired balance, decreased postural control, muscle weakness, sensory changes, and a composite inability to successfully negotiate environmental hazards and obstacles (see conceptual model). [8-12] The majority of falls occur during walking, with incident slips and trips, such that targeted interventions focused on stepping and walking ability may be more effective at improving dynamic balance and reducing falls.[5] Older adults are particularly vulnerable to falls during lateral or diagonal movements.[11] While the mechanism of lateral instability remains under investigation, it is reasonable to suspect deterioration in the hip abductor muscles as a major contributor to their difficulty in maintaining and regaining balance.[11]

Interventions to reduce fall risk require a multi-faceted approach. Well established components include review of medications, sensory exams, home safety inspection, etc. The optimal exercise component, however, remains uncertain (see Cochran review 2012).[15] Tai Chi is recommended by the CDC to prevention falls in older adults and this endorsement widely influences health care policy.[13, 16] Tai Chi improves balance by 12% and may reduce fall rates by perhaps 28% but does not reduced the risk of falling (Cochran).[15] The slow dynamic weight shift that occurs during Tai Chi may generally improve balance, decrease fall risk, and provide general lower body strengthening. However Tai Chi may not sufficiently improve gait and dynamic mobility and nor effectively improve obstacle negotiation, one of the most common scenarios for injurious falls.[4, 5] A multimodal balance intervention (MMBI) that addresses these deficiencies may be more effective than Tai Chi in reducing fall risk. However, there are few studies comparing Tai Chi with another active intervention. [16] Conceptual model

<u>MMBI</u>

<u>Static</u>
- Improved Balance
- Improved Posture
- Improved Lower Extremity Strength
- Improved Hip Abductor Strength

<u>Dynamic</u>
- Improved Gait
- Improved slip/trip recovery
- Improved environmental negotiation

<u>Tai Chi</u>

<u>Static</u>
- Improved Balance
- Improved Posture
- Improved Lower Extremity Strength

Fall Prevention

Our work has demonstrated that, compared to non-fallers, older adults with a history of falls have increased fatty depots in their hip abductor muscles and decreased hip abductor strength.[11] A high degree of abductor fat correlates with greater gait variability and fall risk in older adults.[17] This leads us to propose that, in addition to the established age-associated changes in leg flexors and extensors, similar changes in hip abductor muscles may hinder balance and mobility function. Disuse may contribute to these changes as older adults tend not to engage in activities that require lateral movement. As shown in our conceptual model, a group balance and strengthening program focused on dynamic use of the hip abductors through lateral and diagonal stepping and obstacle negotiation, walking, and lower extremity strengthening may be more effective at improving balance and mobility and reducing falls in older veterans. <u>This research directly benefits veterans as it may lead to new and effective interventions that could reduce fall risk, injury-related hospitalization and death in older veterans. MMBI is also readily exportable to the community and with minimal resources could be widely implemented at other VAs as part of standard of care, similar to MOVE!</u>

Preliminary Studies:

We have assembled a highly qualified team of investigators with extensive expertise in performing exercise rehabilitation studies in older veterans. Seventeen older (75.6 $\pm$ 4.5) adults with a history of falls were recruited for a preliminary study utilizing MMBI. Subjects performed the intervention in our exercise facility 3 times/week for 16 weeks and were instructed in a home regimen to continue after completion of the center-based portion of the intervention.16 out of 17 individuals completed all portions of the study with > 90% adherence to the protocol. Six of the 16 fell at least once during the 4 month study, and an additional six subjects reported at least 1 near fall. Four-square step times (FSST) in those who fell were significantly slower (12.7 $\pm$6.5 seconds) than in those who did not fall (5.98 $\pm$ 2.12 seconds), (p=0.009). Notably, however, these individuals also had the greatest improvement with the intervention. After 16 weeks of MMBI scores on the functional gait assessment (FGA) increased by 12% and the time to complete the FSST decreased by 24%. Individuals with FSST > 10 seconds at baseline made even greater improvements of 40-50% on the FSST and FGA. Furthermore these improvements were maintained for 4 months after the completion of the exercise program. These findings warrant the application of our MMBI program to a larger study of greater duration with an active comparison group, particularly in those with a FSST > 10 seconds at baseline.

