Protocol

Improving Recovery and Outcome Every Day after the ICU (IMPROVE)

IRB #: **1608126693**

Grant Title: **Decreasing Alzheimer's Disease and Related Dementias after Delirium- Exercise and Cognitive Training (DDD-ECT)**
Grant #: **R01AG055391**

Babar Khan, MD, MS
Research Scientist, IU Center for Aging Research
Associate Professor of Medicine, IU School of Medicine
Division of Pulmonary/Critical Care

Table of Contents

1. Background

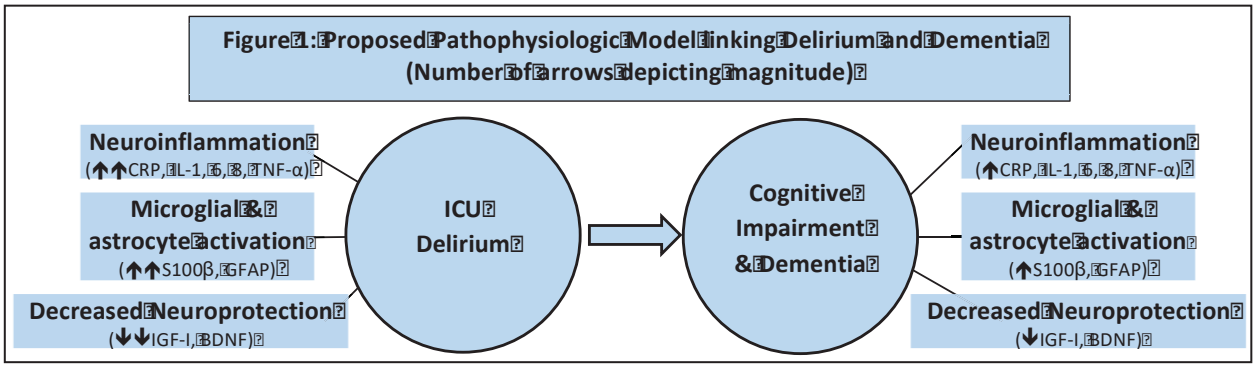
The Aging Brain during and after Critical Illness: Critical illness has deleterious consequences on both acute and chronic cognitive functions.[4-12] Acute cognitive dysfunction manifests itself as delirium in the critically ill especially the elderly. Delirium is a complex neuropsychiatric syndrome characterized by acute and fluctuating changes in cognition and consciousness.[37,38] 60% to 80% of critically ill ventilated older patients and 30% to 50% of those with less illness severity have delirium for at least one day of their ICU or hospital stay.[39-43] Chronic cognitive dysfunction manifests as ICU acquired cognitive impairment and dementia after critical illness, affects multiple cognitive domains and persists years after hospital discharge.[9-12] Up to 71% of critical illness survivors have cognitive impairment at one year after hospital discharge[11] and close to 18% are diagnosed with new dementia including Alzheimer's disease within three years post ICU hospitalization.[12]

Relationship among Delirium, ICU acquired cognitive impairment and dementia: The presence of ICU delirium predisposes ICU survivors to long-term cognitive impairment and dementia.[9-12] Studies showed that delirium was associated with worse cognitive performance 3 and 12 months after an ICU stay even after adjusting for age, education, chronic disease burden, pre-existing cognitive impairment, cerebrovascular disease, severity of acute illness, and exposure to neuroleptics.[10,11] Similar results were observed in a prospective cohort study of 52 delirious patients evaluated locally with only 6 (11.5%) of the 52 ICU survivors having normal cognition on a standardized neuropsychological battery at 3 months.[9] Among ICU survivors with cognitive impairment, 70% had cognitive impairment in at least two cognitive domains such as memory, executive function, language, or constructional praxis; 16% had deficit in memory only; and 14% had deficit in a cognitive domain other than memory.[9] Furthermore, a study performed by Guerra et al. found that acute neurological dysfunction defined as anoxia, encephalopathy or delirium in the ICU was associated with a new diagnosis of dementia or Alzheimer's disease with an adjusted hazard ratio of 2.06 (1.72-2.46) within three years of ICU discharge.[12] The cognitively impaired survivors frequently also have concomitant emotional and functional disabilities.[10,44,45] Whereas only 23% of ICU survivors without cognitive impairment are disabled, 100% of ICU survivors with cognitive impairment are unable to return to work full-time.[44] Despite the high prevalence rates of cognitive and functional disability among ICU survivors, the majority of this vulnerable growing segment of ICU survivors does not receive post-ICU recovery care.[43]

Systemic inflammation, astrocyte and microglial activation, and loss of neuroprotective growth factors, a connecting link between delirium and dementia:

Delirium can be considered as a cytokine mediated inflammatory syndrome with pro-inflammatory cytokines such as interleukin (IL)-1, 6, 8, and tumor necrosis factor (TNF)-α disrupting the blood brain barrier with recruitment and infiltration of peripheral leukocytes into the central nervous system (CNS).[46-48] The resultant microglial activation produces local pro-inflammatory cytokines (IL-1, TNF-α), reactive oxygen species, expansion of microglial population[49] and activation of astrocytes.[50] Astrocyte activation and glial dysfunction results in elevated S-100β and glial fibrillary acidic protein (GFAP) levels.[51-54] The neuroinflammation also promotes cholinergic failure[55] culminating in the neurocognitive syndrome of delirium. This is compounded by lower levels of neurotrophic growth factors such as insulin like growth factor-1 (IGF-1) and brain derived neurotrophic factor (BDNF).[56,57] IGF-1 and BDNF have neurotrophic properties and provide protection against free radical damage and cytotoxic cytokines.[58-60] Both inhibit neuronal apoptosis and promote maintenance, survival, and regeneration of neurons.[58-62] Moreover, IGF-1 increases choline acetyltransferase levels and modulates acetylcholine release, the key neurotransmitter implicated in delirium.[60] Thus a combination of increased neuroinflammation with a state of cholinergic failure in the CNS and depleted neurotrophic factors predispose patients to delirium. The inflammatory cascade, microglial and astrocyte activation, and loss of neuroprotection could persist after surviving critical illness,[63] leading to a chronic, persistent state of neuroinflammation, neurotoxicity, diminished neuroplasticity and cholinergic failure, manifesting as long-term ICU acquired cognitive impairment, dementia or Alzheimer's disease (Figure 1). An intervention modulating the aforementioned factors could provide cognitive recovery and may delay onset of Alzheimer's disease and related dementias among ICU survivors.

Neurobiological Effects of Physical Exercise and Cognitive Training: Animal studies: Physical exercise induces neural proliferation while cognitive training promotes functional integration of these new neural elements into adaptive networks, effects found to be additive in animal studies.[64,65] As shown in an animal study, combination of physical exercise and enrichment (a surrogate for cognitive training in the human model) produced more neurons in adult mice than either intervention alone with each superior to a "standard" environment.[66] An integrative review of decades of animal research concludes that adult neurogenesis occurs in an activity-dependent manner and that both physical and cognitive inputs generate plasticity inducing signals to the brain.[64] Movement stimulates neural precursor cells to proliferate while environments conducive to learning and thinking promote survival of the new cells. Physical activity enhances angiogenesis, neurogenesis, release of neurotrophic factors and neuroplasticity.[16] Only 1 week of exercise resulted in increased vascular endothelial growth factor (VEGF) levels in rats by increasing precursors of angiogenesis, leading to new vessel formation.[67] Physical activity promotes neuronal survival, cell proliferation and raises BDNF and IGF-1 in the somatosensory cortex and hippocampus.[68-71] This translated to enhanced learning and memory in rats that were



allowed to exercise freely.[69] Human studies: Physical exercise increases cerebral blood flow, oxygen extraction and glucose use,[72] and reduces inflammation.[73] Older patients who perform aerobic exercise

showed the greatest increase in blood volume in frontal and parietal lobe white matter, larger hippocampal volumes and better memory, and better white matter integrity.[74-78] Physical exercise appears to mitigate endothelial dysfunction and vascular wall inflammation, and enhances neural substrates BDNF and IGF-1 that maximize the effects of subsequent cognitive stimulation.[79,80] Similarly, cognitive therapy may exert its favorable effect by increasing levels of BDNF. This was shown in a randomized trial of eight weeks of cognitive therapy versus health education among patients with heart failure.[81] Patients randomized into the cognitive therapy arm showed an increase in their BDNF levels at 8 weeks compared to baseline levels as well as improvement in working memory, whereas the BDNF levels decreased in the education control.[81]

Evidence that Cognitive Training improves cognition: Cognitive training has been shown to improve mental abilities[82-85] and functional status in healthy older adults,[86] patients with traumatic brain injury and stroke,[87] and patients suffering from mild cognitive impairment (MCI).[88] The largest and most rigorous investigation of the efficacy of cognitive training in improving cognition and delaying functional loss is the ACTIVE study.[88] ACTIVE enrolled 2,802 community-dwelling adults (65 years and older) without Alzheimer's disease and related dementias, and randomly assigned them to one of four groups (Memory, Reasoning, Speed of Processing training or a no-contact control group). Each ACTIVE intervention produced an immediate improvement in the trained ability with largest improvements observed for the Speed of Processing intervention followed by Reasoning and Memory. Treatment gains declined over time but remained significant at the 5-year follow-up. A recent meta-analysis is consistent with this notion showing that persons with MCI obtain mild to moderate cognitive benefits (effect size range from .27 for working memory to .50 for language domain) from cognitive training that are durable through follow-up.[89] The moderator analysis suggested no effect of subject age or years of education on outcomes and no differences between training delivered by computer versus in-person methods nor was there a difference between groups versus individual instruction.

