Cognitive intervention to improve simple and complex walking (crem)

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SPECIFIC AIMS

The major medical and socioeconomic consequences of disability, especially mobility disability, has led NIH to designate the development of preventive approaches for disability in older adults as high priority.[1] Gait speed is recognized as a vital sign in older adults; a screening measure that reflects integration of health, disease, and fitness.[2-4] Gait speed is used to describe functional recovery[5] and establish thresholds in community based activities such as ability to cross a street.[6] Gait speed is associated with activity levels,[5, 7] frailty,[8-10] and risk of falls in older adults.[11] While exercise is recommended to prevent mobility disability and improve gait speed,[12] less than 10% of U.S. seniors exercise at recommended levels[13, 14] and 25% are inactive,[7, 15] necessitating an urgent exploration of new approaches to improve mobility.

The relationship between specific cognitive functions and mobility in older adults is reproducible, robust and evidenced by studies that involve different methodologies.[16, 17] '*Executive functions*' (EF) are a set of higher cognitive processes that modulate behavior, facilitate allocation of attention during simultaneous tasks (divided attention), and afford adaptation to changing situations.[18, 19] EF has important links to gait speed.[20] EF impairments are associated with slow gait and falls.[21, 22] Training of EF and attention improves cognition and functional status in seniors.[23] Medications targeting these cognitive processes improve gait speed.[24, 25] Despite these promising results, C-REM as a strategy to improve mobility has not been studied. Results from our preliminary study demonstrated for the first time that frail seniors who completed a computerized **cognitive remediation (C-REM)** program targeting EF improved walking during simple (normal pace walking) and complex locomotion (walking while talking) conditions compared to baseline, as well as compared to frail seniors in a usual care group (see **B.5.c**).[26] Our results have been independently replicated in small samples of frail seniors[27] as well as in patients with Parkinson's disease;[28] lending support to our C-REM approach.

Building on the exciting results from these pilot studies,[26-28] we propose to conduct the **first single-blind randomized clinical trial to test the efficacy of cognitive remediation to improve mobility in seniors.** *Our hypothesis is that mobility and EF are linked via frontal cortices, basal ganglia, and their connections; and neuroplasticity can occur in these areas in response to C-REM.* Our primary outcomes are **gait speed during Normal Pace Walking (NPW) and Walking While Talking (WWT) conditions**. Gait variables other than speed (e.g., stride length variability[31]) increase risk of disability and falls.[11] Yet, impairments in these gait variables may not respond to conventional interventions such as exercise (see B.5.b).[32] Hence, we will also examine C-REM effects on an expanded gait and mobility battery as secondary outcomes (C.12.2 and C.12.5). We propose to randomize 420 seniors into either an 8-week C-REM (individualized computerized cognitive training) or health education program (control condition) to test the following predictions.

Primary prediction: Compared to a health control group, C-REM participants will demonstrate:

P1: Significant improvements in gait speed (NPW and WWT conditions) following intervention. We will explore **durability** of C-REM effects on these measures at 6 and 12 months post-intervention.

Secondary prediction: Compared to a health control group, C-REM participants will show:

P 2.1: Improved gait variability and other quantitative gait parameters in NPW & WWT.

P 2.2: Improvements in EF and other mobility related cognitive processes such as speed of processing, attention and divided attention.

Tertiary prediction: Compared to a health control group, C-REM participants will show:

P3: Neuroplasticity will be explored and measured with Functional Near Infrared Spectroscopy (fNIRS), an innovative technology that enables imaging during walking.[33, 34] We reported that older adults showed increased bilateral prefrontal activation on fNIRS during WWT compared to NPW.[16] We predict that after C-REM, participants will demonstrate neuroplasticity, defined as increased oxygenation levels in mobility related prefrontal regions due to compensatory reallocation or shift in activation patterns during WWT.[35-37] We will also account for other patterns or neuroplasticity changes.

Significance: Mobility disability is the most prevalent type of disability in older Americans.[38, 39] The C-REM approach may be an effective, accessible, and low risk method to improve mobility related cognitive functions in vulnerable seniors. Demonstrating mobility gains with C-REM will open new or supplemental treatment options for the majority of U.S. seniors who do not engage in physical exercise due to physical, motivational, or socioeconomic reasons.[38] Establishing mobility gains with C-REM in this preliminary randomized clinical trial (RCT) will provide scientific and feasibility support for a future large-scale multicenter RCT to establish and contrast the independent and combined roles of physical and mental exercises to prevent mobility disability.

RESEARCH STRATEGY: SIGNIFICANCE

B.1. Introduction: 37% of older Americans report a severe disability.[38] Among people 85 and older, 47% report walking disabilities.[38] People with mobility disability have more falls, more days of pain, and experience poorer quality of life.[40, 41] They also have higher morbidity and mortality.[7, 15, 42, 43] The major medical and socioeconomic consequences of mobility disability has led NIH to designate developing interventions for disability in seniors based on understanding underlying biology as high priority research areas.[1]

B.2. Locomotion. Gait speed is considered a vital sign in older adults. Gait speed is associated with changes in activity levels,[5, 7] frailty,[8-10] function,[44, 45] and falls.[11] A federal clinical trials website *(www.clinicaltrials.gov)* lists over 200 RCTs with gait speed as the outcome in different diseases and age groups. The **Walking While Talking (WWT)** test is an ecologically valid test of divided attention during locomotion developed by our group.[46] We reported that WWT speed showed incremental validity over normal pace walking speed (NPW) in predicting falls[47] and disability.[48] Multiple publications support the reliability and validity of WWT.[16, 46, 48-52]

The **Short Physical Performance Battery (SPPB)** includes tests of balance, gait speed, and chair rise[29]. A FDA expert panel recommended gait speed and SPPB as the two functional tests to use as outcomes in clinical trials.[53] Importantly, we demonstrated that WWT speed and SPPB were both independent predictors of frailty, disability and death.[48] Hence, despite the fact that gait speed is a key component in SPPB, inclusion of both measures is justified as they capture different facets of mobility, and provide incremental predictions for major public health outcomes.

To frame our findings in terms of a clearly understood and widely used reference measure and to facilitate future comparisons, we selected post-intervention changes in **gait speed** (**NPW and WWT conditions) and SPPB** performance as our primary outcomes.

B.3. Physical exercise is effective but compliance is low. Physical exercise (PE) RCTs have reported beneficial effects on gait speed in seniors, with improvements ranging from 7-12 cm/s.[8, 12, 54, 55] Despite widely reported benefits,[56] exercise participation is low among older adults (6%, 65–74y and 4% >75y).[57] Adherence is low; 50% drop out in first 6 months.[58] Even in supervised PE trials, attrition ranges from 22 to 76%.[59, 60] Seniors have much to gain from PE; yet, they often have the least access and opportunity. Moreover, PE does not improve mobility in all seniors.[61, 62] A meta-analysis reported that exercise training had only a 57% success rate in improving gait speed.[63] Hence, other approaches to improve mobility need to be explored.

B.4. Targeting cognitive processes shows promise to prevent mobility disability. *Executive functions (EF)* are a set of higher cognitive processes that modulate behavior, allocate attention among simultaneous tasks (divided attention) and adapt to changing situations. We reported that EF are associated with gait speed and falls in seniors.[20, 64] We also reported that impaired divided attention (on WWT) predicts falls.[51] These findings suggest that gait is a complex task for seniors, especially under attention demanding conditions. Better EF in older adults predicts better gait characteristics[20] and slower motor decline.[21] In the ACTIVE study,[23] cognitive training resulted in improvement specific to the cognitive abilities trained that persisted for 5 years.[23] Attention/EF training improved activities of daily living (ADL) and driving skills in ACTIVE and other studies, suggesting some distal transfer of training effects to untrained domains or activities.[23, 65, 66] Pilot studies of medications targeting attention and EF report improvement in gait. Methylphenidate improves attention and gait in children with Attention Deficit Hyperactivity Disorder[67] as well as in older Parkinson's disease patients.[68] Levodopa is well known to improve attention and gait in Parkinson's disease.[21]

Several pilot studies have shown that cognitive-motor training improves gait in cognitively normal and impaired seniors; lending support to our C-REM approach.[27, 28, 69-77] Our pilot C-REM results (see B.5.c) were independently replicated in pilot studies in small samples of frail seniors[27] and Parkinson's disease patients.[28] The C-REM approach is also supported by studies that have shown training on EF dependent dual tasks, such as the WWT,[20] improves mobility and balance in seniors.[71, 77-79] However, these studies were limited by small samples, lack of control conditions, focus on disease groups, and no information of C-REM effects on complex locomotion.[69-77] Based on our preliminary study,[26] we predict that C-REM will improve EF and related cognitive processes, which in turn will lead to better simple and complex locomotion.

B.5.a. C-REM . A US Census Bureau survey in 2010 reported that 41% of seniors had a computer at home.[80] SharpBrains, an industry watchdog, reported that sales of computerized brain fitness programs in the U.S. had increased 35% since 2008, reaching $295 million in 2009, and will continue to grow driven by concerns of an aging but computer savvy baby boomer generation.[81] We share concerns that most brain fitness programs have not been rigorously examined.[82] We reviewed and tested many C-REM programs before choosing **MindFit**. This computerized program has been successfully used by in different settings[83, 84] and in different aging, frail and disease populations.[85-88] It trains a number of cognitive processes besides attention and EF.

B.5.b. C-REM compares favorably to other non-exercise alternatives. There is a paucity of non-exercise interventions for frailty. Pharmacological approaches using androgens,[89] growth hormone,[90, 91] or vitamin D[92-94] show no or minimal improvement in gait speed in seniors. Other non-pharmacological approaches such as nutritional supplements,[95, 96] Tai chi,[97] or Yoga[98] were done in small samples, and show no or modest effects on gait performance. In comparison, the 8 cm/s improvement following C-REM in our pilot study (B.5.c) is promising. C-REM has several advantages over medications: fewer side effects, self-administration, and applicability to seniors with wide fitness levels.

Inferences that can be drawn from other pilot studies of C-REM for mobility and cognitive outcomes:

- C-REM is **feasible** in older adults, including those that are frail or cognitively impaired.[26, 66]
- **Near transfer** to non-trained cognitive domains[99, 100] and **far transfer** of gains (improved motor skills[65, 101]) have been reported after C-REM interventions. The ACTIVE study reported that participants had less difficulty with instrumental ADLs 5 years after training (without boosters).[23, 101]
- A **broad approach** targeting multiple domains may be more effective than targeting a single or limited set of cognitive processes. This may be especially relevant to gait which engages multiple cognitive processes.[20]

B.5.c. COGNITIVE REMEDIATION PILOT (J Gerontol Med Sci 2010[26] 2011[16]) We conducted a pilot study to test efficacy and feasibility of C-REM. We recruited 24 frail seniors (exercise ≤ once weekly and gait speed < 1 m/sec) from the community using our well-established recruitment procedures (described in C.5.12). They were randomized to C-REM and 12 to 'usual care.' The C-REM group got 24 (50 min) sessions over 8 weeks (3/week). Controls attended a fitness workshop and had telephone follow-up. Study assessments were done at baseline and post-intervention. **Transportation** was provided to all participants to ensure adherence to protocol as well as to avoid any indirect increased physical activity as a result of traveling to our center. Due to space limits a summary of main findings is provided. Full details are available in our published papers.[16, 26]

Mobility: At baseline, there were no significant group differences in age, gender, MMSE score or frailty status. 10 C-REM and 10 controls completed the study. Post-intervention, no subject started an exercise program or reported increase in physical activity, though 2 C-REM participants started using computers.

The C-REM group improved gait speed compared to controls on NPW (change: 8.2 ± 11.4 vs. 1.3 ± 6.8 cm/s, p = 0.19) and WWT (change: 19.9 ± 14.9 vs. 2.5 ± 20.1 cm/s, p = 0.05). 60% of C-REM participants improved NPW speed ≥4 cm/s compared to 30% of controls (OR 3.0, 95% CI 0.5-19.6). Two other C-REM participants had smaller improvements. 100% in C-REM group improved WWT walking speed compared to 30% of controls (OR 3.5, 95% CI 1.5-8.0). Exercise training, in comparison, improves gait speed by 57%.[63] We do not expect all seniors to respond equally to C-REM as is the case with exercise programs. It is not our intent to position C-REM as a standalone intervention but proving its efficacy is the first step towards studying combined physical-mental interventions with possibly even higher impact on mobility. *Given the pilot nature of this study, the high proportion of improvers after C-REM in both simple and complex walking conditions is promising*.

Mobility related cognitive processes: The C-REM group had worse Attention Network Test (ANT)[102] scores at baseline compared to controls. But they improved their executive attention network scores from baseline (203±143 ms) to post-intervention (164 ± 99 ms; p=0.09). Whereas, controls only had minimal improvement (pre132±43 vs. post 125±33 ms; p=0.44).

Durability: 9 subjects in each group returned at 6 months. Six C-REM subjects (67%) maintained 4 cm/s or more improvement in NPW speed compared to 3/9 controls (33%). All C-REM subjects (100%) still demonstrated more improvement in WWT speed at 6 months compared to baseline compared to controls (mean change 12.1 cm/s vs. 4.3 cm/s). These preliminary results support durability.

Replication studies: Mobility benefits of C-REM were replicated in two independent pilot studies. Seniors with history of falls and poor balance assigned to C-REM showed mobility benefits on the Timed Up and Go (TUG) task.[27] Interestingly, in the subset of participants with slow gait in this study, higher benefits were seen after C-REM on TUG as well as a divided attention walking task (similar to our WWT task).[27] TUG performance was also reported to improve following C-REM in another pilot study in 18 Parkinson's disease patients.[28]

- **Does C-REM benefit only cognitively impaired subjects?** Even among healthy seniors, there is wide variability in cognition. Of 10 C-REM subjects, 3 with 'low' attention scores 1.5 SD below our norms[103] had less improvement in NPW speed (mean change 1.9 ± 5.4 cm/s) than 7 with 'normal' attention scores (10.8 ± 12.5 cm/s). Given the small number, the results are only meant to be illustrative. A meta-analysis concluded that C-REM benefited both healthy and cognitively impaired seniors.[104] The ACTIVE study reported gains on attention in 2832 seniors (mean MMSE 27).[65] The IMPACT study reported benefits of C-REM on cognition in 487 seniors (mean MMSE 29).[105] We will account for baseline cognitive status as a covariate (see C.14).

- **Duration of C-REM in most previous studies is shorter and less intense**. Three C-REM studies with shorter training periods reported that effects were generalized to ADLs or driving skills.[23, 65, 106] In ACTIVE, 10 one-hour training sessions (compared to our 24x50-min sessions, 20 hours) improved processing speed (by 68%) and reasoning (by 49%) even 2 years after training.[65]
- **C-REM supervision**: Although MindFit was designed for individual home use; we administered it in a structured environment under controlled conditions to protect the study's internal validity. A designated RA supervised administration to ensure compliance and prevent loss of attention and motivation (see C.11.2.).