Parameter (N=16)	Baseline (mean $\pm$ SD	16 week Post-intervention(mean $\pm$ SD)	P value
BMI (kg/m2)	26.9 $\pm$ 3.2	27.0 $\pm$ 3.2	0.40
Four-square (sec)	8.5 $\pm$ 5.3	6.1 $\pm$ 2.7	0.04
Functional gait assessment*	22.7$\pm$ 5.9	25.5$\pm$5.2	0.01
Leg extension strength	278.80 $\pm$ 110.5	299.00 $\pm$ 114.9	0.05

*N of 8, measurement only performed on second cohort

Methods/Study Procedures:

Approach: We will enroll 56 older community dwelling veterans (age > 65 years) with a fall in the past year and evidence of balance dysfunction (FSST > 10 seconds). Our preliminary findings suggest that those with higher FSST benefit the most from MMBI. After baseline testing, individuals will be randomized to either MMBI or to a Tai Chi intervention. All participants will participate in a group exercise class in their assigned intervention for 1 hour, 3 times per week for 24 weeks. To promote camaraderie and accountability among subjects they will be enrolled in intervention cohorts of 8 to 10 subjects. At randomization subjects will be stratified first by gender then by FSST. Assessments will occur at baseline and after completion of the intervention and will include balance, mobility and fall risk, lower extremity strength, and muscle composition (total body DXA scan, hip and thigh CT scan). All participants will be followed from initial enrollment until 6 months after completion of the post-intervention testing (6 months follow up) utilizing calendar diaries, post-cards and monthly phone calls from the study coordinator to determine the number of falls, near falls, injuries and fall related medical visits.

Recruitment and Screening: A variety of methods will be used to recruit older veterans with a history of a fall in the last year, including the Baltimore GRECC subject recruitment registry, advertisements, provider referrals, community outreach, outpatient clinics and the emergency department at the VAMHCS. The use of multiple recruitment strategies will allow us to maximize our outreach to a diversity of veterans including those who have yet to seek routine care at the VA. A fall will be defined as any event that resulted in a person coming to rest unintentionally on the ground or other lower level. Prospective studies have demonstrated that older adults with a history of falls are more likely to experience subsequent falls. Exclusion criteria will include: dementia, unstable angina, poorly controlled hypertension, active substance abuse, poorly controlled diabetes, progressive neurodegenerative disease, and any other major orthopedic or health condition that would limit ability to safely exercise (see human subjects section for more

details). Interested individuals will initially undergo a telephone screen by the project coordinator to assess eligibility for the study using our inclusion/exclusion criteria. Potential participants who pass the phone screen will be invited to our facility. After informed consent, a history and physical will be performed. Based on prior studies we anticipated that 20 to 30% of those brought in for the screening evaluations will not qualify for the study (screening failures).

After the completion of all screening tests eligible participants will be scheduled for baseline testing at the Baltimore GRECC and VAMHC Human Performance Laboratory consisting of: 1) balance testing (Four-square step test), 2) mobility and fall risk assessment (functional gait assessment, clinical gait assessment and gait variability on a GAITrite and 6 minute walk), 3) questionnaires (falls efficacy and ABC) 4) lower extremity isometric strength testing (Biodex), and 6) total body DXA scan, and a CT scan of the abdomen, hips and thighs for determination of lower extremity and core muscle composition. All testing will be conducted by individuals that are blinded to group assignment and not involved with group training.

After completion of baseline testing the veterans will be randomized to either MMBI or a Tai Chi intervention. The MMBI and Tai Chi intervention sessions will be held at different times of the day to minimize cross-contamination between the two groups, with time alternating with different cohorts to minimize any inadvertent training effect due to time of day.