Evidence that Physical Exercise improves cognition: Physical exercise improves cognitive ability,[90,91] brain function,[92] and brain structure of adults.[91,93] A cross-sectional study of 2,736 older women showed that high daytime movement was associated with higher Mini Mental Status Examination (MMSE) scores.[94] A meta-analysis of 18 studies examining the effect of exercise interventions on cognition in well older adults found a net effect size of .31 in favor of exercise over control activities .[89] Executive cognitive ability showed the largest response to exercise as compared to other cognitive domains. Gains were also greater for training that lasted 30-45 minutes (versus longer or shorter) and older subjects (versus ones that were age 55-65). Favorable cognitive effects of physical activity have also been demonstrated for patients with mild cognitive impairment, Alzheimer's disease, stroke, COPD, and traumatic brain injury.[95-101]

Additive Effects of Combined Physical Exercise and Cognitive Training among older adults: As postulated above, it stands to reason that combined physical and cognitive training could have additive effects. Two studies conducted in Europe found large effect sizes (0.9-1.3) on cognition from combined training versus mental or exercise training alone in well older adults.[102,103] One study evaluating combined training did not find an effect; however, it had a very small sample size (< 20 subjects per group), a low dose of exercise (<60 min of exercise per week), and an intervention focused only on memory but not executive function.[104]

Effects of Combined Physical Exercise and Cognitive Training among ICU survivors: Investigators from Vanderbilt and Duke Universities conducted a feasibility trial of combined physical exercise and cognitive training among 21 ICU survivors. These ICU survivors were randomized to usual care (n = 8) or

12 weeks of at-home combined physical exercise and cognitive training intervention, consisting of six in-person visits for cognitive training and six telemedicine visits for physical exercise.[105] At 3-month follow-up, the ICU survivors in the active treatment arm tolerated the combined program and had significantly better cognition as measured by the TOWER test, which is a timed objective measure of executive function (median score: 13.0 vs. 7.5, p<0.01) and functional score as measured by the Functional Assessment Questionnaire (median score: 1.0 vs. 8.0, p=0.04). The findings of this study are promising and provide rationale for our proposed trial. However, the study did not control for attention, had a very small sample size with no power to investigate the impact of the intervention on physical performance and it neither measured the ICU survivors overall quality of life nor their depressive and anxiety symptoms. Also, the isolated effects of physical rehabilitation or cognitive therapy on neuropsychiatric outcomes cannot be evaluated, as both interventions were concurrently administered.

Based on the background above, physical exercise and cognitive training hold promise for improving cognitive outcomes of ICU survivors although the current evidence is limited. We plan to further explore these findings through an efficacy, randomized, 2x2 factorial design clinical trial with four treatment arms, a) physical exercise and cognitive training, b) physical exercise, c) cognitive training, and d) attention control. The trial will not only be able to answer the question whether combined physical and cognitive therapies are superior to either of them alone as compared to attention control, but will also shed light on mechanisms of action of the intervention through use of serum biomarkers. An advanced mechanistic understanding of cognitive recovery after delirium will lead to refined interventions to prevent progression to dementia and Alzheimer's disease.

2. Rationale and Specific Aims

Two million older Americans suffer from an episode of delirium during their intensive care unit (ICU) stay.[1-3] Presence of delirium predisposes the elderly to immediate in-hospital complications including a longer length of ICU and hospital stay, increased risk of in-patient mortality and elevated costs of care.[4-8] In addition, ICU delirium is associated with long-term post-discharge complications such as development of cognitive impairment and dementia.[9-12] Current advances in the management of critical illness have notably improved the survival rates among this vulnerable segment of older adults.[13] However, increased survival comes at a cost with as many as 70% of older ICU survivors who had an episode of delirium suffering from subsequent cognitive impairment and dementia.[9-12] At present, there are no effective and scalable recovery models to remediate ICU acquired cognitive impairment and its attendant elevated dementia or Alzheimer's disease risk.

The inability to develop efficacious interventions to reduce ICU acquired cognitive impairment may stem from a limited understanding of the link between acute brain dysfunction (delirium) and chronic brain dysfunction (ICU acquired cognitive impairment, dementia or Alzheimer's disease). We propose a recovery intervention guided by the pathophysiologic mechanisms implicated in producing critical illness delirium and elevated risk of cognitive impairment.[14-18] The intervention targets inflammation, glial dysfunction and astrocyte activation along with restoration of neurotrophic factors while training function directly across multiple cognitive domains to reduce the burden of cognitive impairment among ICU survivors of delirium.

Over the past five years, Indiana University Center for Aging Research has developed a research infrastructure focused on delirium and delirium associated cognitive impairment, encompassing the ICU and post-ICU periods. This includes developing a bio-repository of serum delirium biomarkers, ICU based delirium trials, and post-ICU exercise and cognitive therapy recovery models.[9,19-26] Building upon our prior work and based on the pathophysiologic mechanisms mentioned above, we now propose a novel **home-based combined physical exercise and cognitive training program** for older ICU survivors to improve cognitive impairment.

Our team is proposing a 2x2 factorial design randomized controlled trial (RCT) called "**D**ecreasing Alzheimer's Disease and Related **D**ementias after **D**elirium-**E**xercise and **C**ognitive **T**raining (DDD-ECT)" to evaluate the efficacy of 12 weeks of combined physical exercise and cognitive training on the primary outcome of cognitive function among older ICU survivors who experienced delirium or subsyndromal delirium during their ICU stay. We propose to deliver these interventions via a facilitator-led, small group format using internet-enabled, multiparty-videoconference delivered directly into the participants' homes to achieve the following aims:

Primary Specific Aim: Determine the effect of the combined physical exercise and cognitive training on the cognitive function of ICU survivors aged 50 and older. Hypothesis: In comparison to older ICU survivors randomized to attention control or either intervention alone, those randomized to 12 weeks of combined physical exercise and cognitive training will have higher total index cognitive scores as assessed by the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)[27] at 3 and 6 months post randomization.

Secondary Specific Aim 1: Determine the effect of the combined physical exercise and cognitive training on physical performance, anxiety and depressive symptoms, and quality of life of ICU survivors aged 65 and older. Hypotheses: In comparison to older ICU survivors randomized to attention control or either intervention alone, those randomized to 12 weeks of combined physical exercise and cognitive training will have higher physical performance as measured by short physical performance battery (SPPB)[28] and two-minute step test,[29] lower mood and anxiety symptoms as measured by Patient Health Questionnaire (PHQ-9)[30,31] and Generalized Anxiety Disorder (GAD-7) scale,[32,33] and higher quality of life as measured by the Medical Outcomes Study 36-item short form (SF-36)[34-36] at 3 and 6-months post randomization.

Exploratory Aim 1: To examine the mechanisms of action of combined training. Hypothesis: At the completion of treatment, the combined intervention group will show reduced serum levels of CRP, IL-1, IL-6, IL-8, TNF-α, S-100β, and GFAP and increased levels of BDNF, VEGF, and IGF-1 compared to the attention control, or either intervention alone groups.

Successful achievement of the aforementioned aims will pave the way for a large effectiveness RCT testing the combined intervention to delay time to a clinical diagnosis of Alzheimer's disease and related dementias.

3. Inclusion/Exclusion Criteria

Inclusion Criteria:
[1] Patients aged ≥ 50 years,

[2] admitted to medical and/or surgical ICUs at IU Health locations (Methodist, University, North, West, Saxony), Eskenazi hospitals
[3] discharged home, sub-acute rehabilitation, long-term acute care, or skilled nursing facility,
[4] able to provide consent or has a legally authorized representative to provide consent,
[5] access to a telephone (study provides computer and broadband) and finally
[6] have at least one episode of subsyndromal delirium or delirium as determined by the Confusion Assessment Method for the ICU-7 (CAM-ICU).[109] The CAM-ICU-7 score is determined by examining the patient for (a) acute and fluctuating changes in mental status, (b) inattention, (c) disorganized thinking, and (d) altered level of consciousness. A CAM-ICU-7 score is considered to be positive for delirium if the patient displays a, b, and c, or a, b, and d, or a, b, c, and d. The CAM-ICU-7 score is considered to be positive for subsyndromal delirium if any one feature of delirium (either a, b, c, or d) is positive. The CAM-ICU diagnosis of delirium was validated against the DSM-III-R delirium criteria determined by a psychiatrist and found to have a sensitivity of 97% and a specificity of 92%.[109]

Exclusion Criteria:
[1] diagnosis of cancer with short life expectancy;
[2] current chemotherapy or radiation therapy (confirmed by electronic medical record);
[3] history of dementing illnesses and other neurodegenerative disease such as Alzheimer's disease, Parkinson disease, or vascular dementia (confirmed by EMR), or current prescription of anti-dementia medication, or ruled out by Functional Activities Questionnaire (FAQ) score defining dementia.
[4] current alcohol consumption > 5 drinks per day (self reported or confirmed by EMR);
[5] vision < 20/80 via Snellen card or confirmed by EMR;
[6] low hearing or communicative ability (examiner rated) that would interfere with interventions and outcome assessments;