B.6. Brain activity while walking. While fMRI and PET are valuable in studying brain activity during cognitive processes, they are limited in imaging the brain during motion.[107] PET scans can infer brain activation during human steady-state locomotion (but not real time), but multiple considerations including but not limited to logistics, costs, risks and invasiveness preclude this method in a large scale study.[108] Mental imagery[109] does not approximate real walking necessitating newer approaches such as fNIRS (see c.12.3).[33, 34, 110-112] Good correlation is seen between fNIRS measured blood flow and PET scan and arterial spin labeling techniques.[113]

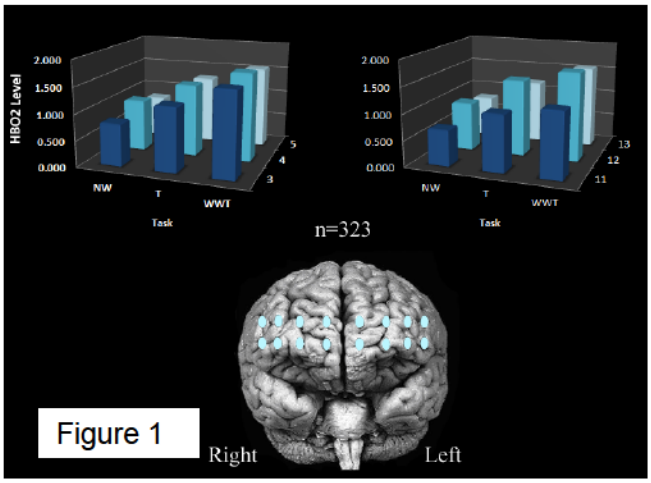

Figure 1

FNIRS: In the same C-REM subjects, we reported increases in brain activation (HbO_2 levels) in WWT task compared to the NPW condition using fNIRS (J Gerontol Med Sci 2011[16]). These findings provided first evidence for the functional involvement of the pre-frontal cortex (PFC) in locomotion, especially under increased attentional demands. Importantly, we have replicated these initial findings in our current cohort (R01AG036921). Our findings demonstrate bilateral increase in oxygenation levels in the PFC in WWT compared to both NPW and talking in a large cohort of 323 older adults (Fig 1). Electrode locations are overlaid on brain for illustrative purposes, and are not intended to convey precise anatomical localizations. These results are promising in that we were able to apply fNIRS to a large cohort, as for this RCT as well as demonstrating functional involvement of the PFC in complex locomotion tasks such as WWT (**P3**).[35, 36]

Neuroplasticity refers to the changes in brain structure and function occurring in response to experiential stimuli.[100] Support comes from studies that show environmental enrichment reduces cognitive deficits even in old animals.[114] Cognitive behavioral therapy in chronic fatigue syndrome patients improved not only physical activity and EF, but also resulted in increased lateral prefrontal cortex grey matter volume.[115] A 2-week healthy lifestyle program including C-REM resulted in reduced dorsal prefrontal cortical metabolism,[116] which was correlated with improved cognition suggesting that change in prefrontal activation patterns is not just a *biological indicator* but is also a *clinically meaningful marker* of neuroplasticity. We will use fNIRS to explore any C-REM induced neuroplasticity that may underlie mobility gains (**P3**). We used fNIRS to demonstrate that that oxygenation levels are increased in the prefrontal cortex during WWT compared to NPW.[16] Consistent with compensatory re-allocation models[35, 36] and our findings,[16] we predict increased prefrontal cortex (PFC) activation during WWT after C-REM, revealing increased PFC utilization in demanding locomotion tasks. We are aware that we may see alternate patterns of fNIRS activation. We have reviewed different compensation mechanisms[37] and will analytically account for other activation patterns.

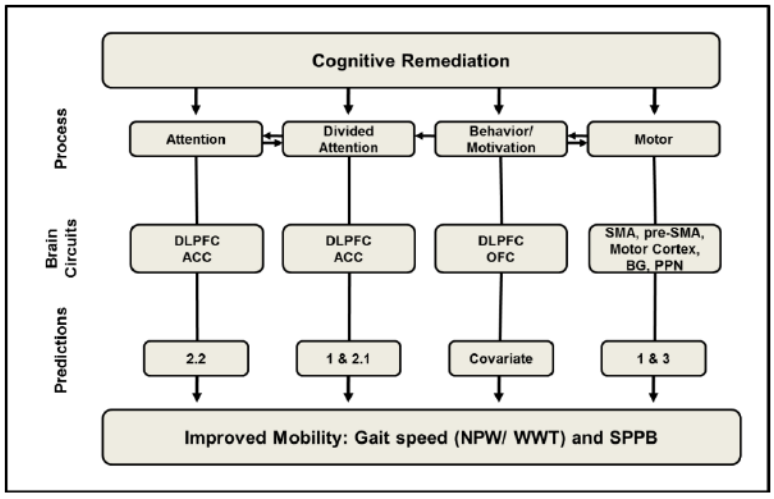

Figure 2. Biological model relating study predictions

B.7. Biological model. Our C-REM approach is based on a neurobiological model built on cognitive neuroscience theory.[105, 116-118] **Fig 2** depicts potential pathways, circuits and brain substrates involved in mobility, and our related hypotheses. **Frontal–subcortical circuits** link specific regions of the frontal cortex to basal ganglia.[117] The motor circuit originating in the supplementary motor area and the oculomotor circuit from the frontal eye fields subserve motor functions. The dorsolateral prefrontal, orbital frontal and anterior cingulate circuits are

dedicated to EF, social behavior and motivation.[119] These circuits are vulnerable to aging,[119, 120] neurodegeneration,[121] and vascular disease,[122] but may be amenable to C-REM.[100, 116, 118] Potential mechanisms for C-REM effects on gait include improving EF or direct effects on brain regions involved in motor control. C-REM can improve **depression and self-efficacy** (though these effects are yet unproven). We will measure (C.12.5) and account for these constructs in our analyses (C.14.1.a). Our aim is to determine neurobiological mechanisms underlying C-REM mobility gains (**P2, P3**).

RESEARCH STRATEGY: INNOVATION

This is the first RCT to test the efficacy of cognitive remediation, targeting both attention and EF, on mobility. While this proposal challenges existing paradigms, it is based on our long history of cognitive-motor research in elderly populations. Our C-REM approach is corroborated by independent pilot studies in small samples of older adults and Parkinson's disease patients.[27, 28] The C-REM approach is also supported by studies that have shown dual task training improves mobility and balance.[71, 77-79] We employ novel approaches such as fNIRS to assess neuroplasticity. If successful, this approach will help shift paradigms in the disability field by introducing cognitive approaches to mobility that can be applied to prevention and rehabilitation. Even if negative, important insights will be gained on the effect of C-REM on a wide array of secondary mobility and cognitive measures, test feasibility of C-REM, as well as offer the potential to conduct future biological and genetic investigations of neuroplasticity (see C.15). This 'proof of concept' RCT will provide scientific and biological support for a future multicenter RCT to examine the combined mobility effects of C-REM and PE as well as the long term impact of C-REM on falls and cognition in healthy, frail, and MCI patient populations.

RESEARCH STRATEGY: APPROACH

C.1. Overview and Design. We propose a single-blind study with 420 sedentary seniors randomized to **cognitive remediation (C-REM)** or **health education** control for 3 sessions per week for 8 weeks (**Fig 3**).

C.2. Alternate designs. We considered a number of alternate designs for this preliminary RCT.

- **Factorial design with C-REM and physical exercise (PE):** Most factorial studies do not account for interaction effects, which is likely between C-REM and PE. However, in order to detect an interaction of the same magnitude with same power, a 4-fold increase in sample is required.[123] With no sample increase, the interaction has to be at least twice as large as the main effects to be detected with the same power.[123] Moreover, with a factorial design we will not be able to establish whether mobility gains are due to C-REM alone or the combination of C-REM and PE. We will consider this design for future studies.
- **Parallel group (C-REM vs. PE vs. control):** The PE arm will increase sample size and budget without addressing our primary hypotheses regarding the effect of C-REM on mobility.
- **Cross over design:** Such a design is useful if there are no carryover effects. However, previous studies suggest that the effect of C-REM may be seen more than two years after initial training.[23, 124]
- **Boosters.** Having booster sessions will increase expenses and interfere with assessing durability. Also, health insurers are unlikely to pay for repeat interventions without clear indications limiting generalizability. However, boosters will be considered in follow-up studies.
- **Dose response.** Training dose was based on MindFit protocols[88] and our pilot.[26] MindFit measures training dosage (*type, time, number*). We will analyze dosing effects on our outcomes. Also see C.11.2.

C.3. Outcomes. Primary outcome is post-intervention change in gait speed (NPW & WWT) and SPPB scores. We extended follow-up to 12 months to explore durability of effects. Secondary is mobility related cognitive processes and other gait variables. The tertiary exploratory outcome is neuroplasticity (fNIRS).

We will assess multiple other mobility and cognitive outcomes (see C.12.2 and 12.5). However, we did not designate all these measures as primary; consistent with CONSORT recommendations for clinical trials.[125, 126]

C.4. Summary. Study procedures and assessments are summarized in **Table 1** below. Study flow in **Figure 3**.

Table 1. Assessment summary

Procedures/assessments	Days 1-3	Week 1 to 8 (3/week)	Week 9	6 mo	12 mo
Screening/ baseline evaluation (C.12.4)	X				
Safety monitoring (E.8)					
Outcome assessment (C.12)			X	X	X
Intervention (8-weeks)					
Post-intervention assessments (C.12.5)			X	X	X X X X X

C.5. Recruitment & screening. We will contact a random sample of individuals age 70 and over from Bronx and Westchester population lists using methods implemented in our current studies. We will also post flyers

and advertisements around the local communities at clinics and medical centers, community centers, and shops. We will also identify potential participants age 70 and older who are patients at Montefiore through Clinical Looking Glass. Finally, we will recruit subjects who have participated in other research projects, but are not currently involved in the studies. We screened 715 subjects by telephone in only 6 days and identified 45 potential subjects for our C-REM pilot.[26]. We have a long history of recruiting seniors in our community for various research studies**.** Dr. Verghese was Clinical Core leader of the Einstein Aging Study that enrolled over 1000 subjects using the same recruitment methods.[127] Dr. Holtzer is PI of an aging study that has recruited over 450 seniors in the past 3 years (R01 AG039330).

Screening is conducted in two phases (telephone and clinic). Our estimate based on our pilot study is that we will need to send letters to 12,000 seniors to obtain 400 subjects over 5 years. A letter explaining our study will be sent followed by a telephone call a few days later. All participants recruited through population lists and Clinical Looking Glass will be recruited using the same letter. Those expressing interest will be screened with the **Mobility Assessment Questionnaire**[128] and our **leisure activity scale,**[129, 130] which includes items from widely used activity scales.[43, 131] Subjects who report being sedentary (exercise once per week or less) will be invited for further in-person assessments. To exclude dementia, we will administer the **Telephone MIS**[127] (sensitivity 85%, specificity 86%[127]) and **AD8** (sensitivity 74%, specificity 86%[132, 133]). Using the MIS and AD8 in our telephone screen in our cohort study we found that of the 450 participants determined to be non-demented and invited for further testing in our research center only 2 participants met criteria for dementia.[134]

C.6. Screening visit. Potential recruits who meet eligibility criteria on the telephone are invited for in-person screening and are told that they will receive a *phone call reminder* the evening before the appointment. All participants recruited through population lists and Clinical Looking Glass will receive the same screening procedures. Written consent and screening will occur in our research center (see Facilities). On arrival, potential participants will review study information and sign consent. Study clinicians will determine final eligibility. Eligible subjects are randomized for interventions at the initial visit.

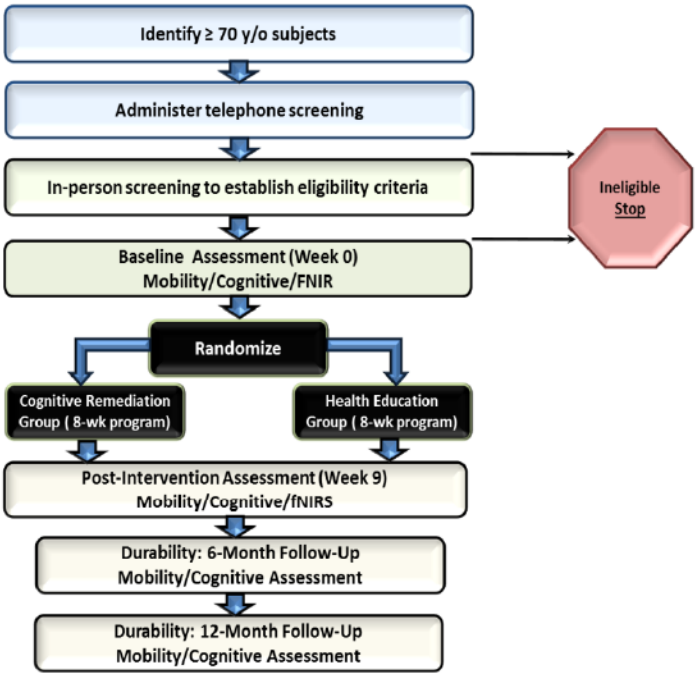

Figure 3. Subject Flow

C.7. Subject eligibility criteria. While healthy or disabled seniors may also benefit from C-REM, we chose to focus first on efficacy (rather than effectiveness) of secondary prevention using C-REM in sedentary frail seniors, a high risk for disability yet highly prevalent group in USA.[29, 135]
Inclusion criteria. 1) age 70 and older; 2) sedentary (exercises ≤ 1/week [43, 129-131]); 3) Ambulates with or without an assistive device. Individuals who require assistive devices will be enrolled if they meet the other criteria; 4) SPPB score ≤9[136] corresponding to frail range; 5) gait velocity ≤1.0cm/s (same criterion was used in our pilot study).[137, 138] Greater mobility benefits of C-REM in slow walkers and frail older adults is suggested from findings in our and other pilot studies.[26-28]
Exclusion criteria: 1) Serious chronic or acute illness. *Mere presence of diseases will not be used to exclude if well controlled.* 2) Musculoskeletal limitations that prevent completion of mobility tests. 3) Hospitalized in past 6 months or plans for surgery affecting mobility in next 6 months. 4) Dementia (screened as above); 5) Participation in any C-REM or other cognitive training in the past 12 months.

C.8. Randomization. The Efron ('biased coin') procedure[139] will be used to assure near-equal sample sizes and good representation on three variables of interest (gender, age < or >80 years, and NPW speed < or > 70 cm/s[137]) in both groups. Also see C.15.e. It will not be efficient to randomize by more categories. Besides, variables such as illness are highly correlated with speed and age, and are dealt analytically as covariates. Group assignment will be dispensed in sealed opaque envelopes generated by Dr. Wang using sequential study numbers so that the assistant who enrolls the participants will be blinded to randomization assignment of the next participant until assigned. Dr. Wang will not be involved with subject testing or interventions.

C.9. Sample size. We will enroll **420 seniors (210 per group)**. Power and assumptions in **section C.14.1.**

C.10. Blinding. Given the nature of our interventions, double-blinding both subjects and testers will not be feasible. But we will include a number of methods (besides randomization) to reduce bias.

- Selection bias will be reduced by concealing treatment allocation until the subject is entered into trial.[140]
- Primary outcome is an objective endpoint (gait speed/SPPB) and not subjective mobility complaints.[140]
- C-REM and health control interventions will be done in different sites and at non-overlapping times.
- The assessment team (and location) will be separate from intervention team.
- Participants and study staff will be instructed not to disclose group assignment or details of interventions.
- **Post-intervention questionnaire** (C.12.5) to assess maintenance of blinding.

C.11. Interventions. Both interventions will be given 3 times weekly for 8 weeks without crossover. C-REM program is supervised by Dr. Holtzer and the health education control by Dr. Ambrose. A **manual of operations** for all study activities will be developed during study setup (see **Table 3** in E.2.). Our intervention is based on a social cognitive model that views health behavior as being acquired and maintained through a complex set of behavioral, cognitive, and environmental conditions. Social cognitive theory concepts will be combined with strategies derived from applications of the Transtheoretical Model to mobility interventions[59, 141] (e.g., consciousness raising early in the program; reinforcement management later in the program).[59, 142]

C.11.1. Pre-intervention: Both C-REM and controls will be informed at baseline about national exercise recommendations.[15] We believe it would be unethical not to provide this advice given proven benefits of exercise. Extra-intervention activities will be tracked closely. Subjects will be given NIH physical fitness brochures and attend a safe walking workshop conducted by Dr. Ambrose pre-intervention. However, in the absence of active supervision seniors are unlikely to exercise. Separate workshops will be held for C-REM and controls. We will not conduct any gait or balance training in either group.