The supervised Tai Chi class will be held 3-times a week for one hour. All Tai Chi classes will be taught in a group setting by an experienced instructor and will have a maximum instructor to participant ratio of 10:1. The Tai Chi intervention will be modeled after the Tai Chi Moving for Better Balance Program (TJQMBB).[1] This specific Tai Chi program is a 24 week established nationwide Tai Chi program aimed at individuals with balance disorders. TJQMBB is a research based balance training regimen with clinical efficacy per the CDC.[1] Using this program will allow us a specific progression of exercises in Tai Chi with a focuses on stimulating musculoskeletal, sensory, and cognitive systems via self-initiated, controlled movements such as unilateral weight-bearing and weight-shifting, trunk rotation, ankle sways, and coordinated eye-head-hand movements, and taxing sensory integration, limits of stability, functional adaption, anticipatory control, compensatory responses, and effective gait patterns. Movements will be adapted as the class progresses to increase the difficulty of weight shift and change in direction over time so that participants balance is continually challenged throughout the 24 weeks. [1] Because all participants will be at high risk for falls in addition to the Tai Chi instructor 1-2 assistants will be present to assist with fall risk prevention and chairs or hand rails will be present for the participants to use as needed for balance recovery.

The MMBI will be held 3-times a week for an hour and will consist of a group dynamic balance class (30 minutes), a supervised obstacle course (10 minutes), and lower extremity and core strengthening (20 minutes). The group exercise class will focus on dynamic weight shifts with an emphasis on the lateral and diagonal directions. Over the 24 weeks of class the exercises will gradually increase in difficulty to challenge balance. A skilled instructor will lead each class and 1-2 assistants will be present to assist with fall risk prevention. The supervised obstacle course will focus on obstacle negotiation, gait over challenging surfaces, and moving in lateral, diagonal, and backward directions. Strength training of the lower extremities and core will focus on strengthening the major muscles of the lower extremity and core (hip flexor/extensors, hip abductors/adductors, knee flexor/extensors, ankle plantar flexor/dorsiflexors, ankle invertors/evertors, and core abdominal/back extensor muscles) utilizing commonly available gym equipment, ankle weights and body weight. Because our group program will utilize commonly available equipment for both the balance training and the strengthening portion our MMBI can be easily implemented in a community environment.

After completion of the intervention, subjects will repeat the baseline assessments. The testers will be blinded to group assignment. All participants will be encouraged to continue performing their exercises at home (home maintenance). They will be followed for an additional

6 months after completion of testing utilizing post-cards and monthly phone calls from the coordinator to determine the number of falls, near falls, injuries and fall related medical visits.[18]

Aim 1: Primary Outcome Measures: Four-Square Step Test (FSST) and Functional Gait Assessment Tests (FGA). The primary outcome measures will be the change from baseline to 24 weeks in the FSST and the FGA. The FSST is a test of dynamic balance ability that assesses an individual's ability to change directions while stepping.[19] Subjects will be timed as they step over four canes set-up in a cross on the floor. Participants will be closely guarded as they perform the test to prevent any falls. The FSST is an ideal outcome measure as it assesses the ability of an individual to dynamically maintain an upright posture while changing directions and weight shifting. It has excellent inter-rater reliability (ICC=0.99), test-retest reliability (ICC=.98), sensitivity (92%) and specificity (93%) in older adults.[19] Older adults who take > 15 seconds to complete the task are at increased risk for multiple falls.
The FGA will also be used as a primary measure of dynamic mobility and balance and to assess fall risk. The FGA is a 10-item clinical gait test that is based on the dynamic gait index (DGI). It tests higher level dynamic gait activities that are part of daily functional mobility such as turning safely, walking at speeds required to safely cross a street, the ability to walk with head turns, gait with a narrow base of support and ambulating backwards. Each of the ten items is scored 0 to 3, with total scores ranging from 0 to 30. Scores below 22 are predictive of future falls. The FGA has excellent inter-rater reliability (ICC=.93) and predictive validity for falls.[20] The FGA is an ideal outcome for this balance study in older veterans.