[7] have any active and untreated American College of Sports Medicine[133] absolute contraindications to exercise (confirmed by EMR) including: acute myocardial infarctions within the past 2 days, ongoing unstable angina, uncontrolled cardiac arrhythmia with hemodynamic compromise, active endocarditis, symptomatic severe aortic stenosis, decompensated heart failure, acute pulmonary embolism, pulmonary infarction, or deep venous thrombosis, acute myocarditis or pericarditis, acute aortic dissection, physical disability that precludes safe and adequate testing, or are unable to obtain provider clearance for physical exercise for any contraindication where medical management is unclear;
[8] have any active and untreated American College of Sports Medicine[133] relative contraindications to exercise (confirmed by EMR) including: known obstructive left main coronary stenosis, moderate to severe aortic stenosis with uncertain relationship to symptoms, tachydysrhythmias with uncontrolled ventricular rates, acquired advanced or complete heart block, recent stroke or transient ischemia attack, mental impairment with limited ability to cooperate, resting hypertension with systolic >200 mm Hg or diastolic >100 mm Hg, uncorrected medical conditions, such as significant anemia, important electrolyte imbalance, and hyperthyroidism, or are unable to obtain provider clearance for physical exercise for any contraindication where medical management is unclear;
[9] recovering from a skeletal fracture (confirmed by EMR), unless cleared by their physician of record to safely participate in exercise,
[10] Acquired neurologic injury (stroke, traumatic brain injury, cerebral edema/swelling, anoxic brain injury, or any other acute/subacute severe neurologic deficit) as the admitting diagnosis or a new event during the course of hospitalization (confirmed by EMR) or
[11] history of drug abuse within the last 3 months confirmed by EMR or self-report with Drug Abuse and Screening Test (DAST-10) score ≥ 3].[110]
[12] Schizophrenia or bipolar disorder (confirmed by EMR)

[13] Have any spinal cord injury with persistent neurologic deficit at the time of study enrollment
[14]Status post tracheostomy and not eligible for a speaking valve
[15] Pregnant or nursing
[16] Incarcerated or homeless at time of study
[17] Lives outside the greater Indianapolis area
[18] Illiterate

Study team will be using electronic medical records to verify eligibility status. The study team will make all efforts to contact the clinical team when a patient's eligibility status is unclear.

4. Enrollment/Randomization

Recruitment Targets:
344 older ICU survivors who experienced delirium or subsyndromal delirium in the ICU will be enrolled.

Clinical Settings and Study Population: The target population for our trial is adults aged 50 and older who have survived a critical illness in the ICU and had a delirium/subsyndromal episode during their ICU stay at Indiana University School of Medicine affiliated hospitals and IU Health hospitals as listed in performing organizations.

Screening and Enrollment:
Study personnel will screen for eligible subjects each day using the ICU census. Eligible individuals (those who meet inclusion criteria and do not meet any exclusion criteria) will be screened up to twice per day for delirium until ICU discharge using the CAM-ICU-7. Patients who screened positive on the CAM-ICU-7 (either with study personnel or patient's care team) and survived the ICU stay will be approached for enrollment into the study. CAM-ICU-7 screenings will continue until hospital discharge for patients who enroll in the study.

Study approach and consent may take place post-discharge if patient is released from the hospital before study personnel have the opportunity to meet the patient. Study brochures may be used to aid recruitment. Surrogate consent may be required for patients who are unable to provide consent. All patients consented via surrogate will be re-consented once deemed competent.[111]

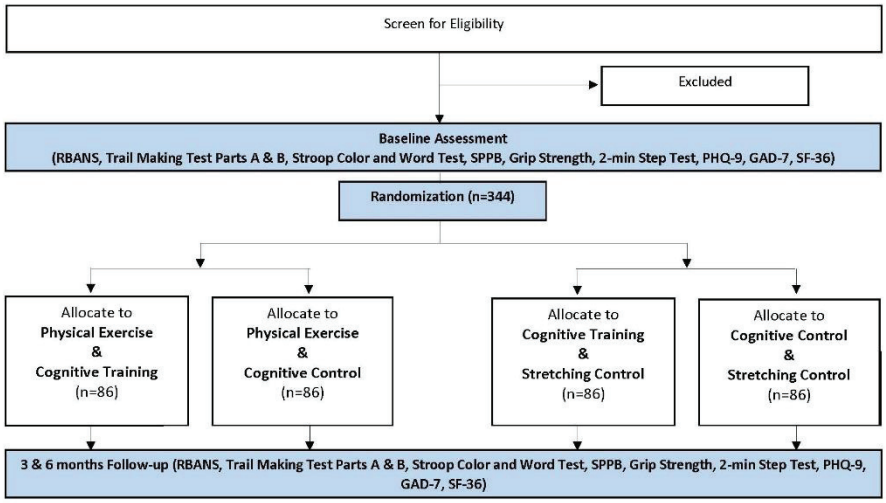
[During COVID-19 health crisis, CAM-ICU/CAM-ICU-7 screenings will be conducted by ICU healthcare personnel only. Screening outcomes will be obtained from EMR. Study approach will be completed by study personnel via phone. Informed consent will be obtained following the IU IRB Flexible Consent Procedures: https://research.iu.edu/compliance/human-subjects/guidance/informed-consent.html. No study procedures will be completed prior to receiving the signed consent and authorization forms from the subject.]
Randomization:
After obtaining an informed consent, study staff will complete a baseline assessment consisting of measures of cognition, physical function, depression and anxiety, and quality of life (see measures section 4.3.l. below). Blood samples will also be collected from the participants at the time of baseline assessment. Baseline may be completed at subject's home after hospital discharge if unable to complete full assessment in the hospital. After initial assessment, study subjects will be randomized to study groups. Randomization will be stratified by discharge location (home, other facility) and managed by the IU site

[During COVID-19 health crisis, baseline assessments will be completed via phone; abbreviated measures of cognition, and no measures of physical function will be obtained due to the limitations of phone administration. Blood samples will not be collected.]

5. Study Procedures

Enrolled subjects randomized to the experimental intervention will receive cognitive training via computer-accessed online training modules 45 minutes per session, 2 days per week for 3 months; and physical exercise delivered by trained facilitators to participants in their homes via internet-based single or multi-party (2-6 per group) videoconference 45 minutes per session, 3 times per week for 3 months (Figure 3).

Figure 3: Study Design



Cognitive Intervention: The cognitive portion of the combined intervention consists of a suite of 24 programs called Brain HQ developed by Posit Science, Inc. The modules are designed to improve time-order judgment, visual discrimination, spatial-match, forward-span, instruction-following, and memory. The program systematically reduces stimulus presentation time to maintain an 85% accuracy rate and launches each new session based on the stopping point of the preceding session.

Cognitive Control: This consists of up to 20 minutes of puzzles and games, 2 days per week for 3 months. We will use on-line Brain HQ Control Games developed by Posit Science, Inc.

Physical Exercise Intervention: The physical exercise portion of the combined intervention consists of 45 minutes of multi-modal physical exercise focused on seated aerobic and progressive resistance training designed to improve aerobic capacity, muscular strength and endurance consistent with current exercise recommendations.[112,113] We will deliver 3 sessions per week for 3 months. Each physical exercise session will be divided as follows: 5 minutes of warm-up, 10 minutes of upper-body, 10 minutes of core, 10 minutes lower-body, 5 minutes of upper-body and lower-body, and 5 minutes of cool-down and flexibility exercises. All exercises are conducted from a seated position in a solid backed chair. We will provide participants with a heart rate monitor watch or pulse oximeter and have participants report their heart rate and oxygen saturation. Their heart rate should be above 55% but not to exceed 70% of their age-adjusted maximum heart rate thus providing moderate-intensity exercise for each participant. Due to limited heart rate response for participants on beta-blocker medications, we will also use the Rating of Perceived Exertion scale (RPE). Participants will be advised to exercise at the RPE level of 5 to 6 on a 10-point scale. Generally, for adults over the age of 40 years, moderate-intensity is 5 to 6 on a 10-

point exertion scale.[114] Participants will also be given Velcro weight bands specific for the wrists and ankles that are color-coded by weight to allow the Interventionist to check that the appropriate weight is used by each participant during video-conference sessions. The initial wrist weights will be 1 pound and the ankle weights will be 2 pounds, although the participants will have the option of 1-pound weight or no weight. Although small group (e.g., 2 to 6) format is the goal, we will start with one-on-one training with escalation into a group. We will continue one-on-one in cases of difficult adherence or unique physical abilities.

Physical Exercise Control: This consists of up to 10 minutes of gentle stretching. We will deliver 3 sessions per week for 3 months. This stretching module was designed specifically as a control condition for exercise trials and was used as such in the NIH-funded LIFE exercise trial.[115] Heart rate, oxygen saturation and RPE will be collected as in the Exercise Intervention.

Intervention Delivery - Computer and Videoconference in the Home: This feature is common to all treatment arms. Study staff will initiate contact within 2 weeks post-ICU discharge to set up the computer and videoconference system in subjects' homes. Afterwards, the interaction between the interventionists and the subjects will happen remotely through a computer video interface. Communication via videoconference can be described as live, interactive television. The participants can hear and see one another and the interventionist; and the interventionist can hear and see the participants. We will use New Inspiron One 20" All-in-One Desktop Dell computers, which have the processor and webcam built-in to the 20" monitor. Internet access will be provided with 4G LTE air cards or jet packs will use Zoom for video conferencing provided by Indiana University. The videoconferences will be security protected with room access provided on an individual level. Information technology support, including computer and software settings, will be reviewed and addressed remotely as needed during sessions using TeamViewer software. We have installation, training, and IT support manuals in place. At the initial installation, our staff will orient the subject and family caregiver to the operational features of the computer and Internet interface. Additional orientation visits can be scheduled at the request of the participant or if the Interventionist detects difficulties in a subject's ability to operate the computer. In addition, we have the capability to run the interventions with smaller groups or even single participant groups as needed.