C. 11.2. C-REM Program

Rationale: Most individual training tasks on our C-REM program (MindFit) have been used in other C-REM trials. EF and related cognitive functions are the core cognitive domains that contribute to the individual tasks used in MindFit. Though EF shows strong associations with gait in our studies,[20] other cognitive processes such as visuospatial skills, memory, and hand eye coordination also contribute to mobility. The training pattern and instructions in individual sessions will be standardized across subjects. The training session will be supervised by Drs. Holtzer and Mahoney, who will also assess each subject's engagement and progress during the intervention. We will include a **computer familiarization session** prior to the C-REM program. In our pilot study,[26] all participants learned to do the C-REM program unassisted despite having no computer experience prior to the study.

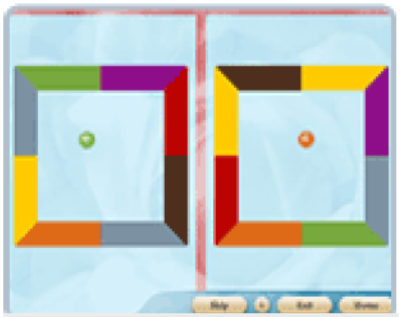

Figure 4. Example of MindFit training task: "Two in One" task trains dual-tasking

Procedure: The training is based on the program's built in baseline evaluation of cognitive processes including: psychomotor skills, digit and visual span, Stroop effect, sustained attention, and EF.[88] Based on distribution of cognitive test scores from the baseline evaluation, the subjects' cognitive abilities are divided into three categories: abilities on which a subject performed well, medium range and low performance. On the first day, the subject will train on a task reflecting his highest scoring ability in each category. On the second day, a new task reflecting his second highest scoring ability, is assigned from abilities on which the subject performed well and the tasks from the day before from the medium scoring abilities and the low scoring abilities are used a second time. On the third day, a new task is selected from the tasks reflecting his second highest scoring abilities from the medium scoring abilities and repeated practice is conducted with one of the familiar tasks in the other two categories. If a category of abilities has no new tasks, new tasks are taken from another category with the next best ranking. This form of practice allocation continues throughout the program, so that a new task is introduced every session. This system ensures that the subject is always working in their comfort zone and practicing stronger abilities before weaker. The system ensures that the participant will practice their weakest cognitive abilities later in the training program in an effort to prevent frustration.

EF training: After a subject has completed a training task it is released into a pool, from which we will select for each subject 'EF tasks' irrespective of baseline cognitive evaluation to ensure adequate training on EF and related cognitive functions (e.g., attention and dual-tasking). However, at the end of the 8 weeks all C-REM subjects will receive the same number and types of scheduled and additional EF training sessions and tasks.

Performance monitoring and dose: MindFit tracks the performance (time spent & level) and provides graphic feedback to participants. This monitoring will serve as a process measure. We can track performance to assess dose response effects, which will help in the design of future studies. Tracking enables us to assess if subjects are fully engaged in C-REM. Amount of training and dosing issues are addressed above as well as in sections C.1 and C.11.5.

Frequency and duration: *Each training session contains 3 tasks that take 20 minutes to complete. The task pool is used for 25 minutes extra EF training after scheduled training is completed. Total training time daily is about **50 minutes.** Over 8 weeks (24 days), each subject will receive 2 complete cycles or 48 training sessions (24 scheduled training sessions and 24 targeted attention executive function training).* We have used this training method successfully in our pilot study.[26]

Supervision: As in our pilot study,[26] C-REM will be administered by a designated RA in our research center in a structured environment under controlled conditions to protect internal validity and to ensure compliance. Each 50 min C-REM session is divided into two 25 min sub-sessions to minimize participants' fatigue as well as reduced attention and motivation.

C-REM duration & intensity. The ACTIVE trial, the largest cognitive intervention study in aging to date, used **10** training days (10 C-REM hours) over 6-weeks.[65] We propose **24** training days (20 C-REM hours) over 8 weeks. Our intervention is of longer duration and greater intensity than most prior studies.[65, 105]

C.11.3. Health education control

Rationale: We were guided by 4 important principles: 1) optimize participant recruitment and retention; 2) minimal effect on outcomes. There is no evidence that health education alone improves mobility. Previous RCTs have found no improvement in mobility after a program of preventive home visits, despite repeated subject and staff contacts.[143, 144]; 3) control for computer exposure and 4) older adults are less inclined to continue participation if they perceive a lack of benefit. The sessions will be supervised by Dr. Ambrose.

Procedure: We propose a health education control for 8 weeks supervised by Dr. Ambrose. We will conduct three 50 minute sessions per week of individualized computer based interactive health education classes to match frequency, computer exposure and intensity of interactions in the C-REM group. A **computer familiarization** session will be conducted at baseline. We chose interactive health topics, designed not to improve mobility outcomes, using public and commercial sources. An example is the Patient Education Institute (*www.patient-education.com*), which has a large library of interactive multimedia tutorials with topics such as 'How to prevent heart disease,' and 'Managing cholesterol.' Subjects take a brief quiz at the end of each session to assess their understanding of content and attention to program (**Fig 5**).

Figure 5. Interactive individual health education – quiz

Dr. Ambrose conducted **focus groups** with our pilot study subjects as well as a group of hospital staff over age 65. Both groups expressed great interest in these interactive computer programs and agreed that the topics provide a useful and interesting mix. They suggested 'take home' fact sheets that we will provide.

- We decided against teaching controls basic computer programs such as word processing to avoid confounding by any possible cognitive benefits of these programs.
- Sessions will be done on the same computer workstations as the C-REM group on non-overlapping days; one subject per computer.
- **Frequency and duration:** *Health education controls have 24 sessions in 8 weeks (20 hours); identical in frequency and duration to the C-REM group.* The individualized computer based interactive health education classes will balance with the C-REM group in computer exposure time and amount/quality of social contacts.
- We will track **dosing** in the health education control group.

Table 2. Intervention summary

	Cognitive remediation	Health education control
Dose frequency	24 sessions/ 8 weeks	24 sessions/ 8 weeks
Volume (subject time)	50 minutes per session	50 minutes per session
Intensity	Maximal focus as per neuropsychologist	Active participation assessed by moderator
Requirements for safety and maximal efficacy	➢ Gradual increase in difficulty as competence demonstrated ➢ 'Coach' to track performance	➢ Low/no C-REM content ➢ Content/topics varied to maintain interest. ➢ 'Coach' to track performance
Assess engagement	➢ MindFit cognitive evaluation	➢ Health literacy quiz

C.11.4. Retention and adherence. Sustaining adherence represents a major challenge in any RCT involving frail seniors. The short duration of the RCT improves likelihood of adherence. Other methods include:

- **Pre-intervention counseling**. Subjects in both groups will be administered questionnaires[141] to identify Transtheoretical model stages and receive stage specific individualized counseling, which has been proven to be successful in promoting adherence and retention in other intervention trials.[141]
- A permanent staff contact will be provided for subjects in the C-REM and health education control groups.
- Door to door transportation will be provided to ensure adherence as well as to avoid any indirect increased physical activity as a result of having to traveling to our center.
- C-REM and controls compensated for attendance ($5/session & $5/post-intervention assessment visit, $135 total consistent with IRB guidelines).

C.11.5. Methods to account for non-compliance and missing data

- We will identify **2 contact persons** who do not live with the subject for when participant cannot be reached.
- Flexible scheduling with makeup sessions on alternate days.
- For each study assessment, we will allow a **one week window** for completion.
- If the participant is acutely ill, is in the hospital, or has a temporary condition that interferes with walking (e.g. ankle sprain), we will attempt to complete the assessment at another time.
- Utilization of the telephone based questionnaire to account for possible non-random drop-out (see C.12.6).
- **Outcome adjudication.** The research team will adjudicate events such as mobility disability in subjects who drop out based on medical interviews, contact interviews, and home assessments as required.
- **Stopping rules** are discussed in section E.

C.12. ASSESSMENT OF OUTCOMES:

Outcomes will be assessed by a research assistant supervised by Dr. Verghese whom will not participate in other aspects of this RCT. Baseline study assessments done in the first week is limited to **90 minutes over 1 day** to avoid fatigue. Testing time per subject is less than in our ongoing aging studies (~180 min), and was demonstrated to be feasible in our pilot study.[26] Telephone assessments are **10 minutes**. Post-intervention assessments conducted at 9 weeks, 6 months, and 12 months will be limited to 90 minutes.

Our group developed or validated many of the primary and secondary outcome measures in this RCT (see resumes and refs[11, 16, 20, 48, 49, 51, 64, 129, 130, 145-154]). We have over 12 years continuous NIH funding for training and supervising assistants to administer these measures in various elderly populations.

C.12.1. PRIMARY OUTCOME (Mobility): We selected the following three primary outcomes to test the efficacy of the C-REM intervention.

C.12.1.a. Gait speed: Gait speed was recommended to FDA as the preferred outcome for RCTs[30] because of its good validity, reliability, sensitivity to change, and predictive validity for multiple adverse outcomes.[30] We have reported that gait speed highly correlates with mobility related activities in our community.[155]

Method: Research assistants will conduct gait evaluations using a 28-foot computerized mat (20-feet recording surface) with embedded pressure sensors (GAITRite). The mat has 4 feet at each end without sensors to account for initial acceleration and terminal deceleration. Subjects will be asked to walk on the mat at their 'normal walking speed' in a quiet and well-lit room. Monitoring devices will not be attached. Our primary outcome is speed (cm/s). However, multiple gait parameters (see ref[147]) will be obtained and available for analyses[147] (**P1, P.2.1**). Subjects will also be assessed walking the course at their fastest speed.

***Reliability*:** We have reported excellent test-retest reliability of gait speed on GAITRite (Kappa >0.9).[46, 128] Gait speed correlates highly with complaints of mobility limitations, falls and dementia in our studies.[128, 134]

Practice effects: Gait speed improved only by <2% when tested twice 8 weeks apart in controls in our pilot study suggesting that longer intervals between gait assessments may help minimize practice effects.

C.12.1.b. Walking while talking test (WWT) is a novel ecologically valid mobility measure developed by our group.[48, 51] Our studies establish the incremental validity of **WWT speed** over NPW speed for predicting adverse outcomes such as falls, frailty and disability.[48, 51] Other investigators have shown that training older adults on WWT like tasks translates into clinically relevant outcomes such as reduced falls, better balance, or improved function.[77, 78] Hence, establishing C-REM effects on our co-primary outcome of WWT speed alone could be of high clinical impact and relevance (irrespective of its effect on NPW speed).

Subjects are asked to walk the GAITRite walkway for two trials while reciting alternate letters of the alphabet. We also record errors while reciting letters.[46] Subjects are given practice. The order of the initial letter on WWT is randomly varied between 'A' and 'B' to minimize practice effects. For further details see refs[46, 49, 51].

***Reliability**:* We reported good inter-rater reliability (r = .602) on a previous WWT version.[51] In 31 EAS subjects, we had excellent test-retest (r = 0.935) and inter-rater reliability (r = 0.918) for WWT speed.

C.12.1.C. Short Physical Performance Battery (SPPB) includes tests of balance, gait speed, and chair rise[29]. A categorical score in each of the three areas (0–4) and a summary score are determined (0–12, higher better). The SPPB can be completed in 5 minutes and has been recommended for use as a primary outcome

measure in clinical trials.[136, 156] We recently demonstrated that WWT gait speed and SPPB performance were significant and independent predictors of frailty, disability and death in high functioning older adults.[48]

C.12.2. SECONDARY OUTCOMES

C.12.2.a. Mobility related cognitive processes: In our research,[20, 64, 149] we have defined EF using clinical neuropsychological measures and a latent variable approach. The **Digit Symbol Substitution test (DSST)**[157] is a potent predictor of mobility outcomes in aging.[21, 158] We showed that DSST has a protective effect against gait speed decline that is amplified in individuals with high cognitive reserve.[159] The DSST is a standardized timed test with established psychometric and normative data; commonly used to assess speed of processing, visual spatial attention and EF.[20] Scores range from 0 to 133, with higher scores indicating better performance.

The **Attention Network Test (ANT)** is a 25-minute computerized test of alerting, orienting, and executive attention.[19, 160] These attention networks are linked to different brain substrates[19, 160] and genetic polymorphisms.[161, 162] The executive attention network is based on the **flanker task** included in the NIH toolbox.[163] Reliability: The ANT is reliable in patient populations.[164] We have reported high reliability and validity of the three networks in 234 non-demented seniors.[102] Importantly, network effects, their relations to mobility and sensitivity to C-REM can be evaluated while accounting for differences in speed of processing, a key factor in cognitive aging.[165]

C.12.2.b. Quantitative gait: Quantitative gait variables (e.g., stride length and gait variability) and summary measures (gait domains derived from factor analysis[147]) are obtained in NPW and WWT conditions.[166] Our studies have established the reliability of gait variability measures[31] and shown that gait variability is a stronger predictor of outcomes such as injurious falls, and dementia than gait speed.[11, 147] Interestingly, we reported that treadmill training in a small sample of frail seniors improved gait speed but not gait variability;[32] suggesting the need for testing new intervention approaches such as C-REM. In contrast, our C-REM pilot showed positive effects on gait variability and speed.

C.12.3. TERTIARY OUTCOME (exploratory)

C.12.3.a. Functional Near Infra-red spectroscopy (fNIRS): *The objective is to identify patterns of brain or network activations and change following C-REM to provide insights into neuroplasticity.* fNIRS is a portable system, developed by our Drexel collaborators,[33, 34, 110-112] that has been implemented in our research center (see **Equipment**). fNIRS can detect brain activation changes in PFC during walking; overcoming limitations of conventional imaging.[167-169] Because oxygenated hemoglobin (HbO_2) and deoxygenated hemoglobin have characteristic optical properties in visible and near-infrared light range, the change in concentration of these molecules during neurovascular coupling can be measured using optical methods.[170] fNIRS measure changes in the ratio of HbO_2 to blood volume in order to assess brain activity through intact skulls in adults.[170, 171]

Protocol: fNIRS recordings are conducted under four conditions: rest, NPW, talking (recite alternate letters) and WWT. See the Equipment section and our published studies[16] for further details of fNIRS procedures. Activation patterns reported as difference between standing baseline and NW, and NW vs. WWT. We selected HbO_2 **concentration** as a marker of cortical activity because it is the most sensitive indicator of mobility related changes.[168, 172] There are considerable individual differences in task-related changes in deoxyHb levels.[173] To avoid these problems, HbO_2 data from each channel is normalized by linear transformation. This normalization is also useful for circumventing the influence of differential path lengths among the subjects and that of cortical regions on the HbO_2 levels.[172] fNIRS hardware supervision and signal processing will be conducted by Dr. K. Izzetoglu and Dr. M. Izzetoglu respectively, as done in our published and ongoing studies.[16]

Feasibility: The fNIRS was successfully implemented in our pilot study.[16] In a population-based study to examine cognitive control mechanisms of mobility (1R01 AG036921-01A1, PI: R Holtzer), we conducted fNIRS studies in NPW and WWT conditions in ~250 individuals in one year (cf. 420 in 5 years in this proposal).

We have administered fNIRS to more adults than reported in previous aging samples, but acknowledge that we have not yet defined longitudinal changes to establish ifNIRS as a biomarker. Hence, this tertiary prediction is exploratory and should help generate hypotheses as well as provide insights into C-REM effects.