Aim 1 Secondary Outcome Measures:
A clinical gait assessment as well as gait variability will be assessed using an instrumented walkway (GAITrite, CIR systems inc. Clifton, NJ). The GAITrite system is a valid and reliable system to evaluate spatial and temporal parameters of gait as well as gait variability. Gait variability is an important predictor of mobility function and fall risk in older adults, and increased gait variability predicts fall risk and mobility limitations in older adults.[21, 22] The GAITrite is a portable walkway mat embedded with pressure sensors that detect steps as the participant walks the length of the mat. Each participant will walk on the GAITrite 25-foot walkway at a comfortable self-selected gait speed during 4 separate trials. Outcomes will include intraindividual gait variability, as indexed by the intra-individual standard deviation for both temporal and spatial gait parameters, and walking speed determined from software provided with the GAITrite.
Questionnaires: Adults who fall may develop a fear of falling that results in curtailment of activities, and may further result in impaired mobility, balance, physical functioning and increased risk for falls. The Falls Efficacy Scale an instrument that assesses fear of falling[23] and the activities-specific balance confidence (ABC).[24] ABC fall scale will both be utilized to assess subjective measures of confidence in performing ambulatory activities without falling.
Lower extremity strength: A biodex dynamometer will be used to assess peak isometric hip abductor, knee extensor, and ankle plantar/dorsiflexor strength as previous work demonstrates that both knee extensor and ankle plantar flexor/dorsiflexor strength is important to mobility and fall risk.[25] We will use standardized protocols as described by biodex.
DXA, CT scans and Muscle Composition Assesment: Using methods developed in our previous studies total and regional % body fat, fat mass, lean tissue mass, and bone mineral content will be determined by DXA.[26] CT scans will be performed of the abdomen, hips, and thighs using a Siemens Somatom Sensation 64 Scanner. Three CT scan slices will obtained; one at L3-L4, one at the level of the mid-thigh and the third proximal to the caput femoris. These scans will be used to quantify muscle composition and muscle attenuation for the primary hip flexors and extensors, abductors and adductors, and for the knee flexor/extensors. The cross-sectional area of the slice as well as the specific muscle group will be manually outlined as a region of interest

and muscle composition as indexed by muscle attenuation will be calculated. We hypothesize that veterans at increased fall risk will have sarcopenia and dynapenia. Training should increase muscle mass and improve muscle quality as indexed by less fat infiltration in muscle.

AIM 2 Exploratory Outcome Measure: number of falls, near falls, injuries and fall related medical visits. We will determine if there is a difference in our interventions in preventing the number of falls, near falls, injuries and fall related medical visits during the 6 month intervention. During the intervention period individuals will be instructed to call the study coordinator to report any details of all falls and near falls within 24 hours of the occurrence after enrollment into the study. The study coordinator will collect all details of the fall and near fall including the location, the activity, and hazards that may have precipitated the loss of balance, and any injuries and medical care that was required. Participants will additionally be asked at each exercise session if any falls or near falls have occurred.[27] After the completion of the intervention all participants will be given monthly pre-stamped post cards to report any falls or near falls that may occur. The study coordinator will phone each participant monthly to follow up on any fall incidence. We have employed similar methodology in a number of studies.

Sample Size Determination and Power Analysis

This is a pilot study with an aim towards developing estimates for effect sizes that can be used to design a larger, confirmatory randomized clinical trial. A sample size of 20 per group will allow us to detect a difference of 25% between groups for our primary outcome of the four square step test. We will enroll 40 subjects. Typical attrition rates are 25 to 30%, primarily due to time conflicts and development of non-study related medical problems. In our preliminary studies, MMBI decreased the time to complete the four square test by 24%, with even greater improvements in the frailest subjects. Time to complete the four-square test has been shown to be an excellent biomarker for fall risk.