[During COVID-19 health crisis, computers will be delivered to subject's homes following a no-contact drop-off protocol. Interventionists will provide instructions via phone on how to set up the computer. As long as in-person research activities are restricted, "additional orientation visits" will not be conducted.]

Safety: We have incorporated exercise program elements that are associated with lower risks of cardiovascular complications and muscular injury. These include warming up, flexibility exercise, moderate intensity exercise, and a gradual progression of exercise intensity and duration.[112-114] The Interventionist will educate subjects about the signs and symptoms of angina, myocardial infarction, and muscle/tendon related injuries and how to respond to them; a procedure recommended by the American College of Sports Medicine and the American Heart Association as effective means of reducing complications to exercise.[112,116] The frequency, duration, and intensity of intervention delivery will be modified as necessary for enrolled subjects who are medically frail. We have outlined our Data and Safety Monitoring Plan including the identification and response to serious cardiac events and orthopedic injuries in the Protection of Human Subjects section. Cognitive training is relatively safe but anxiety and burden will be monitored. As subjects recover from their ICU hospitalization, they may require additional resources to address a variety of ICU survivorship issues. A list of resources will be

provided to all subjects after enrollment. Subjects who express needs to the study team will be referred to resources on the list. If a participant indicates suicidal ideation on the PHQ-9, the patient's care team will be notified. Suicidal ideation of participants at IU affiliated institutions will also be reported to Dr. Khan and Dr. Sophia Wang (clinical psychiatrist working at IU Center for Aging Research) for additional follow up; suicidal ideation of participants at non-affiliated institutions will be reported to the site PI, Dr. Khan, and Dr. Wang.

Potential Problems and Alternative Strategies: We have measures in place to ensure retention including availability of make-up sessions and availability of individual training sessions. We will request Cognitive Intervention adherence data from Posit Science. If retention drops below 80%, we will have the study staff follow-up with the study participant to troubleshoot any technical issues and1 provide coaching. Physical training sessions will be offered throughout the week on varying days and times, including the weekends to provide ample training opportunities and make-up sessions. We will use fair subject payments contingent on the completion of the 3 and 6 months follow-up assessments to maximize participation. Loss of information could occur if subjects are unable to complete outcome assessments. To estimate the treatment effect in key domains, a "step-down" battery, consisting of a subset of outcome measures, will be administered when a participant is not able to tolerate the full outcome assessments. This "step-down" battery may also be administered via phone if subject is unable to complete an in-person assessment for the 3 or 6 month outcomes. We also can provide assistive devices (glasses, headphones or pocket talker) if a participant's visual or auditory acuity declines and interferes with interventions or outcome assessments.

Outcomes Assessments: Trained and blinded research assistants will complete 3 and 6 months outcomes assessments consisting of measures of cognition, physical function, depression and anxiety, and quality of life (see Outcome Measures section 9 and Figure 3). Data will be collected using Research Electronic Data Capture (REDCap). We will employ multiple techniques to ensure concealment of outcomes assessment.[117,118] Our research assistants are trained not to inquire about study assignments. They will be conducting structured assessments that do not provide room for qualitative interviewing that should prevent unblinding. They will not be involved in study assignments and training interventions. Subjects will be instructed not to discuss their training intervention with the research assistants.

The following instruments will be used during outcome assessments: Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)[27], Trail Making Test Part A and B, Stroop Color and Word Test, Short Physical Performance Battery (SPPB), Grip Strength, 2-minutes Step Test, Patient Health Questionnaire–9 (PHQ-9), Generalized Anxiety Disorder Scale (GAD-7), Medical Outcome Study Short Form (SF-36), and the International Physical Activity Questionnaire (modified).

[During COVID-19 health crisis, outcomes assessments will be completed via phone; abbreviated measures of cognition, and no measures of physical function will be obtained due to the limitations of phone administration. Blood samples will not be collected.]

6. Reporting of Adverse Events or Unanticipated Problems

PROTECTION OF HUMAN SUBJECTS

Risks to Human Subjects:

Human Subjects Involvement, Characteristics, and Design**:** As many as 50% of ICU survivors aged 65 and older who had an episode of delirium are left with newly acquired "Post-Intensive care Syndrome" (PICS) characterized by cognitive, physical, or psychological symptoms that have onset in the peri-ICU period and persist among ICU survivors for a long period of time with some patients never recovering from such devastating symptoms. We are proposing a behavioral intervention targeting ICU older survivors who have experienced delirium as a means of improving cognitive and functional outcomes. ICU survivors with delirium constitute a growing segment of older American who are vulnerable to develop post ICU cognitive, physical, and psychological disability. The current system does not offer an effective recovery care for this population.

The target population is 344 English-speaking adults aged 50 and older who have been admitted to a critical care unit, have had at least one episode of delirium and are discharged home. This intervention targets cognitively impaired individuals suffering from delirium and will also include women and minorities who meet the inclusion criteria, as these vulnerable populations are at risk of Post-Intensive Care Syndrome.

Sources of Materials**:** During the hospital stay, research assistants will review the medical records and conduct delirium screening to assess the eligibility criteria for potential subjects. Furthermore, blinded assessors will complete the baseline assessment within the hospital or within the subject's home as necessary. The data obtained from subjects will include self-report of demographics, health history, current medications, anxiety and mood symptoms, and quality of life questionnaire. The Assessors will also be collecting information on cognitive and physical performance via objective tests and physiologic status (blood pressure, height, weight, heart rate, oxygen saturation). Finally, the assessors will also conduct a medical record review to assess subject's chronic conditions (Charlson index) and severity of medical illness (APACHE index). In addition to recording attendance, subject's effort and use of modifications, the Trainers will be collecting information on RPE, heart rate and oxygen saturation, while Brain HQ will monitor cognitive performance, for each subject at each training session.

Data will be linked to participants through the use of a unique identifying number. Only persons on the research team will have access to the data. All data are collected for research purposes only. All data will be entered via a password-protected, study specific REDCap (Research Electronic Data Capture) database. Case Report Forms (CRFs) will be stored in locked filing cabinets at Regenstrief Institute. CRFs completed at non-affiliated institutions will be stored locally at their facility and, once the subjects are off-study, transferred to their long-term storage facility, per their local policy.

Potential Risks**:**

(1) *Fatigue, anxiety, stress, or embarrassment from the training or testing sessions.* Emotional distress may result from answering health and behavior questions. Testing may also create anxiety, stress, or embarrassment at perceived performance. Participants may also become fatigued during the testing and/or training sessions.

(2) *Falls and/or muscle stiffness and soreness from exercise.* The exercise intervention components proposed in this study are consistent with standard recommendations for exercise among older adults. Based on piloting and published studies, the most common risk associated with increased exercise is mild muscle stiffness and soreness. Moderate-intensity physical activities are associated with a very low

risk of musculoskeletal complications. There is a low risk of fall given all exercises in the physical intervention are seated.

(3) *Cardiovascular complications from exercise.* The risks of cardiovascular complications do increase transiently during periods of strenuous physical activity.

(4) *Exposure of confidential information.* There is the potential for loss of privacy or confidentiality due to the data collection efforts of this study.

(5) *Discomfort with biological samples collection*. Two blood samples will be collected from each participant, one during their hospital stay and the other at 3-months follow-up. Drawing blood could be associated with pain, bruising, and anxiety.

Adequacy of Protection Against Risks:

Recruitment and Informed Consent**:** Eligible subjects will be identified through the intensive care units census to which they are admitted. Study personnel will consent the patient or their legally authorized representative (if the patient is unable to consent for themselves) during their ICU hospitalization. If LAR provides consent, study personnel will seek consent from subject when capacity is regained, either at hospital or home.

Protections Against Risk**:**

(1) *Fatigue, anxiety, stress, or embarrassment from the training or testing sessions.* All questions planned for this study are part of validated standardized instruments, and we are not asking any questions that do not directly relate to the study purpose. Both Interventionists and Assessors will be trained in their proper use and in the importance of privacy and sensitivity to the participant's time. They will be trained to be alert and sensitive to signs of fatigue and other symptoms and to take appropriate actions when they are present. Breaks from testing will be offered as needed; assessment sessions can also be split into two sessions if a participant is tired or physically uncomfortable.

(2) *Falls and/or muscle stiffness and soreness from exercise.* We have minimized the risk of a fall through the use of seated endurance exercise training; the stiffness and soreness from adoption of exercise training are minimized by the moderate nature of the exercise program; any soreness that may occur early in the training will subside within a few days and be unlikely to occur again with adherence. Participants with persistent or very severe soreness will be encouraged to contact their primary care provider. In the ~2,000 in-home assessments that we have done in the African-American Health study which has an extensive physical exam protocol, we have not had a single fall or other adverse event. We attribute this to our very careful training and supervision procedures, which we will also be using in the proposed trial. We will have an emergency plan in place to handle any emergencies that might occur.