C.12.4. OTHER MEASURES: The effect of C-REM will be assessed on these additional measures. They also serve to define the baseline characteristics of the groups, assess confounding, and as covariates in analyses.

a. **Other Cognitive**: Standard tests to determine cognitive status, rule out dementia and as process measures for C-REM. Test battery not described due to space limitations but are available in our referenced papers.[20, 102, 103] These tests will enable examination of C-REM effects on cognition. If funded, we will seek supplementary grants to study effects of C-REM on cognitive decline.
b. **Duke Activity Status Index**[174] will be used to adjust for baseline cardiac fitness.
c. **Pain and fatigue scales**.[175, 176-178]
d. **Handgrip/quadriceps strength**.[10, 177]

e. **Additional mobility measures:** To examine a wider range of C-REM mobility effects, measures developed or used in our studies will be used as secondary outcomes. **i.** Stair climbing time: Stair climbing is considered the most challenging mobility tasks for older adults.[153, 179] We developed and established norms for this measure, and demonstrated its incremental validity over gait speed in predicting disability;[153] **ii.** Disability scale developed by Gill and colleagues for use in community studies of older adults.[180, 181]
f. **Psychosocial status:** See rationale in section B.8 and analytical approach in **C.14.1**. Subjects will be screened for depression (Geriatric depression scale)[182] and anxiety (Beck inventory[183]). These scales have high reliability and validity in community-based samples.[182]
g. **Rosenberg Self-Esteem Scale[184]:** Widely-used self-esteem measurement scale with high internal consistency (alpha coefficients 0.72 to 0.87)[184] and test-retest reliability (0.85).[185]
h. **Falls Self-efficacy scale.[186]**
i. **Marlowe-Crowne Scale.** *Socially desirable responding* is the tendency to tailor responses for purposes of looking good resulting in measurement error, and will be assessed with the Marlowe-Crowne Scale.[187]
j. **The Berg Balance Scale (BBS)** was developed to measure balance among older people with impairment in balance function by assessing the performance of functional tasks. It is a valid instrument used for evaluation of the effectiveness of interventions and for quantitative descriptions of function in clinical practice and research.
k. **Gait initiation** refers to the phase between motionless standing and steady-state locomotion, and will be assessed as participants walk on the GAITRite mat while the fNIRS sensors are connected to their forehead.

C.12.5. POST-INTERVENTION: We propose assessments at post-intervention visits at 6 and 12-months. We will also track via telephone calls at months 4/5/7-11. We have experience tracking mobility outcomes by telephone in over 1000 participants in our funded studies.[145]

a. **Telephone-Mobility Assessment Questionnaire[128]** will be used to track mobility (months 4/5/7-11).
b. **Falls.** Given the short duration of this RCT we lack sufficient power to address falls. Nonetheless, we will track falls on our telephone and in-house interviews using established criteria to define falls.[188]
c. **Leisure and CHAMPS physical activity scales[130]** will be used to measure leisure and physical activities post-intervention. This will enable us to monitor lifestyle changes that may be related to C-REM.
d. **Post-intervention questionnaire** will be administered to both groups to assess maintenance of blinding.
e. **Health literacy questionnaires**[189] will be given pre- and post-intervention in both groups. This will serve as a process measure for the efficacy of our health education intervention in the control group.

C.13. TIMELINE. We propose to screen and intervene in 210 subjects per group (assuming 20% attrition); 24-26 subjects will be randomized at a time into C-REM or health education programs (17 cycles over 54 months). We have recruited and evaluated larger samples in our other aging studies. Screening will start in month 2, and the interventions in month 4. A planned interim analysis by the DSMB (E.8.) will be conducted when 210 subjects are accrued (month 27 – Table 3). The final intervention group will have their post-intervention assessment in month 51. We will extend data collection to month 57 to enable us to collect outcomes to test durability till 12 months for the final intervention group. Detailed timetable with milestones and goals is in E.2.

C.14. DATA ANALYSIS.

Analytical Overview: Our goal in this preliminary RCT is to define the role of C-REM on improving simple and complex locomotion in sedentary frail seniors. Baseline distribution of covariates will be compared to assess adequacy of randomization to produce comparable groups of participants using appropriate graphical procedures and summary statistics.

C.14.1.a. Primary outcomes analysis: We will employ linear mixed effects model to compare the changes in gait speed and SPPB scores (**P1**) at post-intervention (week 9) as well as at 6 and 12 months post-intervention in C-REM versus controls.[193] The variance will be allowed to differ between C-REM and controls. The primary comparison between the two groups is post-intervention change in gait speed during NPW and WWT conditions and on SPPB. For WWT, we will also consider percent change in WWT speed from normal walking (*dual task cost*). We can define improvers on NPW and WWT by using cutscores on these measures as done in our pilot study (see C.14.2 and ref[26]), and compare proportion of improvers vs. non-improvers in the two groups using generalized linear mixed effects models.[193]

- We will use **intention to treat (ITT) analysis**, which includes all randomized participants in the groups assigned, regardless of adherence with entry criteria, whether C-REM was received, and subsequent withdrawal or deviation from the protocol.[194] ITT analysis is pragmatic because it admits noncompliance and protocol deviations, and gives an unbiased estimate of the intervention effect. Handling missing data is a major issue in ITT, and is dealt with by imputation or sensitivity analysis.[195-197] The linear mixed effects

model is good in handling missing data due to drop out assuming MAR mechanism.[193, 198-200] Our statistician, Dr. Wang, is very experienced in these methods; see C.15.[201-203]

Last observation carried forward is used to deal with missing data, but there are major limitations (see refs[204, 205] for reviews). Hence, we do not propose to use this method.

- We will utilize closed testing methods, involving step-wise procedures, for addressing multiple comparisons/multiple testing, since they are more powerful than single step methods (e.g. Bonferroni).[206]
- If sessions attended vary, **'dose' effect** will be examined in both groups – discussed in C.11.
- **Mediation analysis** (product of coefficients method[207]) will be conducted to examine whether depression, psychosocial measures (mood, self-esteem, and self-efficacy) as well as changes in proximal cognitive outcomes (attention and EF) mediates C-REM effects on gait speed in NPW and WWT conditions.
- **Gender:** Almost all observational and intervention studies in aging populations have a female preponderance; reflected in our target recruitment table. This gender distribution has been our experience recruiting over 2000 participants to various aging studies at our center for over 10 years.

  While gender differences in EF are reported,[190, 191] there is insufficient information to assume that there will be gender-based differences in C-REM effects on mobility. Gender explained only a very small portion (2.2%) of the individual variance in EF dependent Card Sorting test in a large NIH toolbox validation study.[190] Repeated training on an EF task (DSST) improved performance on the test; but did not show gender differences.[192] The ACTIVE study reported that adjusting for gender did not change main results in their intervention study.[65] Hence, we decided against gender-based recruitment.

  Nonetheless, given our sample size we can explore any gender based intervention effects in our study. We shall adjust for gender and conduct gender-stratified analysis.
- **Covariates:** The following pre-specified set of baseline covariates[21, 25, 191] were selected to determine their influence on the treatment: age, gender, education, chronic illnesses, cognitive test performance, pain, arthritis and cardiac fitness.[178] This method is preferred to adjusting for covariates that are imbalanced between treatment groups using significance testing, because it is possible for a covariate to have a strong confounding effect even if the difference in the average value of that variable between the parallel arms is not significant.[192] We will also monitor any change in these measures over the intervention period and analytically account for their effects by including these measures (baseline levels as well as change) in linear mixed effect models to account for possible confounding.
- Adjusting for performance on baseline **cognitive tests** and stratified analysis by baseline cognitive status in the C-REM group will be done.
- Our **dual-task procedures** have been replicated and validated in many published papers.[4, 13, 24, 29, 75] We recognize that participants may employ, despite the standardized instructions, different strategies when dual-tasking. In the context of the linear mixed effects models, we will examine whether performance and decline on the cognitive interference task (reciting alternate letters of the alphabet alone and in WWT) was related to dual-task costs observed on the primary walking task and will interpret the results accordingly.

C.14.1.b. Power for primary outcome: The primary hypothesis examines change in gait speed (during NPW and WWT conditions) and SPPB. Improvement in speed is ~10 cm/s after 8-12 week PE interventions.[41, 46, 79, 80] In contrast, gait speed in the non-intervention controls show minimal improvement,[79] unchanged,[46] or declined.[41, 80] B*ased on these PE effects and our pilot study,[26] we conservatively estimate a 5 cm/s improvement post-C-REM, which is ~50% of the mobility effect in PE trials and less than that achieved in our pilot study (**8 cm/s**)*. This magnitude of change also corresponds to that recommended as small but clinically meaningful change in gait in aging studies.[10, 11]

The sample size (420) provides >80% power to detect clinically meaningful differences at significance level of 0.05. The conservative Bonferroni correction for multiple testing was used in sample size calculations. Based on conservatively estimated SDs of 12 cm/s, 20 cm/s and 1.5 points for NPW, WWT and SPPB, respectively, to detect clinically meaningful differences of 5 cm/s for NPW and 0.5 points for SPPB with 80% power,[10, 11] and a conservatively estimated 10 cm/s for WWT (16 cm/s WWT speed improvement in our pilot study[13]), at least 169 subjects per group are needed. To take account the projected 20% drop out rate at end of intervention, 210 subjects per group will be enrolled.

5 cm/s is the minimal detectable intervention change that we can study with 80% power, and is not the maximal threshold of change expected after C-REM in this RCT. Any improvement >5 cm/s by C-REM will increase power. For instance, we observed **8 cm/s** improvement in our pilot study[26] ('substantial improvement' range[136, 193]), which will provide us >90% power to test our hypothesis in this RCT.

Durability: Assuming cumulative dropout rates of 25% at 6 months, with n=210 per group, we will have 92%, 99% and 75% power for detecting differences of 5cm/sec, 10 cm/s and 0.5 points in NPW, WWT and SPPB, respectively. At 1 year of follow-up, assuming 30% cumulative dropout, we will have 90%, 98% and 72% power

for detecting differences of 5 cm/sec, 10 cm/s and 0.5 points in NPW, WWT and SPPB, respectively. If the difference in SPPB is substantial (1 point), the power will be more than 95% at both time points. However, given the lower power to reliably estimate SPPB change, we designate the durability examination as an exploratory aim. We will seek additional funding to extend examination of durability.

- **Is our minimal detectable difference a clinical important difference?** We addressed clinical relevance of our estimate of change in multiple ways including validating effect size,[57] correlation with activity limitations, and expert opinion.[78, 150] In the LIFE-P study, small clinical meaningful change in gait speed after a one-year PE intervention was 3-5 cm/s (substantial 8 cm/s).[10] Perera et al recommended a 5 cm/s improvement in gait velocity as a small clinical meaningful change and 10 cm/s as substantial change over one year. We collaborated with Perera to develop clinical meaningful change estimates in gait velocity in our local population;[57] 4 cm/s was small meaningful change and 10 cm/s substantial change in one year.[57]

  Preliminary analysis in the Einstein Aging Study shows that a >4 cm/s gait speed improvement over one-year was associated with 13% reduced risk of activity limitations and 11% reduced risk of disability. Hence, the gait speed change selected is not only a statistically significant but also a clinically meaningful change in our population.

  Direct extrapolation is limited as most previous studies report change over one year periods. In contrast, a 5 cm/s change or higher is predicted over only 8 weeks in this preliminary RCT.

C.14.2.a. Secondary outcomes: Quantitative gait variables other than speed (especially variability) and gait domains will be considered using linear mixed effects models as described above.[193] We will explore neurobiological mechanisms underlying C-REM by studying its effect on mobility related cognitive processes. With a sample size of 210 per group, assuming 25% and 30% cumulative dropout rate at 6 and 12 months, we can detect, with 80% power, differences of 0.29 and 0.30 SD units, in the change in each secondary outcome between C-REM and control at 6 months and 1 year.

C.14.2.b. Tertiary outcome: In addition to PFC oxygenation levels on fNIRS, alternative measures such as areas activated, bilateral versus unilateral activation, and any reduction in activation will be considered simultaneously using linear mixed effects model.[193] There is limited data to reliably estimate power for the tertiary outcome (fNIRS). Nonetheless, the sample of 420 should provide adequate power to examine this outcome. In our pilot study we were able to demonstrate significant cross-sectional differences in prefrontal activation on fNIRS during WWT and NPW conditions in 11 older and 11 younger persons.[26] While we have major cross-sectional experience in administering fNIRS in large aging samples, we do not have experience in longitudinal fNIRS data. Hence, this tertiary prediction is exploratory and should help generate hypotheses.

C.15. Potential pitfalls and solutions.

a. **Missing data.** Losses to follow-up can be classified into non-informative (missing at random) and informative censoring (drop out depends on the unobserved outcomes). No adjustment is necessary for non-informative censoring. However, for informative censoring, parameter estimates and resulting tests on hypotheses will be biased without further adjustment. The best way to handle missing data is to avoid it. However, we recognize that despite all our efforts (see C.11.5), there will be missing data.
b. **Dropouts**: We will follow-up with participants who dropped out of the study to determine both their mobility status[120] and reasons for withdrawal. We now propose intention to treat analysis (C.14.1.a). A rich set of telephone-based information (T-MAQ[120]) will be collected even for those subjects who may drop out. We will utilize this auxiliary information to assess the MAR assumption and combine it into the main model through joint modeling and multiple imputation approaches.[203] Dr. Wang has applied these approaches to eliminate or reduce bias in presence of informative censoring in our other aging studies.[201]
c. **Regression to mean.** To parse out the effects of treatment versus regression we utilize a primary outcome (gait speed/SPPB) with high reliability, a control group, and will analytically examine this effect.
d. **Confounders.** To account for key confounders such as age, sex, and gait speed, we propose to use block randomization. Baseline cognitive/physical/ cardiac fitness will be accounted in our analysis.
e. **Speed ≤70 cm/s.** We will use this widely used slow gait cutscore as one of our randomization variables.[150] If we exclude all with slow gait we may bias against enrolling oldest subjects who have mean gait speeds that are lower than the 70 cm/s cutscore.[30] We will stratify analysis by this cutscore and examine effects.
f. **Feasibility.** In our pilot study,[13] 50% of subjects met Fried frailty criteria[43] but completed interventions. We propose to over-enroll by 20% to account for any attrition. We have incorporated multiple methods to promote adherence and reduce possibility of missing data. We have also built in stopping rules.
g. **Which aspects of the cognitive training are responsible for improvements?** While it is important to show that the overall C-REM program improves mobility; Mindfit also tracks training patterns that will help us refine the C-REM program for future studies. The availability of such extensive data will enable us to

develop individual and/or group models of growth using techniques such as growth curve analysis. One can also investigate the relation between growth patterns on tasks and mobility benefits. Dose is also studied.

h. **Negative findings:** We will employ several strategies to assess potential negative findings. 1) We showed that the protective effect of attention/EF against decline in gait speed is moderated by cognitive reserve.[6] We will evaluate whether cognitive reserve moderates the effect of C-REM on mobility; 2) We will apply for additional funding to establish a bio-repository for this cohort. This will provide an opportunity to evaluate whether genetic factors or biomarkers such as brain derived neurotrophic factor (BDNF) may mediate the effect of C-REM on mobility.[208-210] 3) We have the opportunity to examine C-REM effects on other mobility, cognitive, mood, and psychosocial outcomes.

C.16. Summary: This proof of concept RCT provides a rigorous test of the efficacy of an innovative C-REM approach to improving mobility in vulnerable frail seniors as well as providing insights into underlying biological mechanisms (neuroplasticity). If successful, this approach will help shift paradigms in the disability field by introducing cognitive approaches to mobility that can be applied to prevention and rehabilitation in diverse settings. These results will help design future studies in healthy seniors as well as those with frailty and diseases such as mild cognitive impairment, Parkinson's disease, strokes, and traumatic brain injury.