For our second exploratory Aim the outcome will be the rate of falls and the proportion of fallers during the intervention. The sample size estimate is determined primarily by three factors; the baseline rate of falls in the study population, the duration of follow-up, and the differential impact of the two interventions on the fall rates. For example in the Lifestyle integrated Functional Exercise (LiFE) program,[28] which embedded balance and lower limb strength training into habitual daily routines there was a statistical significant 31% reduction in fall rates (1.66 per person years) compared to controls (2.28 per person years), whereas the structured lower limb strength and balance exercises had a non-significant 19% reduction (1.90 per person years) in fall rate compared with the controls. Based on this and other literature we estimate that setting the power at 80%, alpha at 5% and with a drop-out rate of 20%, a sample size of 90 is required in each group to detect a clinically significant difference of 25% reduction in falls frequency between the two groups. Due to the budgetary limitations and duration of this VA SPIRE grant it is not feasible for us to enroll and study 180 subjects. Thus we recognize that we might not have sufficient power to see a difference in fall rate and number of falls between groups. Results from this study will be used to power a larger randomized clinical trial that will examine the effectiveness of the two interventions to reduce rate of falls and risk of falling in older veterans at high risk for falls.

Statistical Analysis: Data analyses will be performed using SAS. We will first perform an exploratory analysis to look for extreme values to make sure they are not the result of data entry error. All analyses will be conducted using the intention-to-treat principle. Statistical significance will be at an alpha of 0.05 (two-tailed). Demographic and clinical characteristics at baseline will be summarized with standard descriptive statistics.

For aim 1, to compare changes (defined as 24-week value minus baseline value) in mobility, balance and strength between our two groups (tai chi and MMBI) after 24 weeks of intervention we will use ANOVA for all continuous outcome measures (change=group).

For Aim 2 We will use Poisson regression (or, if the data are overdispersed Quasipoisson or negative binomial regression) to compare the number of falls in our two experimental groups. This methodology has been employed in the LiFe trial and other studies.[28]

Project time line: Prior to the start of the funding, we will obtain regulatory approvals from the IRB and VA R&DC. We will recruit 3 sets of intervention cohorts. Recruitment and baseline testing of the first cohort will start at the start of the funding period and they will enter intervention at month 3. While this first cohort is undergoing intervention we will recruit and perform baseline testing on the second cohort who will enter the intervention approximately 6 months after the start of the study. Post intervention testing on the first cohort will commence at 9 months. Recruitment for the third cohort will be done while the second cohort is in intervention and the third cohort will start their intervention at 9 months. During months 21 to 24 we will perform data analysis, and start writing manuscripts. We have used a similar strategy of staggered cohorts in prior studies. The study will be completed in a two years.

Anticipated Results and Alternate Findings: While we do not anticipate that Tai Chi will result in larger improvements in balance and falls than MMBI it is possible. The strength, balance, and gait tests that we are performing allow us to evaluate the contribution each makes to improving balance. This information can be used to design a future larger study aimed at decreasing falls.

Barriers: 1) Recruitment is always a potential challenge in clinical investigation. We have a long history of enrolling veterans into intervention studies. We have established a patient recruitment core and subject registry. We will work with this core to recruit veterans into this study. Given the high prevalence of older veterans who experience falls, we do not anticipate difficulties in recruiting and enrolling the requisite number of veterans into this RCT. 2) Poor adherence is also a potential problem. In our pilot study 16 out of 17 individuals completed our MMBI protocol with > 90% adherence. The majority of the individuals enjoyed the group sessions and looked forward to attending. We anticipate that we will have similar adherence to this program.

Project management plan: Dr. Katzel will meet on a weekly basis with the investigative team to discuss: review of newly screened and enrolled volunteers; study conduct, adverse events; quality of data, and monthly to discuss the status of subject testing and training (show rate, completion rate, exercise logs); review of rates of enrollment; new literature findings that may impact on the conduct of the study

Quality Assurance Plan: The BVAMC GRECC has well established quality management, quality assurance and safety monitoring plans that will be employed in the oversight of this study. The principal investigator is responsible for ensuring that all research conducted in this study follows good clinical practice guidelines and are carried out according to IRB regulations.

Future Directions: We have designed this study with community integration in mind. Both the Tai Chi and MMBI are easily exportable to a community program. Our MMBI program uses commonly available equipment for both balance training (chairs, cushions, step benches etc) and strength training (body weight, ankle weights, or commonly available gym equipment). We plan to use the results of this pilot project to write a multicenter QUERI grant or multisite Merit that focuses on community integration of these projects for fall prevention. We anticipate that the results of this project will support the development of an MMBI program in other VAs.

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