(3) *Cardiovascular complications from exercise.* We have incorporated exercise program elements that are associated with lower risks of cardiovascular complications, such as employing a warm up, flexibility exercise, using moderate intensity exercise, and a gradual progression of exercise intensity and duration. Supervised exercise programs also have a low rate of complications suggesting that the use of well-trained exercise instructors will also provide a margin of safety to the participants. Participants and interventionists will be instructed in the signs and symptoms of cardiovascular complications and how to respond to them both during the exercise sessions and at other times.

(4) *Exposure of confidential information.* Indiana University requires certification of training in protection of human subjects in research. The investigators, interventionists, assessors, and all key personnel have or will have successfully completed training and certification in these courses. All research involving the use of these data must be reviewed and approved by the IRB. We will assure the privacy of subjects and confidentiality of study data by assigning unique identifiers to track participants' data (rather than using names or hospital or social security numbers) and keep all records under lock with access only by study personnel. These procedures have been dutifully adhered to in prior studies. The final data files for this study will be merged, maintained, and analyzed on servers managed by the Division of Biostatistics, Department of Medicine, Indiana University School of Medicine. This group has extensive experience in the handling and security of PHI. None of the individual participant data will be identifiable in published reports or manuscripts and the analyzable datasets will not contain the participant's unique identifier.

(5) *Discomfort with biological samples collection*. A small amount of blood will be required (maximum 44 ml over the entire study course) for the specified laboratory analyses. We will attempt to coordinate all blood sampling with that done for clinical purposes or from indwelling catheters to avoid added venipuncture. Sample collection at 3-month's follow-up will be performed by an experienced phlebotomist. We have collected blood samples at homes of our participants in our other projects and have not encountered any serious adverse events. Blood will be stored in de-identified tubes and will be transported by personnel who have obtained certification in specimen handling and transfer. In addition we are planning to have continuous feedback from the patient, the caregiver, the physician, and the nursing staff to discuss any problems encountered during the data collection.

Potential Benefits of Proposed Research to Human Subjects and Others.

The study participants will be engaged in national health guideline-level physical activity with all its attendant positive results (e.g., decreased fall risk, improved cardiovascular function, improved strength, improved pulmonary capacity, potentially reduced insulin resistance). Participants will also receive small payments for participation. This research could also provide a non-pharmacological treatment for cognitive impairment in patients suffering from ICU acquired cognitive impairment. Despite the high prevalence rates of cognitive and physical disability among ICU survivors, only ICU patients who survived major stroke, traumatic brain injury, or cardiac surgery receive formal cognitive or physical rehabilitation leaving a large percentage of ICU survivors with no such rehabilitation and higher risk for hospital readmission or death.

The intervention proposed in this study builds on prior research and may hold promise for an effective and scalable recovery model for this population. This intervention does require additional resources that will cost additional money; however, it is possible that these short-term costs will be offset by reductions in overall costs to patients and the healthcare system. Patients enrolled in our study and randomized to receive our proposed intervention might have a reduction in post-ICU symptoms and, subsequently, may experience improved cognitive and physical function, improved mood, and quality of life. Our intervention might also improve other health outcomes such as a lower rate of hospital acquired complications, a higher probability of survival, lower institutionalization rates, and decreased length of hospital stay, thereby decreasing health care utilization and cost. The intervention may delay onset of Alzheimer's disease and related dementias among ICU survivors.

Importance of Knowledge Gained.

Up to 70% of ICU survivors aged 65 and older develop long-term cognitive impairment and other functional and psychological sequelae of critical illness. Currently there are no effective and scalable recovery models to remediate or treat ICU acquired cognitive impairment and its deleterious effects on

quality of life and independence of the growing segment of ICU survivors. Our proposed intervention may provide a conceptual and scalable recovery model to remediate or treat post-delirium cognitive impairment and its deleterious effects on quality of life and independence of the growing segment of ICU survivors.

7. Study Withdrawal/Discontinuation

Participants who wish to withdraw from the study will notify the study team verbally or via letter as outlined in the HIPAA authorization document.

8. Statistical Considerations

To verify the comparability of the randomized groups, patients' baseline characteristics among the four groups will be compared using analysis of covariance (ANCOVA) for continuous variables and the Cochran-Mantel-Hansel statistic for categorical variables while adjusting for age group. We will examine the distributions of continuous variables and use alternative approaches such as transformation or nonparametric methods in cases of violation to the normal distribution assumption. We will also examine the frequency distribution of all categorical variables and adopt exact inference procedures in cases of zero or small cell size. All analyses will be conducted using the SAS 9.4 (SAS Institute, Carey, North Carolina).

Primary Specific Aim: Mixed effects models will be used with repeated RBANS scores collected at baseline, 3 months and 6 months as the outcome measures, group, time and a group by time interaction as independent variables while adjusting for stratification variables and other potential baseline covariates found to be significantly different in univariate comparisons. A significant interaction between group and time would indicate differences in changes of cognitive functions over time among the four groups. Post-hoc comparisons will be conducted following a significant interaction between group and time to compare the effect of the combined training group to the other three groups (attention control, cognitive training only, and exercise only groups) at 3 month for immediate training effect and at 6 month for sustained training effect. Separate mixed effect models will also be used for repeated, Trail Making A&B, and Stroop Color and Word Test scores.

Secondary Specific Aim 1: Separate mixed effects models will be used with repeated measures (SPPB, 2-minutes step, PHQ-9, GAD-7, SF-36 PCS and MCS) as the outcome variables, group, time and interactions between group and time as independent variables while adjusting for stratification variables and other baseline covariates that may be different among the four groups. Significant interactions between group and time in these models would indicate differences in changes of functional outcomes, depressive symptoms, and anxiety levels or quality of life over time among the four groups. Post-hoc analyses will also be conducted following significant interactions in the mixed effects models to compare the combined training group to the other three groups and to determine how early a group difference can be detected and whether the effect extends beyond the training period.

Exploratory Aim 1: Changes in the serum levels of CRP, IL-1, IL-6, IL-8, TNF- α, S-100β, GFAP, BDNF, VEGF, and IGF-1 will be calculated and used as the dependent variables in ANCOVA models with group as the independent variable and adjusting for stratification variables and baseline covariates that are

found to be different among the groups in univariate comparisons. Post-hoc comparisons will be used following a significant group effect to compare biomarker levels in the combined training group to the other three groups.

Missing Data: Two types of missing data are anticipated in this trial. The first is due to death during follow-up. Our previous studies on ICU survivors have shown that most post-ICU deaths happen within the first 30 days of discharge. We do not expect rates of death to differ among the four randomized groups. The second type of missing data comes from participant withdrawal during follow-up. There may be a potential for higher rate of withdrawal in those enrolled in the intervention groups than in the control group. The mixed effects model approach we propose to use is robust under the missing at random assumption, i.e. the probability of missing is unrelated to the missing observations. We will compare baseline characteristics of subjects with missing outcomes due to death or dropout during follow-up to detect potential violation to the missing at random assumption. Intention to treat analysis will be used in all models. Further sensitivity analyses will be performed using various methods of imputation or a full parametric likelihood approach assuming various patterns of missing data.[131]

Sample Size and Power: Cognitive training had been found to have a moderate effect size of approximately 0.5 SD and the combined training was found to have a larger effect size of 0.9 SD when comparing to the control group in healthy elderly subjects.[102,103,132] Assuming effect sizes of 0.4 SD in the cognitive training only group and the exercise only groups at 3 and 6 month post baseline compared to the attention control group and effect size of 0.8 SD in the combined training group at 3 and 6 month post baseline compared to the attention group, a sample size of 60 patients in each group will yield 83% power at detecting a significant group by time interaction in a mixed effect model adjusting for correlations of 0.2 for outcomes measured 3 month apart and correlations of 0.1 for outcomes measured 6 month apart at α=0.05. The power estimation was conducted using the GLMPower procedure in SAS. To further assume that 30% patients may miss some post-baseline assessments, we will need to enroll a total of 344 patients into the study (86 patients per group). Outcomes in Secondary Aim 1 will also have 83% power to detect effect sizes similar to those described for the Primary Aim. For Secondary Aim 2, we will have 81.7% power to detect an overall treatment effect in changes in biomarkers with effect sizes of 0.31 SD in the cognitive training only and the exercise only groups and 0.62 SD in the combined training groups at α=0.05 using one-way ANOVA and the Power procedure in SAS.

9. Outcome Measures

[During COVID-19 health crisis, outcomes assessments will be completed via phone; abbreviated measures of cognition, and no measures of physical function will be obtained due to the limitations of phone administration. Blood samples will not be collected.]

Cognitive Outcome Measures: The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)[27] total index score will provide the primary outcome for the trial. Secondary outcomes will be assessed using individual neuropsychological tests of processing speed, executive control, and new learning ability as follows: Trail Making Test Parts A and B (seconds to complete),[120] and Stroop Color and Word Test (interference trial).[121] These measures sample major domains of cognition affected in ICU survivors.[10]

Physical Performance and Cardiovascular fitness: Physical training effects on balance and strength will be assessed via the Short Physical Performance Battery (SPPB),[28] a validated objective assessment. The SPPB yields a performance score of 0-12 (0-4 poor, 5-7 intermediate, 8-12 good). A difference of 1 point indicates a significant change in function. Physical training effects on cardiovascular fitness will be assessed via the 2-minute step test.[29] We have selected the 2-minute step test for cardiovascular fitness because it is a validated measure of aerobic capacity, does not require equipment, and can be used in the home setting.[29] Grip strength with dominant hand will also be measured.