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E. HUMAN SUBJECTS

E.1.Study population:

The characteristics of the subjects, recruitment methods, inclusion and exclusion criteria, and minimum numbers to be studied are described in Section C. The study interviewer will conduct the initial telephone-screening interview. Potential subjects will be invited for further in-person evaluations. Study evaluations, enrollment, and in-person interventions will be done at our research center. The study clinician (Dr. Ambrose/ Verghese) will diagnose and exclude cases following clinical and neuropsychological testing. The statistician will assign unique study ID to each subject. Research assistants at enrollment will determine eligibility.

General inclusion criteria:

1. Adults aged 70 and older, residing in the community. The age criterion is intended to maximize rates of incident mobility disability.
2. Plan to be in area for next three or more years.

3. Able to speak English at a level sufficient to undergo our cognitive assessment battery.
4. Ambulatory. Subjects are classified as 'non-ambulatory' if they are unable to leave the confines of their home and attend a clinic visit. These include subjects who are bed-bound as a result of severe medical illness or those who require assistive medical devices (respiratory support or ventilators) that cannot be transported or those who cannot complete our gait protocols. **We will not exclude subjects who use walking aids (canes, crutches) for ambulation. Subjects who require walking aids to walk outside but are able to complete our gait protocols without an assistive device or the assistance of another person will not be excluded.** Subjects who become non-ambulatory during follow-up will continue participation in the study via telephone interviews and mailed questionnaires.
5. Gait velocity ≤1.0 cm/s.
6. Short Physical Performance Battery score ≤9.

General exclusion criteria (one or more criteria):

1. **Presence of dementia** (Telephone based Memory Impairment Screen score (T-MIS) of <5, AD8, or dementia diagnosed by study clinician at initial visit). These cut scores and procedures have been validated in our and other aging studies.
2. **Serious chronic or acute illness** such as cancer (late stage, metastatic, or on active treatment), chronic pulmonary disease on ventilator or continuous oxygen therapy or active liver disease. Individuals with recent cardiovascular or cerebrovascular event (MI, PTCA, CABG, or stroke) will not be excluded if they meet above inclusion criteria. *Many of these chronic conditions are very common in older adults. Hence, mere presence of these conditions will not be used to exclude subjects if well controlled or of mild severity and if subjects are able to complete training and mobility tasks.*
3. **Mobility limitations solely due to musculoskeletal limitation or pain** (e.g., severe osteoarthritis) that prevent subjects from completing mobility tests. Prevalence of arthritis is ~60% in the Einstein Aging Study,[1] so mere presence of disease will not be used to exclude subjects if they can complete the mobility tasks.
4. Any **medical condition or chronic medication use** (e.g., neuroleptics) in the judgment of the screening clinician that will compromise safety or affect cognitive functioning or terminal illness with life expectancy less than 12 months.
5. **Progressive, degenerative neurologic disease** (e.g., Parkinson's disease or ALS) diagnosed by study clinician and as per medical history.
6. **Hospitalized** in the past 6 months for severe illness or surgery that specifically affects mobility (e.g., hip or knee replacement) and that prevent subjects from completing mobility tests or plans for surgery affecting mobility in the next 6 months.
7. **Severe auditory or visual loss**: Vision is screened using a Snellen chart by the psychological assistant. Also, the neurologist tests visual fields using confrontation perimetry and near vision using Jaeger test types. Significant loss of vision is defined as corrected vision (using reading glasses) less than 20/400 on the Snellen chart with both eyes and inability to read any test sentence on the Jaeger test card with both eyes. Hearing is initially evaluated as part of the screening telephone interview. Subjects who attend the clinic visit will be excluded only if they are unable to follow questions asked in a loud voice (even with hearing aid in place).
8. **Active psychoses or psychiatric symptoms** (such as agitation) noted during the clinic visit that will prevent completion of study protocols. Past history of these symptoms or presence of psychiatric illness not used as exclusion criteria.
9. Living in **nursing home**.
10. **Participation in intervention trial**. Subjects can participate in other observational studies.

We acknowledge that we cannot control for all possible confounders, and that residual confounding can occur in all clinical trials. However, the randomization process in the clinical trial design will allow for equal allocation of potential confounders and effect modifiers between the two study groups.[2, 3]

E.2. Recruitment: To achieve our study aims aged adults will be recruited from a random sample of the Bronx and Westchester County residents, which is comprised of individuals age 70 and over who are in voter rolls by virtue of having voted in local or national elections in the past two years. We will also post flyers and advertisements at local clinics, stores, community centers and offices. We have had experience using this source to recruit over 1000 participants for various aging studies in the past 10 years including our pilot

intervention study. We will also identify potential participants age 70 and older who are patients at Montefiore through Clinical Looking Glass. The timeline for subject recruitment is shown in Table 3 below. The assumptions made in projecting the number of telephone screening interviews necessary to achieve the aims are based on experience in recruitment for the Einstein Aging Study as well as in our pilot study experience described in section B.5.c.[1, 4, 5] Once telephone contact is achieved and the interview is complete, we assume that there will be a 20% loss due to lack of interest in the study and failure to meet general eligibility requirements and an additional 10% failure on the cognitive instrument (T-MIS). There is an additional 10% loss in the remaining sample due to failure to meet eligibility requirements. We will explore durability of effects up to 12 months follow-up. Due to study logistics and power considerations, durability will be examined as an exploratory sub-aim till month 57.

Table 3. Timetable and projected subject numbers at baseline and at post-intervention assessments.

Year:	1				2				3				4				5			
Quarters:	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Study set up																				
Screening	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Intervention, n		26	26	26	26	26	26	26	26	26	26	26	26	26	28	28	26			
Post-intervention tests, n		21	21	21	21	21	21	21	21	21	21	21	21	21	23	23	21			
6 month follow-up, n				15	15	15	15	15	15	15	15	15	15	15	15	15	15	15		
12 month follow-up, n					14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	
Data cleaning/analysis																				
Interim analysis (DSMB)								X (when 210 subjects complete intervention)												
Manuscript preparation																				

E.3. Sources for research material: Research material obtained from human subjects will be the results of clinical and neuropsychological testing obtained from study assessments and telephone interviews. The subject and their primary care physician will be informed of all clinical results that are relevant to patient care.

E.4. Potential risks: Answering health questionnaires and mental state examinations involve minimal psychological, social, or other risks. We do not expect any serious adverse events during these non-invasive tests and training programs of attention and executive function. The C-REM interventions involve mental but no physical effort by the participants. The health education control involves computer based health education. The fNIRS procedures utilize light in visible spectrum and do not pose any risk. Minimal discomfort may be experienced from local forehead pressure. Since there are no significant risks associated with the procedures, this study is justified because useful new scientific knowledge will be obtained.

E.5. Protection against risk: The research staff and investigators will be present during all testing. All questionnaire completion will be done at a slow enough pace so as not to tire individuals. If subjects express physical or mental tiredness or discomfort during any of the assessments or training procedures, the procedure will be terminated immediately. Drs. Verghese or Ambrose will be available onsite or by pager at all times to address any safety concerns or clinical issues during the interventions.

Confidentiality will be preserved by use of ID code numbers for identification. ID and name associations will be password protected in an encrypted master file to which only the PIs and statistician will have access. Randomization procedures were discussed in section C.8. Participant data, including computer data disks, will be kept in a locked room. Identifying information about a subject will not be used during the discussion or presentation of any research data. To ensure confidentiality and anonymity during the study, each subject will be assigned a confidential study number. Access to the subject study identification codes or other information will be restricted to the PIs, co-investigators, and study staff, and upon written request, to the Institutional Review Board or other regulatory agencies, or by written request of the subject, released to others. Paper records will be stored in locked file cabinets in the investigators' offices, and all computers used for data management and analysis will be password-protected and located in secure offices.

Dissemination of information: Results of physical examination, questionnaires, and routine clinical tests as requested will be provided to the subjects, who will be encouraged to share them with their personal physician. Results of experimental procedures will not be reported to the participants or their primary physicians as such findings do not bear direct effects on their health or medical care. Subjects will be advised that the results may be published in a manuscript, but their identities will not be divulged.

This clinical trial will be registered prior to study onset with **ClinicalTrials.gov**, which offers the public up-to-date information for locating federally and privately supported clinical trials for a wide range of diseases and conditions.

E.6. Benefits: Our previous experience, the non-invasive nature of most proposed procedures, the general acceptance by practicing physicians of the procedures to be used, and the close supervision and monitoring of the subjects all minimizes the potential risks. Although there are no benefits to the participant other than careful documentation of current cognitive, mobility and functional abilities, which may be useful in evaluating any future changes, there also are no risks to the participant.

E.7. Importance of the knowledge to be gained: The information that is expected to result from these studies should be of importance for understanding the biology, better diagnosing, and treating mobility disability in the aged. The results expected from this project should improve the treatment of mobility and provide information needed for rehabilitation of mobility disability.

E.8. DATA AND SAFETY MONITORING PLAN.

E.8.a. Introduction: All data collection in this clinical trial will be monitored to assure subject comfort, safety, and confidentiality. The clinical trial protocols, data collection instruments, subject recruitment letters, and consent forms will be reviewed and approved by the **Albert Einstein College of Medicine Committee for Clinical Investigations (AECOM-CCI)**. The AECOM-CCI will also approve the creation and structure of the Data and Safety Monitoring Plan.

E.8.b. Membership:
The Data and Safety Monitoring Board (DSMB) will be appointed in consultation with the responsible program official at NIA and in line with federal and IRB guidelines if the study is funded.

E.8.c. Safety Monitoring:
Prior to beginning data collections, Dr. Verghese and the DSMB Chair will reconfirm that our site has appropriate safety measures in place. The DSMB will meet with the entire research team to review the study protocols. Particular attention will be paid to outcome definition, study design, procedures for recording and reporting adverse events, and informed consent procedures and documentation.

At the initial meeting, the DSMB may recommend modifications or clarification of the protocol, and it will formulate its operating procedures (e.g., meeting schedule, reports due dates for the study statistician, unblinding policy, and what interim data may be released to the investigators). At the initial meeting the plans for interim monitoring for efficacy and futility will be presented to the DSMB as an aid for monitoring the trial (see E.8.h. below).

We will train competent staff to conduct the interventions and assessments, ensure they understand the nature of the interventions, and understand adverse event reporting requirements. Trained clinical assistants, who will monitor the subject for any adverse events, will perform all assessments. We do not expect any serious adverse events during these non-invasive interventions. The clinical assistant will stop the testing procedures if subjects feel stressed or get embarrassed by their performance, and relay the information immediately to Dr. Verghese, Dr. Ambrose, or Dr. Holtzer. At least one investigator will be present onsite during all testing and intervention sessions. In addition Drs. Verghese and Ambrose will be available by pager and cellular telephone at all times to address any safety concerns or clinical issues.

E.8.d. Data Monitoring:

Participant confidentiality will be maintained by assigning each subject a unique study ID upon entry to identify and link subject data. ID and name associations will be password protected in an encrypted master file to which only the data manager and PIs have access. Further protection for confidentiality is assured in that we will avoid telnet or FTP remote access. For added security, database copies will be kept in two separate physical locations in locked, fire-resistant containers. Also see E.5.

E.8.e. Interim meetings:

Both closed and open meetings of the DSMB will be held at six-month intervals. In addition the DSMB will meet more frequently as study progress dictates. The study statistician will prepare databases to be sent to the DSMB statistician for the closed session at least 7 days prior to the meeting. The DSMB statistician will bring reports for the closed session to that meeting. She will collect all copies of these reports at the conclusion of the closed session to ensure that study investigators remain blinded to the interim results.

The open session report will focus on patient accrual and demographics, data completeness, and other study performance measures. Only aggregate data will be presented during the open session (i.e., not segregated by treatment). The closed session report will divide study participants according to coded treatment assignment (C-REM or health education control), comparing participant demographics and baseline characteristics, rates and reasons for treatment discontinuation and loss to follow-up, and rates of serious adverse events. The interim efficacy analysis will be included only in the report for the closed session. In addition to reports prepared by the statistician, the Principal Investigators may prepare a report addressing concerns he anticipates the DSMB will have regarding the conduct of the study.

The interim data reports will include:

- Monthly and cumulative accrual
- Baseline characteristics, overall and by treatment group
- Summary of completeness and quality of data collection forms
- Status of enrolled patients, overall and by treatment group
- Assessments of whether study personnel have followed eligibility criteria and other protocol requirements
- Assessment of participant adherence, overall and by treatment group
- Sample size assumptions
- Outcome rates, overall and by treatment group along with monitoring boundaries for efficacy and futility (if the planned interim look is due)
- Listing of serious adverse events by participant ID number and a table of event-specific cumulative rates, overall and by treatment group
- A summary description of all serious adverse events

Only the closed session report will include the comparisons by treatment group.

E.8.f. Adverse Event Monitoring:

Process: DSMB chair, to be named, will perform data and safety monitoring on an ongoing basis. She/he will not be otherwise involved in assessments or interventions in this clinical trial. The PIs or research staff will see all volunteers. All abnormal findings from the clinical, mobility, and neuropsychological assessments done on Day 1 will be documented on a case report form and reviewed by the DSMB chair. Periodic audits from the AECOM-CCI ensure compliance with confidentiality guidelines and adverse events monitoring.

Reporting: All adverse events will be compiled and reported in summary form on an annual basis to the AECOM-CCI, and at the conclusion of the study. Unanticipated (non-serious) adverse events will be reported to the AECOM-CCI within 30 days via submission of an Adverse Event Report. Serious adverse events will be reported to the AECOM-CCI within 48 hours by phone, email or fax. A completed Adverse Event Report will be submitted within 10 days of initial notification. All deaths will be reported to the AECOM-CCI within 48 hours.

E.8.g. Recruitment Monitoring:

Process: The DSMB chair will assess the recruitment and retention of study subjects on an ongoing basis. The recruitment goal for this protocol is 420 subjects.

Reporting: Summary statistics regarding recruitment and retention of study subjects will be reported to the AECOM-CCI on an annual basis, and at the conclusion of the study.

E.8.h. Early Study Termination:

Process: Due to the non-invasive nature of the protocol, it is not expected that early termination will be required due to adverse events. However, constant monitoring of the participants by members of the DSMB, Dr. Verghese, other investigators, and research staff will be maintained to ensure that adverse events are not occurring. Early study termination will occur in the event of any unanticipated serious adverse event determined to be possibly, probably or definitely related to study procedures, failure to recruit at least 50% of the projected number of subjects within 4 months, or failure to retain at least 75% of study subjects to the conclusion of the protocol.

Early stopping rules: An interim look for monitoring both efficacy and futility is proposed after approximately half the total numbers of subjects (n=210) are screened and finish post intervention assessments.

First, based on O'Brien-Fleming spending function,[6] if the intervention group is significantly better than the control group at an alpha level of 0.003, the trial will stop early and conclude that the intervention group is significantly better. Since the O'Brien-Fleming stopping rule requires extreme evidence of efficacy at the midpoint of the trial, it does not inflate much the overall type I error rate.[6] Therefore, with n=420 subjects total, our study still have more than 80% to detect a minimum detectable difference of 4 cm/s in velocity at an overall type I error rate of 5%. Second, we will compute the conditional power to determine if early stopping for futility is necessary.[2] The conditional power is defined as the probability of eventually rejecting the null hypothesis of no intervention effect given the current data and the data yet to be collected assuming the alternative hypothesis is true, specifically, a mean difference of 4 cm/s in gait velocity change (minimal detectable difference) between the intervention group and the control group. If the conditional power is below 10%, this trial will stop early for futility because there is little evidence of a beneficial intervention effect.[2]

Interim data reports:
The study statistician will prepare data reports and send them directly to the DSMB. The DSMB statistician will conduct the interim analyses. The interim analyses will be performed blinded to the study investigators. Based on the results from the interim analyses, the DSMB will recommend either early termination or continuation of the trial.

E.8.i. Reporting:
At the conclusion of each DSMB meeting, the Board will provide a verbal report to the PIs indicating areas of concern regarding performance and safety. The Board will take care not to convey any information that could lead to unblinding of the investigator. If the DSMB recommends a protocol modification, it must be approved by the NIA representative and the AECOM-CCI. If early termination is required, the DSMB Chair will report the decision to the AECOM-CCI within 48 hours of this determination, and submit a narrative description of the reasons for early termination within 10 days. The investigators will maintain a file of all adverse events that will be used to submit summary reports to the AECOM-CCI on an annual basis.

Communication from study investigators: The PIs will monitor performance and safety issues on a day-to-day basis. If they become aware of issues that threaten the integrity of the trial or participant safety, they will alert the NIA representative to the DSMB who will consult with the DSMB Chair as to whether a special meeting or conference call of the DSMB should be held.

References (Section E)

1. Verghese J, LeValley A, Hall CB, Katz MJ, Ambrose AF, Lipton RB. Epidemiology of gait disorders in community-residing older adults. Journal of the American Geriatrics Society. 2006;54(2):255-61.
2. Whitehead J. The design and analysis of sequential clinical trials. Second revised ed. Chichester: Wiley; 1997.
3. Altman DG. Practical Statistics for Medical Research. 2 ed: Chapman & Hall/CRC; 2006.
4. Verghese J, Mahoney J, Ambrose AF, Wang C, Holtzer R. Effect of cognitive remediation on gait in

sedentary seniors. J Gerontol A Biol Sci Med Sci. 2010;65(12):1338-43. PubMed PMID: 20643703.
5. Verghese J, Wang C, Lipton RB, Holtzer R, Xue X. Quantitative gait dysfunction and risk of cognitive decline and dementia. Journal of Neurology, Neurosurgery & Psychiatry. 2007;78(9):929-35.
6. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics. 1979;35(3):549-56. PubMed PMID: 497341.

Amendment Form (Version 25.0)

1.0 General Information

The version you are using is: August 2017

1.2 Study Information

Study Title:

Cognitive intervention to improve simple and complex walking

Principal Investigator:

Joe Verghese

Submission Reference #:

034955

1.3 Please click Save and Continue.

2.0 Amendment Information

2.1 Select the modifications being made below:

- [ ] Change in PI
- [ ] Change in key personnel and study contacts
- [x] Changes to IRB Application
- [ ] Changes to or additon of new informed consent documents
- [x] Changes to or addition of other study documents (protocol, investigator brochures, questionnaires, protocol, investigators brochure, recruitment materials, instruments, case report forms, study handouts or other miscellaneous documents)
- [ ] Adding external funding (grant application must be uploaded and the IRB application must be updated)

2.2 Provide a brief summary of the changes:

Added a new recruitment strategy to the application including to include recruitment of participants who have participated in other studies, but are not currently involved in another research project.

If this is a sponsored amendment, and the sponsor has provided a document with a summary of changes, provide a summary of the **key changes in the space above (i.e., administrative changes to the protocol, corrected protocol regarding test X and updated the consent document accordingly, etc.). The IRB cannot accept "see attached". The IRB also cannot accept just a copy of the list of changes instead of a summary.*
***For the addition of key personnel, please also indicate whether the individual(s) added will be conducting the informed consent process.*

2.3 Provide a justification for the amendment.

We will be recruiting participants who have completed the study protocol #2016-7153.

2.4 For an amendment generated by a study sponsor, provide the amendment version information, e.g. "Amendment #2 dated 11August2011".

This information will be used in the approval letter for the amendment.

2.5 Did the amendment originate from a drug company, a national study group, etc.? If "Yes," a copy of the correspondence must be attached to this amendment application.

○ Yes ◉ No

3.0 IRB Application Revision

Instructions:

1. Click on the grey bar labeled "Click here to attach the application." A new window will open up.
2. Click on "Add Revision" on the right and then click on "OK" on the popup window.
3. Make the revision to the relevant section of the application. Click "Save and Continue to Next Section" after every application section until you get to the very end of the application. If you are given the option to convert your application to a newer version, you must do so before completing your submission.
    a. If you convert to the newest version of the application all but the first three sections of the application will disappear. Click on "Save and Continue to Next Section" after each section to recreate the application. You may need to answer new questions.
4. Once the application has been completely revised, you will then be sent back to the "Attach Study Application" page and the study application listed will have a new version number (i.e., version 1.2). Click on "Save Attachment".

Edit/ View	Version	Title
	1.15	Human Research Application (Version 1.15) - Attached

4.0 Study Document Revision or Addition

Study documents include the protocol, grant application, investigator brochures, questionnaires, recruitment materials, instruments, case report forms, study handouts or other miscellaneous documents.

To revise approved study documents, create a REVISED copy of the document in iRIS in order for the system to properly VOID the previously approved study document. Do NOT attach new documents unless they are for types of study documents that have never been previously approved.
GUIDANCE ON REVISING DOCUMENTS IS AVAILABLE IN THE AMENDMENT HANDBOOK IN THE HELP MENU.

Version	Title	Category	Expiration Date	Document Outcome	Checked Out	View Document
1.6	Protocol	Protocol		Approved		974.97 KB

Only the following types of files may be uploaded into iRIS:.doc, .docx, .rtf, .txt, .pdf. The use of other file formats may delay IRB review and approval of your submission.

Protocol Requirements and Recommendations

1. The IRB requires that revised protocols have a version number and/or version date on the protocol document.
2. The IRB strongly recommends that revised protocol have page numbers.

3. The IRB must have a complete and up-to-date version of the protocol on record at all times. You may not upload additions to the protocol instead of a complete revised document. You may, however, upload only a tracked changes version of the protocol.

Other Study Document Recommendations

1. The IRB strongly recommends that if you have more than one similar study document (e.g. ads for different populations), distinguish between the documents using footers or other clear text in the document. Do not use the header function, since iRIS stamps documents in the upper right-hand corner.

Document Revision Requirements

1. If both the old version and the new version are Word documents, you may upload only a clean version of the new document.
2. If either the old version or the new version is a PDF file, you must also upload a tracked changed version or a document with the list of changes.

☑ I understand that incorrectly uploading revised study documents will result in a delay of IRB review and approval.

5.0 Signature Instructions
READ THESE INSTRUCTIONS BEFORE PROCEEDING

5.1 To go to the signature routing pages:
Coordinators: Click "Save and Continue" and then "notify PI to signoff" (on the next page) to continue to the signature routing pages.
PIs: Click "Save and Continue" and then "Signoff and Submit" to continue to the signature routing pages

5.2 Signature Requirements
Only the signature of the PI is required on the first signature routing page. You may deselect other study staff from the routing list.
If you are changing PI or making changes that prompt signatory requirements (click here for details), departmental or other signatories must be added on the second routing page.

5.3 ***If you have any additional comments that you would like to convey to the IRB staff, please enter them here:***

Amendment Form (Version 18.1)

1.0 General Information

The version you are using is: 12 February 2015 version C

1.2 For all studies migrated from PATS or West Campus/paper:

Amendments may NOT be submitted before a Migration Completion Form has been approved by the IRB. If your Migration Completion Form has not been approved, this amendment will be rejected by the IRB.

Questions? Please contact **iris-support@einstein.yu.edu**.

1.3 Study Information

Study Title:

Cognitive intervention to improve simple and complex walking

Principal Investigator:

Joe Verghese

Submission Reference #:

032221

1.4 Please click Save and Continue.

2.0 Amendment Information

2.1 Select the modifications being made below:

- ☐ Change in PI
- ☐ Change in key personnel and study contacts
- ☑ Changes to IRB Application
- ☐ Changes to or additon of new informed consent documents
- ☑ Changes to or addition of other study documents (protocol, investigator brochures, questionnaires, protocol, investigators brochure, recruitment materials, instruments, case report forms, study handouts or other miscellaneous documents)

2.2 Provide a brief summary of the changes:

We will be identifying potential participants for recruitment by accessing medical/clinical records without consent.

If this is a sponsored amendment, and the sponsor has provided a document with a summary of changes, provide a summary of the **key changes in the space above (i.e., administrative changes to the protocol, corrected protocol regarding test X and updated the consent document accordingly, etc.). The IRB cannot accept "see attached". The IRB also cannot accept just a copy of the list of changes instead of a summary.*
***For the addition of key personnel, please also indicate whether the individual(s) added will be conducting the informed consent process.*

2.3 Provide a justification for the amendment.

We are planning to get a list of patients from Clinical Looking Glass who are patients at the Montefiore Geriatrics Ambulatory Practice to mail recruitment letters to and follow-up with a telephone screening interview using the same recruitment letter and screening procedures that are already approved.

2.4 For an amendment generated by a study sponsor, provide the amendment version information, e.g. "Amendment #2 dated 11August2011".

This information will be used in the approval letter for the amendment.

2.5 Did the amendment originate from a drug company, a national study group, etc.? If "Yes," a copy of the correspondence must be attached to this amendment application.

○ Yes ◉ No

3.0 IRB Application Revision

Instructions:

1. Click on the grey bar labeled "Click here to attach the application." A new window will open up.
2. Click on "Add Revision" on the right and then click on "OK" on the popup window.
3. Make the revision to the relevant section of the application. Click "Save and Continue to Next Section" after every application section until you get to the very end of the application. If you are given the option to convert your application to a newer version, you must do so before completing your submission.
    a. If you convert to the newest version of the application all but the first three sections of the application will disappear. Click on "Save and Continue to Next Section" after each section to recreate the application. You may need to answer new questions.
4. Once the application has been completely revised, you will then be sent back to the "Attach Study Application" page and the study application listed will have a new version number (i.e., version 1.2). Click on "Save Attachment".

Edit/ View	Version	Title
	1.14	Human Research Application (Version 1.14) - Attached

4.0 Study Document Revision or Addition

Study documents include the protocol, investigator brochures, questionnaires, protocol, investigators brochure, recruitment materials, instruments, case report forms, study handouts or other miscellaneous documents.

To revise approved study documents, create a REVISED copy of the document in iRIS in order for the system to properly VOID the previously approved study document. Do NOT attach new documents unless they are for types of study documents that have never been previously approved.
GUIDANCE ON REVISING DOCUMENTS IS AVAILABLE IN THE AMENDMENT HANDBOOK IN THE HELP MENU.

Version	Title	Category	Expiration Date	Document Outcome	Checked Out	View Document
1.5	Protocol 6.9.2016	Protocol		Approved		 974.40

				KB

Only the following types of files may be uploaded into iRIS:.doc, .docx, .rtf, .txt, .pdf. The use of other file formats may delay IRB review and approval of your submission.

Protocol Requirements and Recommendations

1. The IRB requires that revised protocols have a version number and/or version date on the protocol document.
2. The IRB strongly recommends that revised protocol have page numbers.
3. The IRB must have a complete and up-to-date version of the protocol on record at all times. You may not upload additions to the protocol instead of a complete revised document. You may, however, upload only a tracked changes version of the protocol.

Other Study Document Recommendations

1. The IRB strongly recommends that if you have more than one similar study document (e.g. ads for different populations), distinguish between the documents using footers or other clear text in the document. Do not use the header function, since iRIS stamps documents in the upper right-hand corner.

Document Revision Requirements

1. If both the old version and the new version are Word documents, you may upload only a clean version of the new document.
2. If either the old version or the new version is a PDF file, you must also upload a tracked changed version or a document with the list of changes.

☑ I understand that incorrectly uploading revised study documents will result in a delay of IRB review and approval.

5.0 Signature Instructions
READ THESE INSTRUCTIONS BEFORE PROCEEDING

5.1 To go to the signature routing pages:
Coordinators: Click "Save and Continue" and then "notify PI to signoff" (on the next page) to continue to the signature routing pages.
PIs: Click "Save and Continue" and then "Signoff and Submit" to continue to the signature routing pages

5.2 Signature Requirements
Only the signature of the PI is required on the first signature routing page. You may deselect other study staff from the routing list.
If you are changing PI or making changes that prompt signatory requirements (click here for details), departmental or other signatories must be added on the second routing page.

5.3 ***If you have any additional comments that you would like to convey to the IRB staff, please enter them here:***

Amendment Form (Version 9.1)

1.0 General Information

The version you are using is: 12 February 2015 version C

1.2 For all studies migrated from PATS or West Campus/paper:

Amendments may NOT be submitted before a Migration Completion Form has been approved by the IRB. If your Migration Completion Form has not been approved, this amendment will be rejected by the IRB.

Questions? Please contact **iris-support@einstein.yu.edu**.

1.3 Study Information

Study Title:

Cognitive intervention to improve simple and complex walking

Principal Investigator:

Joe Verghese

Submission Reference #:

019847

1.4 Please click Save and Continue.

2.0 Amendment Information

2.1 Select the modifications being made below:

- [ ] Change in PI
- [x] Change in key personnel and study contacts
- [x] Changes to IRB Application
- [x] Changes to or additon of new informed consent documents
- [x] Changes to or addition of other study documents (protocol, investigator brochures, questionnaires, protocol, investigators brochure, recruitment materials, instruments, case report forms, study handouts or other miscellaneous documents)

2.2 Provide a brief summary of the changes:

The following bullet was added to the consent form: "clinicians and staff at Montefiore who review your records for your care"

Recruitment strategy in the protocol now includes posting flyers and posters at local clinics, community centers and shops. A new document to provide to patients who express interest in the CREM study is included.

Crismeldy Veloz was added as a new research associate who will be involved in recruiting and consenting new participants.

If this is a sponsored amendment, and the sponsor has provided a document with a summary of changes, provide a summary of the **key changes in the space above (i.e., administrative changes to the protocol, corrected protocol regarding test X and updated the consent document accordingly, etc.). The*

IRB cannot accept "see attached". The IRB also cannot accept just a copy of the list of changes instead of a summary.
***For the addition of key personnel, please also indicate whether the individual(s) added will be conducting the informed consent process.*

2.3 Provide a justification for the amendment.

The language was added to the consent in compliance with the IRB. The recruitment strategy in the protocol was revised to include advertising in the community using flyers that were previously approved, and a new document to provide to potential participants was added. The study staff added is a new research associate.

2.4 For an amendment generated by a study sponsor, provide the amendment version information, e.g. "Amendment #2 dated 11August2011".

Amendement #8 9June2016

This information will be used in the approval letter for the amendment.

2.5 Did the amendment originate from a drug company, a national study group, etc.? If "Yes," a copy of the correspondence must be attached to this amendment application.

○ Yes ◉ No

3.0 Change Key Personnel

3.1 Update study personnel using the form below:

The current list of Study Contact(s) for this study is listed below :
(if the list is blank, try clicking on "Refresh Constant Fields" in the upper right corner)

Note that only the PI and the Study Contact will receive iRIS communications and have full access to the study.
Please make sure that there are active personnel listed as Study Contact(s).

If applicable, please add the new Principal Investigator for the Study:

If applicable, please select the new Research Staff personnel:

A) Additional Investigators

B) Research Staff

☐ Veloz, Crismeldy
Research Associate

If applicable, please add any new Study Contact:

Ayers, Emmeline

If applicable, please add a new Faculty Advisor:

If applicable, please select any existing Personnel you wish to remove:

3.2 If you are submitting a change in PI note the following:

- **The PI must have a current conflict of interest (COI) disclosure on file (see the Amendment Handbook in the Help Menu for details). Note: The submission will be denied if the PI does not have a current COI disclosure on file.**
- **The PI must have a current CITI course on file (see the Amendment Handbook in the Help Menu for details)**
- **Upload a copy of the new PI's CV/resume in the Study Documents section of the Amendment Form**
- **If necessary, upload a revised consent document with the new PI's name**
- **Route the amendment form for approval by the new PI's department chair**

See the Amendment Form Handbook in the help menu (orange and white question mark in the upper right corner) for further details on submitting these items.