Self-reported Mood and Anxiety symptoms: We will use the Patient Health Questionnaire–9 (PHQ-9)[30,31] and Generalized Anxiety Disorder Scale (GAD-7)[32,33] to determine the impact of the intervention on ICU's survivors' mood and anxiety. The PHQ-9 is a nine-item depression scale with a total score from 0 to 27 and the GAD-7 is a seven-item anxiety scale with a total score from 0 to 21. Both of these scales are derived from the Patient Health Questionnaire, have good internal consistency, and test–retest reliability as well as convergent, construct, criterion, procedural and factorial validity for the diagnosis of major depression and general anxiety disorder.[30-33]

Self-reported quality of life outcomes: ICU survivors' health–related quality of life will be assessed using the Medical Outcome Study Short Form (SF-36).[34-36] This scale has eight components (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health) that are aggregated into a Physical Component Summary (PCS) and a Mental Component Summary (MCS).[34-36] We will use both the PCS and the MCS as the quality of life outcomes. Changes that differ between groups by 2 or more points on a scale of 0 to 100 have been shown to be clinically or socially meaningful.[36]

Collection of Biological samples: The blood will be collected and stored according to biological samples protocol to maximize sample quality and decrease sample variability due to sample collection and processing techniques. Blood samples will be collected at baseline and at 3 months. The 3-month time-point is chosen because this marks the immediate post-training assessment phase, a point where we expect to see the maximum effect of interventions, improvements in the neurobiology and concomitant biomarker profile. Two tubes (one lavender- and one red- top) will be used to collect 20 ml of blood from each patient. These tubes will then be labeled with pre–printed labels with a de-identified code. To avoid biomarker degradation and platelet activation, these samples will be centrifuged immediately at 3000 x g. The supernatants will be removed and stored in aliquots so that multiple episodes of freezing and thawing will be unnecessary during assay procedures. An additional 4ml fresh blood will be collected at Baseline and/or 3 months for DNA extraction. The tubes will be placed on dry ice for transport. Once at the storage facility, the aliquots will be placed in pre-labeled boxes and the boxes stored at -80 ^{o}C.

Biomarkers: The conceptual model holds that the cognitive benefit of combined physical exercise and cognitive training is achieved through modulation of physiologic process (Secondary specific aim 2). As a result, we will measure circulating levels of the pro-inflammatory cytokines (IL-1, 6, 8, TNF-α); the acute-phase reactant (CRP); neurotrophic factors (IGF-1, VEGF, BDNF); and markers of glial dysfunction and astrocyte activation (S-100β, GFAP). Serum marker quantifications will be performed in duplicates using pre-validated commercially available assay kits. Each kit employs 1-2 positive control(s) of known concentration and a negative control in every run. We will follow manufacturer provided established protocols for these assays.

APOE Collection and Assay: Genomic DNA will be extracted from blood samples using the DNeasy Blood & Tissue Kit (Qiagen, Inc., Valencia, CA) according to the manufacturer's protocol. Approximately 50ng of genomic DNA will be used for amplification. APOE genotypes will be determined by restriction enzyme digestion of amplified DNA.[123]

Plasma amyloid-β Aβ42/Aβ40: As number of recent studies have reported that a low ratio of plasma amyloid-β Aβ42 over Aβ40 is associated with increased Alzheimer's disease risk and greater cognitive decline,[124,125] we will explore the effect of a low ratio on our intervention. Samples will be analyzed using standard analysis techniques.[124]

Acute Health Care Utilization: In addition to patient reported emergency department and hospital admission data, we will use the local data-warehouse to capture all of the data needed to determine utilization. Furthermore, we will also use the data from the Indiana Network for Patient Care (INPC) to complement any data use outside of our health system. INPC is the primary health information exchange in the state of Indiana and it provides data for acute care services from all of the health care systems within the state of Indiana. We will determine the number of emergency department visits and the number of re-hospitalizations during follow-up as well as the diagnoses associated with each utilization episode.

Other data collection: At hospital discharge and baseline we will measure subject's age, race, gender, years of education, visual acuity, height, weight, body mass index, heart rate, blood pressure, Charlson Comorbidity Index,[126] APACHE II score,[127] activities and instrumental activities of daily living (ADL/IADL) prior to ICU admission through Katz and Lawton scales,[128,129] cognitive status prior to admission through IQCODE,[130] cognitive and physical activity levels prior to admission, admission and discharge diagnoses, duration of mechanical ventilation, duration of delirium, ICU/hospital length of stay, and ICU and in-home medications. These measures will be used to describe the ICU survivors characteristics and as potential confounders.

Study team will request physical therapy, occupational therapy, and speech therapy records from rehab facilities to identify physical and cognitive training received between ICU discharge and study intervention for subjects discharged to a facility.

10. Privacy/Confidentiality Issues

Loss of confidentiality is a risk in this type of data collection. Our data management and quality assurance techniques have proven effective in past trials in maintaining confidentiality and all study personnel have completed training in Human Subjects Research and HIPAA standards.

11. Follow-up and Record Retention

This is a five-year study and study documents will be destroyed seven years after the end date of the study.

12. References:

1. Inouye SK. Predisposing and precipitating factors for delirium in hospitalized older patients. *Dement. Geriatr. Cogn. Disord.* 1999;10:393–400.
2. Inouye SK. Delirium in hospitalized older patients: recognition and risk factors. *J. Geriatr. Psychiatry Neurol.* 1998;11:118–125.
3. US Department of Health and Human Services. CMS statistics. Washington, DC: Centers for Medicare and Medicaid Services; 2004. (publication no. 03445)
4. Lin SM, Liu CY, Wang CH, et al. The impact of delirium on the survival of mechanically ventilated patients. *Critical care medicine.* Nov 2004;32(11):2254-2259.
5. Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA : the Journal of the American Medical Association.* Apr 14 2004;291(14):1753-1762.
6. Ely EW, Gautam S, Margolin R, et al. The impact of delirium in the intensive care unit on hospital length of stay. *Intensive care medicine.* Dec 2001;27(12):1892-1900.
7. Milbrandt EB, Deppen S, Harrison PL, et al. Costs associated with delirium in mechanically ventilated patients. *Critical care medicine.* Apr 2004;32(4):955-962.
8. van den Boogaard M, Schoonhoven L, Evers AW, van der Hoeven JG, van Achterberg T, Pickkers P. Delirium in critically ill patients: impact on long-term health-related quality of life and cognitive functioning. *Critical care medicine.* Jan 2012;40(1):112-118..
9. Khan BA, Lasiter S, Boustani MA. Critical Care Recovery Center. Making the case for an innovative collaborative care model for ICU survivors. . *American Journal of Nursing.* 2015 March; 115 (3); 24-31
10. Pandharipande PP, Girard TD, Jackson JC, et al. Long-term cognitive impairment after critical illness. *The New England journal of medicine.* Oct 3 2013;369(14):1306-1316.
11. Girard TD, Jackson JC, Pandharipande PP, et al. Delirium as a predictor of long-term cognitive impairment in survivors of critical illness. *Crit Care Med* 2010; 38: 1513-1520
12. Guerra C, Linde-Zwirble WT, Wunsch H. Risk factors fro dementia after critical illness in elderly Medicare beneficiaries. *Crit Care* 201216: R233
13. Needham DM, et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. *Crit Care Med* 2012; 40(2):502-9.
14. Khan B, Zawahiri M, Campbell N, Boustani M. Biomarkers for Delirium- A Review. *Journal of American Geriatrics Society.* Nov 2011. 59:S256-S261
15. Cerejeira J, Firmino H, Vaz-Serra A, Mukaetova-Ladinska EB. The neuroinflammatory hypothesis of delirium. *Acta Neuropathol*. 2010 Jun;119(6):737-54
16. Hopkins RO, Suchyta MR, Farrer TJ, Needham D. Improving post-intensive care unit neuropsychiatric outcomes. *AJRCCM* 2012. 186 (12) 1220-1228
17. Girard TD. Dittus RS, Ely EW. Critical illness brain injury. *Annu Rev Med* 2016. 67: 497-513
18. Wilcox ME, Brummel NE, Archer K et al. Cognitive dysfunction in ICU patients: risk factors, predictors, and rehabilitation interventions. *Crit Care Med* 2013; 41: S81-S98
19. Campbell N, Khan B, Farber M, et al. Improving the care of delirium in the ICU: Design of a pragmatic study. *Trials.* 2011 Jun 6; 12:139.
20. Khan BA, Guzman O, Campbell NL et al. Comparison and agreement between two sedation scales; Richmond Agitation Sedation Scale and Sedation Agitation Scale in evaluating patients' eligibility for Delirium assessment in the Intensive Care Unit. *CHEST.* 2012 Jul; 142(1):48-54.
21. Khan BA, Farber MO, Campbell NL et al. S-100 calcium binding protein as a biomarker for delirium duration in the intensive care unit. An exploratory analysis. *IJGM.* 2013:2 (6) 855-861.