3.3 If you are submitting a change in Additional Investigators note the following:

- **Have a current conflict of interest (COI) disclosure on file (see the Amendment Handbook in the Help Menu for details). Note: The submission will be denied if any Investigators do not have current COI disclosures on file.**
- **The Additional Investigators must have a current CITI course on file (see the Amendment Handbook in the Help Menu for details)**

See the Amendment Form Handbook in the help menu (orange and white question mark in the upper right corner) for further details on submitting these items.

3.4 If you are submitting a change in Research Staff note the following:

- **The Research Staff must have a current CITI course on file (see the Amendment Handbook in the Help Menu for details)**

4.0 IRB Application Revision

Instructions:

1. Click on the grey bar labeled "Click here to attach the application." A new window will open up.
2. Click on "Add Revision" on the right and then click on "OK" on the popup window.
3. Make the revision to the relevant section of the application. Click "Save and Continue to Next Section" after every application section until you get to the very end of the application. If you are given the option to convert your application to a newer version, you must do so before completing your submission.
    a. If you convert to the newest version of the application all but the first three sections of the application will disappear. Click on "Save and Continue to Next Section" after each section to recreate the application. You may need to answer new questions.
4. Once the application has been completely revised, you will then be sent back to the "Attach Study Application" page and the study application listed will have a new version number (i.e., version 1.2). Click on "Save Attachment".

Edit/ View	Version	Title
	1.5	Human Research Application (Version 1.5) - Attached

5.0 Consent Document Revision or Addition

To revise approved consent documents, create a REVISED copy of the document in iRIS in order for the system to properly VOID the previously approved consent document. Do NOT attach new documents unless they are for types of informed consent documents that have never been previously approved. **GUIDANCE ON REVISING DOCUMENTS IS AVAILABLE IN THE AMENDMENT HANDBOOK IN THE HELP MENU.**

Version	Title	Category	Language	Expiration Date	Consent Outcome	Checked Out	View Document
1.10	Informed Consent Authorization document v 1.5	Consent	English	01/20/2017	Void		

Only the following types of files may be uploaded into iRIS:.doc, .docx, .rtf, .txt, .pdf. The use of other file formats may delay IRB review and approval of your submission.

Consent Document Requirements and Recommendations

1. Consent documents must have a 1" margin at the top of all pages.
2. The IRB strongly recommends that all revised consent documents be given page numbers if they do not already have them.
3. The IRB strongly recommends that if you have more than one similar consent document (e.g. for different populations), distinguish between the documents using footers or other clear text in the document. Do not use the header function, since iRIS stamps documents in the upper right-hand corner.

Document Revision Requirements

1. If both the old version and the new version are Word documents, you may upload only a clean version of the new document.
2. If either the old version or the new version is a PDF file, you must also upload a tracked changed version or a document with the list of changes.

☑ I understand that incorrectly uploading revised consent documents will result in a delay of IRB review and approval.

5.2 Does the amendment include submission of translated consent documents?

○ Yes ◉ No

If "Yes," were how were they translated?

○ translation service (An 'Affidavit of Accuracy' is required.)
○ "in house" (see requirements below)

Translation Service
Upload the Affidavit of Accuracy below:

Version	Title	Category	Expiration Date	Document Outcome	Checked Out	View Document
No Document(s) have been attached to this form.						

In house requirements:
If "**in house**," who translated the consent documents?

- Specify in the table below both the individual who translated the English document into the appropriate language and the second individual who translated the foreign language document back into English.
- Specify in the table below the qualifications of the individuals who translated and back-translated the consent documents. State "see attached" if you have documentation of their credentials (and attach them as study documents below).

Translation Direction	Translator's Name	Translator's Qualification

To foreign language:		
From foreign language:		

For "**in house**" translations, attach the following required documentation as specified below:

- The translated consent (as a consent document above)
- The back-translated consent (as a study document below)

The two English documents will be compared side by side for accuracy and completeness.

Version	Title	Category	Expiration Date	Document Outcome	Checked Out	View Document
No Document(s) have been attached to this form.						

6.0 Study Document Revision or Addition

Study documents include the protocol, investigator brochures, questionnaires, protocol, investigators brochure, recruitment materials, instruments, case report forms, study handouts or other miscellaneous documents.

To revise approved study documents, create a REVISED copy of the document in iRIS in order for the system to properly VOID the previously approved study document. Do NOT attach new documents unless they are for types of study documents that have never been previously approved.
GUIDANCE ON REVISING DOCUMENTS IS AVAILABLE IN THE AMENDMENT HANDBOOK IN THE HELP MENU.

Version	Title	Category	Expiration Date	Document Outcome	Checked Out	View Document
1.4	Protocol 6.9.2016	Protocol		Approved		1.07 MB
1.0	CREM cards	Recruitment Material		Acknowledged		194.90 KB

Only the following types of files may be uploaded into iRIS:.doc, .docx, .rtf, .txt, .pdf. The use of other file formats may delay IRB review and approval of your submission.

Protocol Requirements and Recommendations

1. The IRB requires that revised protocols have a version number and/or version date on the protocol document.
2. The IRB strongly recommends that revised protocol have page numbers.
3. The IRB must have a complete and up-to-date version of the protocol on record at all times. You may not upload additions to the protocol instead of a complete revised document. You may, however, upload only a tracked changes version of the protocol.

Other Study Document Recommendations

1. The IRB strongly recommends that if you have more than one similar study document (e.g. ads for different populations), distinguish between the documents using footers or other clear text in the document. Do not use the header function, since iRIS stamps documents in the upper right-hand corner.

Document Revision Requirements

1. If both the old version and the new version are Word documents, you may upload only a clean version of the new document.

2. If either the old version or the new version is a PDF file, you must also upload a tracked changed version or a document with the list of changes.

☑ I understand that incorrectly uploading revised study documents will result in a delay of IRB review and approval.

7.0 Signature Instructions
READ THESE INSTRUCTIONS BEFORE PROCEEDING

7.1 To go to the signature routing pages:
Coordinators: Click "Save and Continue" and then "notify PI to signoff" (on the next page) to continue to the signature routing pages.
PIs: Click "Save and Continue" and then "Signoff and Submit" to continue to the signature routing pages

7.2 Signature Requirements
Only the signature of the PI is required on the first signature routing page. You may deselect other study staff from the routing list.
If you are changing PI or making changes that prompt signatory requirements (click here for details), departmental or other signatories must be added on the second routing page.

7.3 If you have any additional comments that you would like to convey to the IRB staff, please enter them here:

Amendment Form (Version 6.0)

1.0 General Information

The version you are using is: 12 February 2015 version C

1.2 For all studies migrated from PATS or West Campus/paper:

Amendments may NOT be submitted before a Migration Completion Form has been approved by the IRB. If your Migration Completion Form has not been approved, this amendment will be rejected by the IRB.

Questions? Please contact **iris-support@einstein.yu.edu**.

1.3 Study Information

Study Title:

Cognitive intervention to improve simple and complex walking

Principal Investigator:

Joe Verghese

Submission Reference #:

016608

1.4 Please click Save and Continue.

2.0 Amendment Information

2.1 Select the modifications being made below:

- ☐ Change in PI
- ☐ Change in key personnel and study contacts
- ☐ Changes to IRB Application
- ☑ Changes to or additon of new informed consent documents
- ☑ Changes to or addition of other study documents (protocol, investigator brochures, questionnaires, protocol, investigators brochure, recruitment materials, instruments, case report forms, study handouts or other miscellaneous documents)

2.2 Provide a brief summary of the changes:

The consent form has been revised to clarify of the number of days that will be required from participants during training sessions (See the 'What will happen if I participate in the study?' section in the consent). Additional revisions to the consent form and protocol clarify the number of days/amount of time the baseline and post-intervention assessment visits will take. Specifically, section C.12 in the protocol and the 'What will happen if I participate in the study?' section in the consent were revised to say that baseline and all post-intervention study assessments will be limited to 90 minutes per visit.

If this is a sponsored amendment, and the sponsor has provided a document with a summary of changes, provide a summary of the **key changes in the space above (i.e., administrative changes to the protocol, corrected protocol regarding test X and updated the consent document accordingly, etc.). The IRB cannot accept "see attached". The IRB also cannot accept just a copy of the list of changes instead of a summary.*

***For the addition of key personnel, please also indicate whether the individual(s) added will be conducting the informed consent process.*

2.3 Provide a justification for the amendment.

The revisions to the consent form and protocol have been made to satisfy requirements of the DSMB in order to start recruitment.

2.4 For an amendment generated by a study sponsor, provide the amendment version information, e.g. "Amendment #2 dated 11August2011".

Amendment #6 17Feb2016

This information will be used in the approval letter for the amendment.

2.5 Did the amendment originate from a drug company, a national study group, etc.? If "Yes," a copy of the correspondence must be attached to this amendment application.

○ Yes ◉ No

3.0 Consent Document Revision or Addition

To revise approved consent documents, create a REVISED copy of the document in iRIS in order for the system to properly VOID the previously approved consent document. Do NOT attach new documents unless they are for types of informed consent documents that have never been previously approved. **GUIDANCE ON REVISING DOCUMENTS IS AVAILABLE IN THE AMENDMENT HANDBOOK IN THE HELP MENU.**

Version	Title	Category	Language	Expiration Date	Consent Outcome	Checked Out	View Document
1.8	Informed Consent Authorization document v 1.4	Consent	English	01/20/2017	Void		

Only the following types of files may be uploaded into iRIS:.doc, .docx, .rtf, .txt, .pdf. The use of other file formats may delay IRB review and approval of your submission.

Consent Document Requirements and Recommendations

1. Consent documents must have a 1" margin at the top of all pages.
2. The IRB strongly recommends that all revised consent documents be given page numbers if they do not already have them.
3. The IRB strongly recommends that if you have more than one similar consent document (e.g. for different populations), distinguish between the documents using footers or other clear text in the document. Do not use the header function, since iRIS stamps documents in the upper right-hand corner.

Document Revision Requirements

1. If both the old version and the new version are Word documents, you may upload only a clean version of the new document.
2. If either the old version or the new version is a PDF file, you must also upload a tracked changed version or a document with the list of changes.

☑ I understand that incorrectly uploading revised consent documents will result in a delay of IRB review and approval.

3.2 Does the amendment include submission of translated consent documents?

○ Yes ◉ No

If "Yes," were how were they translated?

○ translation service (An 'Affidavit of Accuracy' is required.)
○ "in house" (see requirements below)

Translation Service
Upload the Affidavit of Accuracy below:

Version	Title	Category	Expiration Date	Document Outcome	Checked Out	View Document
No Document(s) have been attached to this form.						

In house requirements:
If "**in house**," who translated the consent documents?

- Specify in the table below both the individual who translated the English document into the appropriate language and the second individual who translated the foreign language document back into English.
- Specify in the table below the qualifications of the individuals who translated and back-translated the consent documents. State "see attached" if you have documentation of their credentials (and attach them as study documents below).

Translation Direction	Translator's Name	Translator's Qualification
To foreign language:		
From foreign language:		

For "**in house**" translations, attach the following required documentation as specified below:

- The translated consent (as a consent document above)
- The back-translated consent (as a study document below)

The two English documents will be compared side by side for accuracy and completeness.

Version	Title	Category	Expiration Date	Document Outcome	Checked Out	View Document
No Document(s) have been attached to this form.						

4.0 Study Document Revision or Addition

Study documents include the protocol, investigator brochures, questionnaires, protocol, investigators brochure, recruitment materials, instruments, case report forms, study handouts or other miscellaneous documents.

To revise approved study documents, create a REVISED copy of the document in iRIS in order for the system to properly VOID the previously approved study document. Do NOT attach new documents unless they are for types of study documents that have never been previously approved.
GUIDANCE ON REVISING DOCUMENTS IS AVAILABLE IN THE AMENDMENT HANDBOOK IN THE HELP MENU.

Version	Title	Category	Expiration Date	Document Outcome	Checked Out	View Document
1.3	Protocol 2.17.2016	Protocol		Approved		1.06 MB

Only the following types of files may be uploaded into iRIS:.doc, .docx, .rtf, .txt, .pdf. The use of other file formats may delay IRB review and approval of your submission.

Protocol Requirements and Recommendations

1. The IRB requires that revised protocols have a version number and/or version date on the protocol document.
2. The IRB strongly recommends that revised protocol have page numbers.
3. The IRB must have a complete and up-to-date version of the protocol on record at all times. You may not upload additions to the protocol instead of a complete revised document. You may, however, upload only a tracked changes version of the protocol.

Other Study Document Recommendations

1. The IRB strongly recommends that if you have more than one similar study document (e.g. ads for different populations), distinguish between the documents using footers or other clear text in the document. Do not use the header function, since iRIS stamps documents in the upper right-hand corner.

Document Revision Requirements

1. If both the old version and the new version are Word documents, you may upload only a clean version of the new document.
2. If either the old version or the new version is a PDF file, you must also upload a tracked changed version or a document with the list of changes.

☑ I understand that incorrectly uploading revised study documents will result in a delay of IRB review and approval.

5.0 Signature Instructions
READ THESE INSTRUCTIONS BEFORE PROCEEDING

5.1 To go to the signature routing pages:
Coordinators: Click "Save and Continue" and then "notify PI to signoff" (on the next page) to continue to the signature routing pages.
PIs: Click "Save and Continue" and then "Signoff and Submit" to continue to the signature routing pages

5.2 Signature Requirements
Only the signature of the PI is required on the first signature routing page. You may deselect other study staff from the routing list.
If you are changing PI or making changes that prompt signatory requirements (click here for details), departmental or other signatories must be added on the second routing page.

5.3 If you have any additional comments that you would like to convey to the IRB staff, please enter them here:

The revisions included in this amendment were very minor but were required by the DSMB prior to recruitment. We need to respond to the DSMB as soon as possible and provide the IRB approved revised consent form and protocol to get approval to start the study. Thanks!

Amendment Form (Version 5.1)

1.0 General Information

The version you are using is: 12 February 2015 version C

1.2 For all studies migrated from PATS or West Campus/paper:

Amendments may NOT be submitted before a Migration Completion Form has been approved by the IRB. If your Migration Completion Form has not been approved, this amendment will be rejected by the IRB.

Questions? Please contact **iris-support@einstein.yu.edu**.

1.3 Study Information

Study Title:

Cognitive intervention to improve simple and complex walking

Principal Investigator:

Joe Verghese

Submission Reference #:

016197

1.4 Please click Save and Continue.

2.0 Amendment Information

2.1 Select the modifications being made below:

- ☐ Change in PI
- ☐ Change in key personnel and study contacts
- ☐ Changes to IRB Application
- ☑ Changes to or additon of new informed consent documents
- ☑ Changes to or addition of other study documents (protocol, investigator brochures, questionnaires, protocol, investigators brochure, recruitment materials, instruments, case report forms, study handouts or other miscellaneous documents)

2.2 Provide a brief summary of the changes:

We have revised the consent form to comply with the DSMB. Changes were minimal and help clarify the amount of time needed for participation. They include:
1. Clarification of the number of days/time participants will be asked to participate in the intervention program.
2. The number of visits that participants will be paid the $135 for.
3. The length of the post intervention assessment visits.