22. Khan BA, Calvo-Ayala E, Campbell NL, et al. Clinical Decision Support System and Incident Delirium among Cognitively Impaired Hospitalized Older Adults Transferred to the Intensive Care Unit. *Am J Crit Care.* 2013 May; 22(3):257-62.
23. Khan BA, Fadel WF, Tricker JL, et al. Effectiveness of Implementing a Wake Up and Breathe Program on Sedation and Delirium in the ICU. *Critical care medicine.* 2014 Dec;42(12):e791-e795.
24. Khan BA, Perkins A, Hi SL, et al. Relationship between African-American Race and Delirium in the Intensive Care Unit. *CCMED* 2016. In press.
25. Wang S, Lasiter S, Zarzaur B, Campbell T, Boustani M, Khan B. Critical Care Recovery Center (CCRC): Can a Geriatric Model of Care Guide Recovery of ICU Survivors? *Best Practices in Mental Health*. 2016; 12(2) (In press)
26. Oles SK, Stephens N, Bubp CA, Shepard P, Campbell T, Boustani MA, Khan BA. Development and Implementation of a Novel Cognitive Rehabilitation Protocol for Intensive Care Unit Survivors. *Am J Respir Crit Care Med* 191;2015:A4504
27. Randolph C, Tierney MC, Mohr E, et al. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): Preliminary Clinical Validity. *J Clin Exp Neuropsyc.* 1998;Vol. 20, No. 3:310-319.
28. Guralnik JM, Ferrucci L, Pieper CF, et al. Lower extremity function and subsequent disability: Consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences.* Apr 2000; 55(4):M221-231
29. Rikli R, Jones CJ. *American College of Sports Medicine: Senior Fitness Test Manual.* Human Kinetics2001
30. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *Journal of general internal medicine.* Sep 2001; 16(9):606-613, PMCID: PMC1495268.
31. Lowe B, Unutzer J, Callahan CM, Perkins AJ, Kroenke K. Monitoring depression treatment outcomes with the patient health questionnaire-9. *Medical care.* Dec 2004; 42(12):1194-1201.
32. Kroenke K, Spitzer RL, Williams JB, Monahan PO, Lowe B. Anxiety disorders in primary care: prevalence, impairment, comorbidity, and detection. *Annals of internal medicine.* Mar 6 2007; 146(5):317-325.
33. Spitzer RL, Kroenke K, Williams JB, Lowe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Archives of internal medicine.* May 22 2006; 166(10):1092-1097.
34. Ware JE, Sherbourne CD. The MOS 36 item Short-Form Health Survey. *Med Care*. 1992; 30(6): 473-481.
35. Ware JE, Kosinski M, Keller SD. SF-36 Physical and Mental Health Summary Scales: A User's Manual. Boston MA: The Health Institute: New England Medical Center; 1994.
36. Ware JE, Bayliss MS, Rogers WH et al. Differences in 4–year health outcomes for elderly and poor, chronically ill patients treated in HMO and fee-for-service systems; results from the medical outcomes study. *JAMA*, 1996; 276(13): 1039-1047
37. American Psychiatric Association : Diagnostic and statistical manual of mental disorders. text revision. 2000.
38. Morandi A, Pandharipande PP, Jackson JC, Bellelli G, Trabucchi M, Ely EW. Understanding terminology of delirium and long-term cognitive impairment in critically ill patients. *Best practice & research. Clinical anaesthesiology.* Sep 2012;26(3):267-276.
39. Pisani MA, Kong SY, Kasl SV, Murphy TE, Araujo KL, Van Ness PH. Days of delirium are associated with 1-year mortality in an older intensive care unit population. *American journal of respiratory and critical care medicine.* Dec 1 2009;180(11):1092-1097.

40. Pandharipande PP, Pun BT, Herr DL, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. *JAMA : the journal of the American Medical Association.* Dec 12 2007;298(22):2644-2653.
41. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet.* May 30 2009;373(9678):1874-1882.
42. Brummel NE, Jackson JC, Pandharipande PP, et al. Delirium in the ICU and subsequent long-term disability among survivors of mechanical ventilation. *Critical care medicine.* Feb 2014;42(2):369-377.
43. Gibson V. Update on NICE guidance CG83 Rehabilitation after Critical Illness. *Nursing in critical care.* Jul-Aug 2010;15(4):222-223.
44. Rothenhausler HB, Ehrentraut S, Stoll C et al. The relationship between cognitive performance and employment and health status in long-term survivors of acute respiratory distress syndrome: results of an exploratory study. *Gen Hosp Psychiatry* 2001. 23:88-94
45. Jackson JC, Pandharipande PP, Girard TD et al. Depression, Posttraumatic Stress Disorder, and Functional Disability in Survivors of Critical Illness: results from the BRAIN ICU (Bringing to light the Risk Factors And Incidence of Neuropsychological dysfunction in ICU survivors) Investigation: A Longitudinal Cohort Study. *Lancet Respir Med*. 2014 May ; 2(5): 369–379
46. Hofer S, Bopp C, Hoerner C, et al. Injury of the blood brain barrier and up-regulation of ICAM-1 in polymicrobial sepsis. *J Surg Res*. 2008;146:276-281
47. Nishioku T, Sohgu S, Takata F. et al. Detachment of brain pericytes from the basal lamina is involved in disruption of the blood-brain barrier caused by lipopolysaccharide-induced sepsis in mice. *Cell Mol Neurobiol*. 2009;29(3):309-316.
48. Semmler A, Okulla T, Sastre M, Dumitrescu-Ozimek L. Heneka M. Systemic inflammation induces apoptosis with variable vulnerability of different brain regions. *J Chem Neuroanat*. 2005;30:144-157.
49. Block ML, Zecca L, Hong JS. Microglia mediated neurotoxicity: uncovering the molecular mechanisms. *Nat Rev Neuroscience*. 2007; 8(1):57-69.
50. Cardona AE, Li M, Liu L, Savarin C, Ransohoff RM. Chemokines in and out of the central nervous system: much more then chemotaxis and inflammation. *J Leukoc Biol*. 2008;84(3):587-94.
51. Pinto SS, Gottfried C, Mendez A, et al. Immunocontent and secretion of S100B in astrocyte cultures from different brain regions in relation to morphology, *FEBS Letters.* 2000;486:203–7.
52. Porter JT, McCarthy KD. Astrocytic neurotransmitter receptors in situ and in vivo. *Progress Neurobiol.* 1997;51:439–455.
53. Santamaria-Kisiel L, Rintala-Dempsey AC, Shaw GS. Calcium-dependent and -independent interactions of the S100 protein family, *Biochem. J.* 2006;396:201–14.
54. Korley FK, Diaz-Arrastia R, Wu AHB et al. Circulating Brain-Derived Neurotrophic Factor Has Diagnostic and Prognostic Value in Traumatic Brain Injury. *JOURNAL OF NEUROTRAUMA* 33:215–225 (January 15, 2016)
55. Hshieh TT, Fong TG, Marcantonio ER, Inouye SK. Cholinergic deficiency hypothesis in delirium: a synthesis of current evidence. *J Gerontol A Biol Sci Med Sci*. 2008;63(7):764-72
56. Morandi A, Gunther ML, Pandharipande PP, et al. Insulin-like growth factor-1 and delirium in critically ill mechanically ventilated patients: a preliminary investigation. *Int Psychogeriatri*. 2011 Sep;23(7):1175-81.
57. Grandi C, Tomasi CD, Fernandes K, et al. Brain-derived neurtrophic factor and neuron-specific enolase, but not S100 β levels are associated to the occurrence of delirium in intensive care unit patients. *J Crit Care*. 2011;26:133-7