If this is a sponsored amendment, and the sponsor has provided a document with a summary of changes, provide a summary of the **key changes in the space above (i.e., administrative changes to the protocol, corrected protocol regarding test X and updated the consent document accordingly, etc.). The IRB cannot accept "see attached". The IRB also cannot accept just a copy of the list of changes instead of a summary.*

***For the addition of key personnel, please also indicate whether the individual(s) added will be conducting the informed consent process.*

2.3 Provide a justification for the amendment.

These changes were recommended by the DSMB prior to initiating recruitment.

2.4 For an amendment generated by a study sponsor, provide the amendment version information, e.g. "Amendment #2 dated 11August2011".

Amendment #5 3Feb2016

This information will be used in the approval letter for the amendment.

2.5 Did the amendment originate from a drug company, a national study group, etc.? If "Yes," a copy of the correspondence must be attached to this amendment application.

○ Yes ◉ No

3.0 Consent Document Revision or Addition

To revise approved consent documents, create a REVISED copy of the document in iRIS in order for the system to properly VOID the previously approved consent document. Do NOT attach new documents unless they are for types of informed consent documents that have never been previously approved. **GUIDANCE ON REVISING DOCUMENTS IS AVAILABLE IN THE AMENDMENT HANDBOOK IN THE HELP MENU.**

Version	Title	Category	Language	Expiration Date	Consent Outcome	Checked Out	View Document
1.7	Informed Consent Authorization document v 1.4	Consent	English	01/20/2017	Void		

Only the following types of files may be uploaded into iRIS:.doc, .docx, .rtf, .txt, .pdf. The use of other file formats may delay IRB review and approval of your submission.

Consent Document Requirements and Recommendations

1. Consent documents must have a 1" margin at the top of all pages.
2. The IRB strongly recommends that all revised consent documents be given page numbers if they do not already have them.
3. The IRB strongly recommends that if you have more than one similar consent document (e.g. for different populations), distinguish between the documents using footers or other clear text in the document. Do not use the header function, since iRIS stamps documents in the upper right-hand corner.

Document Revision Requirements

1. If both the old version and the new version are Word documents, you may upload only a clean version of the new document.
2. If either the old version or the new version is a PDF file, you must also upload a tracked changed version or a document with the list of changes.

☑ I understand that incorrectly uploading revised consent documents will result in a delay of IRB review and approval.

3.2 Does the amendment include submission of translated consent documents?

○ Yes ◉ No

If "Yes," were how were they translated?

○ translation service (An 'Affidavit of Accuracy' is required.)
○ "in house" (see requirements below)

Translation Service
Upload the Affidavit of Accuracy below:

Version	Title	Category	Expiration Date	Document Outcome	Checked Out	View Document
No Document(s) have been attached to this form.						

In house requirements:
If "**in house**," who translated the consent documents?

- Specify in the table below both the individual who translated the English document into the appropriate language and the second individual who translated the foreign language document back into English.
- Specify in the table below the qualifications of the individuals who translated and back-translated the consent documents. State "see attached" if you have documentation of their credentials (and attach them as study documents below).

Translation Direction	Translator's Name	Translator's Qualification
To foreign language:		
From foreign language:		

For "**in house**" translations, attach the following required documentation as specified below:

- The translated consent (as a consent document above)
- The back-translated consent (as a study document below)

The two English documents will be compared side by side for accuracy and completeness.

Version	Title	Category	Expiration Date	Document Outcome	Checked Out	View Document
No Document(s) have been attached to this form.						

4.0 Study Document Revision or Addition

Study documents include the protocol, investigator brochures, questionnaires, protocol, investigators brochure, recruitment materials, instruments, case report forms, study handouts or other miscellaneous documents.

To revise approved study documents, create a REVISED copy of the document in iRIS in order for the system to properly VOID the previously approved study document. Do NOT attach new documents unless they are for types of study documents that have never been previously approved.
GUIDANCE ON REVISING DOCUMENTS IS AVAILABLE IN THE AMENDMENT HANDBOOK IN THE HELP MENU.

Version	Title	Category	Expiration Date	Document Outcome	Checked Out	View Document
1.2	Protocol 2.3.2016	Protocol		Approved		1.07 MB

Only the following types of files may be uploaded into iRIS:.doc, .docx, .rtf, .txt, .pdf. The use of other file formats may delay IRB review and approval of your submission.

Protocol Requirements and Recommendations

1. The IRB requires that revised protocols have a version number and/or version date on the protocol document.
2. The IRB strongly recommends that revised protocol have page numbers.
3. The IRB must have a complete and up-to-date version of the protocol on record at all times. You may not upload additions to the protocol instead of a complete revised document. You may, however, upload only a tracked changes version of the protocol.

Other Study Document Recommendations

1. The IRB strongly recommends that if you have more than one similar study document (e.g. ads for different populations), distinguish between the documents using footers or other clear text in the document. Do not use the header function, since iRIS stamps documents in the upper right-hand corner.

Document Revision Requirements

1. If both the old version and the new version are Word documents, you may upload only a clean version of the new document.
2. If either the old version or the new version is a PDF file, you must also upload a tracked changed version or a document with the list of changes.

☑ I understand that incorrectly uploading revised study documents will result in a delay of IRB review and approval.

5.0 Signature Instructions
READ THESE INSTRUCTIONS BEFORE PROCEEDING

5.1 To go to the signature routing pages:
Coordinators: Click "Save and Continue" and then "notify PI to signoff" (on the next page) to continue to the signature routing pages.
PIs: Click "Save and Continue" and then "Signoff and Submit" to continue to the signature routing pages

5.2 Signature Requirements
Only the signature of the PI is required on the first signature routing page. You may deselect other study staff from the routing list.
If you are changing PI or making changes that prompt signatory requirements (click here for details), departmental or other signatories must be added on the second routing page.

5.3 If you have any additional comments that you would like to convey to the IRB staff, please enter them here:

Changes in this amendment were minor but required by the DSMB prior to recruitment. We need to respond to the DSMB as soon as possible and provide the IRB approved revised consent form to get approval to start the study.

Amendment Form (Version 3.1)

1.0 General Information

The version you are using is: 12 February 2015 version C

1.2 For all studies migrated from PATS or West Campus/paper:

Amendments may NOT be submitted before a Migration Completion Form has been approved by the IRB. If your Migration Completion Form has not been approved, this amendment will be rejected by the IRB.

Questions? Please contact **iris-support@einstein.yu.edu**.

1.3 Study Information

Study Title:

Cognitive intervention to improve simple and complex walking

Principal Investigator:

Joe Verghese

Submission Reference #:

014402

1.4 Please click Save and Continue.

2.0 Amendment Information

2.1 Select the modifications being made below:

- ☐ Change in PI
- ☑ Change in key personnel and study contacts
- ☑ Changes to IRB Application
- ☐ Changes to or additon of new informed consent documents
- ☑ Changes to or addition of other study documents (protocol, investigator brochures, questionnaires, protocol, investigators brochure, recruitment materials, instruments, case report forms, study handouts or other miscellaneous documents)

2.2 Provide a brief summary of the changes:

The following tests and procedures will be added to the study protocol: Berg Balance test Gait initiation.

The following personnel are added to study staff:
Audrey McCalley
Kelly Cotton

If this is a sponsored amendment, and the sponsor has provided a document with a summary of changes, provide a summary of the **key changes in the space above (i.e., administrative changes to the protocol, corrected protocol regarding test X and updated the consent document accordingly, etc.). The IRB cannot accept "see attached". The IRB also cannot accept just a copy of the list of changes instead of a summary.*
***For the addition of key personnel, please also indicate whether the individual(s) added will be conducting the informed consent process.*

2.3 Provide a justification for the amendment.

The tests and procedures added will provide additional data about the effects of the programs.

The study personnel are newly hired RAs.

2.4 For an amendment generated by a study sponsor, provide the amendment version information, e.g. "Amendment #2 dated 11August2011".

Amendement 15Nov2015

This information will be used in the approval letter for the amendment.

2.5 Did the amendment originate from a drug company, a national study group, etc.? If "Yes," a copy of the correspondence must be attached to this amendment application.

○ Yes ◉ No

3.0 Change Key Personnel

3.1 Update study personnel using the form below:

The current list of Study Contact(s) for this study is listed below :
(if the list is blank, try clicking on "Refresh Constant Fields" in the upper right corner)

Joe Verghese, Emmeline Ayers

Note that only the PI and the Study Contact will receive iRIS communications and have full access to the study.
Please make sure that there are active personnel listed as Study Contact(s).

If applicable, please add the new Principal Investigator for the Study:

If applicable, please select the new Research Staff personnel:

A) Additional Investigators

B) Research Staff

☐ McCalley, Audrey
Research Associate

☑ Cotton, Kelly
Research Associate

If applicable, please add any new Study Contact:

If applicable, please add a new Faculty Advisor:

If applicable, please select any existing Personnel you wish to remove:	

3.2 If you are submitting a change in PI note the following:

- **The PI must have a current conflict of interest (COI) disclosure on file (see the Amendment Handbook in the Help Menu for details). Note: The submission will be denied if the PI does not have a current COI disclosure on file.**
- **The PI must have a current CITI course on file (see the Amendment Handbook in the Help Menu for details)**
- **Upload a copy of the new PI's CV/resume in the Study Documents section of the Amendment Form**
- **If necessary, upload a revised consent document with the new PI's name**
- **Route the amendment form for approval by the new PI's department chair**

See the Amendment Form Handbook in the help menu (orange and white question mark in the upper right corner) for further details on submitting these items.

3.3 If you are submitting a change in Additional Investigators note the following:

- **Have a current conflict of interest (COI) disclosure on file (see the Amendment Handbook in the Help Menu for details). Note: The submission will be denied if any Investigators do not have current COI disclosures on file.**
- **The Additional Investigators must have a current CITI course on file (see the Amendment Handbook in the Help Menu for details)**

See the Amendment Form Handbook in the help menu (orange and white question mark in the upper right corner) for further details on submitting these items.

3.4 If you are submitting a change in Research Staff note the following:

- **The Research Staff must have a current CITI course on file (see the Amendment Handbook in the Help Menu for details)**

4.0 IRB Application Revision

Instructions:

1. Click on the grey bar labeled "Click here to attach the application." A new window will open up.
2. Click on "Add Revision" on the right and then click on "OK" on the popup window.
3. Make the revision to the relevant section of the application. Click "Save and Continue to Next Section" after every application section until you get to the very end of the application. If you are given the option to convert your application to a newer version, you must do so before completing your submission.
    a. If you convert to the newest version of the application all but the first three sections of the application will disappear. Click on "Save and Continue to Next Section" after each section to recreate the application. You may need to answer new questions.
4. Once the application has been completely revised, you will then be sent back to the "Attach Study Application" page and the study application listed will have a new version number (i.e., version 1.2). Click on "Save Attachment".

Edit/ View	Version	Title
	1.3	Human Research Application (Version 1.3) - Attached

5.0 Signature Instructions
READ THESE INSTRUCTIONS BEFORE PROCEEDING

5.1 To go to the signature routing pages:
Coordinators: Click "Save and Continue" and then "notify PI to signoff" (on the next page) to continue to the signature routing pages.
PIs: Click "Save and Continue" and then "Signoff and Submit" to continue to the signature routing pages

5.2

Signature Requirements

Only the signature of the PI is required on the first signature routing page. You may deselect other study staff from the routing list. If you are changing PI or making changes that prompt signatory requirements (click here for details), departmental or other signatories must be added on the second routing page.

5.3 ***If you have any additional comments that you would like to convey to the IRB staff, please enter them here:***

Amendment Form (Version 8.0)

1.0 General Information

The version you are using is: 12 February 2015 version C

1.2 For all studies migrated from PATS or West Campus/paper:

Amendments may NOT be submitted before a Migration Completion Form has been approved by the IRB. If your Migration Completion Form has not been approved, this amendment will be rejected by the IRB.

Questions? Please contact **iris-support@einstein.yu.edu**.

1.3 Study Information

Study Title:

Cognitive intervention to improve simple and complex walking

Principal Investigator:

Joe Verghese

Submission Reference #:

017415

1.4 Please click Save and Continue.

2.0 Amendment Information

2.1 Select the modifications being made below:

- ☐ Change in PI
- ☐ Change in key personnel and study contacts
- ☐ Changes to IRB Application
- ☐ Changes to or additon of new informed consent documents
- ☑ Changes to or addition of other study documents (protocol, investigator brochures, questionnaires, protocol, investigators brochure, recruitment materials, instruments, case report forms, study handouts or other miscellaneous documents)

2.2 Provide a brief summary of the changes:

We have revised the recruitment letter to specify how much time is required for the intervention.

If this is a sponsored amendment, and the sponsor has provided a document with a summary of changes, provide a summary of the **key changes in the space above (i.e., administrative changes to the protocol, corrected protocol regarding test X and updated the consent document accordingly, etc.). The IRB cannot accept "see attached". The IRB also cannot accept just a copy of the list of changes instead of a summary.*
***For the addition of key personnel, please also indicate whether the individual(s) added will be conducting the informed consent process.*

2.3 Provide a justification for the amendment.

The recruitment letter now specifies the amount of time required for participation in the intervention.

2.4 For an amendment generated by a study sponsor, provide the amendment version information, e.g. "Amendment #2 dated 11August2011".

Amendment #7 14 March 2016

This information will be used in the approval letter for the amendment.

2.5 Did the amendment originate from a drug company, a national study group, etc.? If "Yes," a copy of the correspondence must be attached to this amendment application.

○ Yes ◉ No

3.0 Study Document Revision or Addition

Study documents include the protocol, investigator brochures, questionnaires, protocol, investigators brochure, recruitment materials, instruments, case report forms, study handouts or other miscellaneous documents.

To revise approved study documents, create a REVISED copy of the document in iRIS in order for the system to properly VOID the previously approved study document. Do NOT attach new documents unless they are for types of study documents that have never been previously approved.
GUIDANCE ON REVISING DOCUMENTS IS AVAILABLE IN THE AMENDMENT HANDBOOK IN THE HELP MENU.

Version	Title	Category	Expiration Date	Document Outcome	Checked Out	View Document
1.4	Recruitment Letter	Recruitment Material		Approved		53.16 KB

Only the following types of files may be uploaded into iRIS:.doc, .docx, .rtf, .txt, .pdf. The use of other file formats may delay IRB review and approval of your submission.

Protocol Requirements and Recommendations

1. The IRB requires that revised protocols have a version number and/or version date on the protocol document.
2. The IRB strongly recommends that revised protocol have page numbers.
3. The IRB must have a complete and up-to-date version of the protocol on record at all times. You may not upload additions to the protocol instead of a complete revised document. You may, however, upload only a tracked changes version of the protocol.

Other Study Document Recommendations

1. The IRB strongly recommends that if you have more than one similar study document (e.g. ads for different populations), distinguish between the documents using footers or other clear text in the document. Do not use the header function, since iRIS stamps documents in the upper right-hand corner.

Document Revision Requirements

1. If both the old version and the new version are Word documents, you may upload only a clean version of the new document.
2. If either the old version or the new version is a PDF file, you must also upload a tracked changed version or a document with the list of changes.

☑ I understand that incorrectly uploading revised study documents will result in a delay of IRB review and approval.

4.0 Signature Instructions
READ THESE INSTRUCTIONS BEFORE PROCEEDING

4.1 To go to the signature routing pages:
Coordinators: Click "Save and Continue" and then "notify PI to signoff" (on the next page) to continue to the signature routing pages.
PIs: Click "Save and Continue" and then "Signoff and Submit" to continue to the signature routing pages

4.2 Signature Requirements
Only the signature of the PI is required on the first signature routing page. You may deselect other study staff from the routing list.
If you are changing PI or making changes that prompt signatory requirements (click here for details), departmental or other signatories must be added on the second routing page.

4.3 ***If you have any additional comments that you would like to convey to the IRB staff, please enter them here:***