58. Broadhurst C, Wilson K. Immunology of delirium: new opportunities for treatment and research. *British Journal of Psychiatry*. 2001;179:288-89.
59. Demarinis L, Mancini D, Valle A. Hypothalamic derangement in traumatized patients: growth hormone and prolactin reponse to thyrotropin-releasing hormone and GHRH. *Clinical Endocronology.* 1999;50:741-47.
60. Lackey BR, Gray SL, Hendricks DM. Actions and interactions of the IGF system in Alzheimer's disease: review and hypothesis. *Growth Horm IGF Res.* 2000 Feb;10(1):1-13.
61. Cohen-Cory, S., Kidane, A. H., Shirkey, N. J., and Marshak, S. (2010). Brain-derived neurotrophic factor and the development of structural neuronal connectivity. Dev. *Neurobiol*. 70, 271–288.
62. Huang, E. J. and Reichardt, L. F. (2001). Neurotrophins: roles in neuronal development and function. *Annu. Rev. Neurosci.* 24, 677– 736.
63. Van Gool WA, van de beek D, Eikelenboom P. Systemic inflammation and delirium: When cytokine collide. Lancet 2010; 375: 773-775
64. Kempermann G, Fabel K, Ehninger D, et al. Why and how physical activity promotes experience-induced brain plasticity. *Frontiers in neuroscience.* 2010;4:189.
65. Erickson KI, Kramer AF. Aerobic exercise effects on cognitive and neural plasticity in older adults. *British journal of sports medicine.* Jan 2009;43(1):22-24.
66. Fabel K, Wolf SA, Ehninger D, Babu H, Leal-Galicia P, Kempermann G. Additive effects of physical exercise and environmental enrichment on adult hippocampal neurogenesis in mice. *Frontiers in neuroscience.* 2009;3:50.
67. Ding YH, Luan XD, Li J, Rafols JA, Guthinkonda M, Diaz FG, Ding Y. Exercise-induced overexpression of angiogenic factors and reduction of ischemia/reperfusion injury in stroke. *Curr Neurovasc Res* 2004;1: 411–420.
68. Eadie BD, Redila VA, Christie BR. Voluntary exercise alters the cytoarchitecture of the adult dentate gyrus by increasing cellular proliferation, dendritic complexity, and spine density. *J Comp Neurol* 2005;486:39–47.
69. van Praag H, Shubert T, Zhao C, Gage FH. Exercise enhances learning and hippocampal neurogenesis in aged mice. *J Neurosci* 2005;25:8680–8685.
70. loughman M, Granter-Button S, Chernenko G, Tucker BA, Mearow KM, Corbett D. Endurance exercise regimens induce differential effects on brain-derived neurotrophic factor, synapsin-I and insulin- like growth factor I after focal ischemia. *Neuroscience* 2005;136:991– 1001.
71. Vaynman S, Ying Z, Gomez-Pinilla F. Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition. *Eur J Neurosci* 2004;20:2580–2590.
72. Churchill JD, Galvez R, Colcombe S, Swain RA, Kramer AF, Greenough WT. Exercise, experience and the aging brain. *Neurobiol Aging* 2002; 23:941–955.
73. Michael Gleeson, Nicolette C. Bishop, David J. Stensel et al.Th e anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. *Nature Reviews, Immunology* 2011. 607-615
74. Colcombe SJ, Erickson KI, Scalf PE, Kim JS, Prakash R, McAuley E, Elavsky S, Marquez DX, Hu L, Kramer AF. Aerobic exercise training increases brain volume in aging humans. *J Gerontol A Biol Sci Med Sci* 2006;61:1166–1170.
75. Erickson KI, Prakash RS, Voss MW, Chaddock L, Hu L, Morris KS, White SM, Wojcicki TR, McAuley E, Kramer AF. Aerobic fitness is associated with hippocampal volume in elderly humans. *Hippocam- pus* 2009;19:1030–1039.
76. Erickson KI, Raji CA, Lopez OL, Becker JT, Rosano C, Newman AB, Gach HM, Thompson PM, Ho AJ, Kuller LH. Physical activity pre- dicts gray matter volume in late adulthood: the Cardiovascular Health Study. *Neurology* 2010;75:1415–1422.
77. Marks BL, Katz LM, Styner M, Smith JK. Aerobic fitness and obesity: relationship to cerebral

white matter integrity in the brain of active and sedentary older adults. *Br J Sports Med* 2011;45:1208–1215.
78. Marks BL, Madden DJ, Bucur B, Provenzale JM, White LE, Cabeza R, Huettel SA. Role of aerobic fitness and aging on cerebral white matter integrity. *Ann N Y Acad Sci* 2007;1097:171–174.
79. Voss MW, Nagamatsu LS, Liu-Ambrose T, Kramer AF. Exercise, brain, and cognition across the life span. *J Appl Physiol.* Nov 2011;111(5):1505-1513.
80. Ribeiro F, Alves AJ, Duarte JA, Oliveira J. Is exercise training an effective therapy targeting endothelial dysfunction and vascular wall inflammation? *International journal of cardiology.* Jun 11 2010;141(3):214-221.
81. Pressler SJ, Titler M,Koelling TM et al. Nurse-Enhanced Computerized Cognitive Training Increases Serum Brain-Derived Neurotropic Factor Levels and Improves Working Memory in Heart Failure. *Journal of Cardiac Failure* 2015. Vol. 21 No. 8
82. Ball K, Berch DB, Helmers KF, et al. Effects of cognitive training interventions with older adults: a randomized controlled trial. *JAMA : the journal of the American Medical Association.* Nov 13 2002;288(18):2271-2281.
83. Ball K, Edwards JD, Ross LA. The impact of speed of processing training on cognitive and everyday functions. *The journals of gerontology. Series B, Psychological sciences and social sciences.* Jun 2007;62 Spec No 1:19-31.
84. Ball KK, Beard BL, Roenker DL, Miller RL, Griggs DS. Age and visual search: expanding the useful field of view. *Journal of the Optical Society of America. A, Optics and image science.* Dec 1988;5(12):2210-2219.
85. Smith GE, Housen P, Yaffe K, et al. A cognitive training program based on principles of brain plasticity: results from the Improvement in Memory with Plasticity-based Adaptive Cognitive Training (IMPACT) study. *Journal of the American Geriatrics Society.* Apr 2009;57(4):594-603.
86. Willis SL, Tennstedt SL, Marsiske M, et al. Long-term effects of cognitive training on everyday functional outcomes in older adults. *JAMA : the journal of the American Medical Association.* Dec 20 2006;296(23):2805-2814
87. Cicerone KD, Langenbahn DM, Braden C, et al. Evidence-based cognitive rehabilitation: updated review of the literature from 2003 through 2008. *Archives of physical medicine and rehabilitation.* Apr 2011;92(4):519-530.
88. Unverzagt FW, Kasten L, Johnson KE, et al. Effect of memory impairment on training outcomes in ACTIVE. *Journal of the International Neuropsychological Society : JINS.* Nov 2007;13(6):953-960.
89. Li, H.J., et al., Cognitive intervention for persons with mild cognitive impairment: A meta-analysis*. Ageing Research Reviews*, 2011. 10(2): p. 285-296
90. Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: a meta-analytic study. *Psychological science.* Mar 2003;14(2):125-130.
91. Baker LD, Frank LL, Foster-Schubert K, et al. Effects of aerobic exercise on mild cognitive impairment: a controlled trial. *Archives of neurology.* Jan 2010;67(1):71-79.
92. Colcombe SJ, Kramer AF, Erickson KI, et al. Cardiovascular fitness, cortical plasticity, and aging. *Proceedings of the National Academy of Sciences of the United States of America.* Mar 2 2004;101(9):3316-3321.
93. Colcombe SJ, Erickson KI, Scalf PE, et al. Aerobic exercise training increases brain volume in aging humans. *The journals of gerontology. Series A, Biological sciences and medical sciences.* Nov 2006;61(11):1166-1170.
94. Barnes DE, Blackwell T, Stone KL, Goldman SE, Hillier T, Yaffe K. Cognition in older women: the importance of daytime movement. *J Am Geriatr Soc* 2008;56:1658–1664.
95. Laurin D, Verreault R, Lindsay J, MacPherson K, Rockwood K. Physical activity and risk of

cognitive impairment and dementia in elderly persons. *Arch Neurol* 2001;58:498–504.
96. Palleschi L, Vetta F, De Gennaro E, Idone G, Sottosanti G, Gianni W, Marigliano V. Effect of aerobic training on the cognitive performance of elderly patients with senile dementia of Alzheimer type. *Arch Gerontol Geriatr* 1996;22:47–50.
97. Pyoria O, Talvitie U, Nyrkko H, Kautiainen H, Pohjolainen T, Kasper V. The effect of two physiotherapy approaches on physical and cog- nitive functions and independent coping at home in stroke rehabili- tation. A preliminary follow-up study. *Disabil Rehabil* 2007;29:503– 511.
98. Quaney BM, Boyd LA, McDowd JM, Zahner LH, He J, Mayo MS, Macko RF. Aerobic exercise improves cognition and motor function poststroke. *Neurorehabil Neural Repair* 2009;23:879–885.
99. Ozdemir F, Birtane M, Tabatabaei R, Kokino S, Ekuklu G. Comparing stroke rehabilitation outcomes between acute inpatient and non- intense home settings. *Arch Phys Med Rehabil* 2001;82:1375–1379.
100. Etnier JL, Berry M. Fluid intelligence in an older COPD sample after short- or long-term exercise. *Med Sci Sports Exerc* 2001;33:1620–1628.
101. Grealy MA, Johnson DA, Rushton SK. Improving cognitive function after brain injury: the use of exercise and virtual reality. *Arch Phys Med Rehabil* 1999;80:661–667.
102. Fabre, C., et al., Improvement of cognitive function by mental and/or individualized aerobic training in healthy elderly subjects*. International Journal of Sports Medicine*, 2002. 23(6): p. 415-421.
103. Oswald, W.D., et al., Differential effects of single versus combined cognitive and physical training with older adults: The SimA study in a 5-year perspective*. European Journal of Ageing*, 2006. 3: p. 179-1
104. Legault, C., et al., Designing clinical trials for assessing the effects of cognitive training and physical activity interventions on cognitive outcomes: The Seniors Health and Activity Research Program Pilot (SHARP-P) Study, a randomized controlled trial*. BMC Geriatrics*, 2011. 11(1): p. 27.
105. Jackson JC, Ely EW, Morey MC, et al. Cognitive and physical rehabilitation of intensive care unit survivors: results of the RETURN randomized controlled pilot investigation. *Critical care medicine.* Apr 2012;40(4):1088-1097
106. Hall AK, Stellefson M, Bernhardt JM. Healthy Aging 2.0: the potential of new media and technology. *Preventing chronic disease.* 2012;9:E67.
107. Khan B, Perkins A, Gao S, Boustani M. Pharmacological management of delirium (PMD) trial. *AJRCCM* 2016: A7801
108. Mosher C, Sheikh A, Gutteridge D, Gliroy G, Khan BA. Risk factors associated with post ICU psychiatric disorders in ICU delirium survivors. *AJRCCM* 2016: A5256
109. Ely EW, Margolin R, Francis J, et al. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). *Critical care medicine.* Jul 2001;29(7):1370-1379
110. Skinner H. The Drug Abuse Screening Test. *Addict Behav* 1982. 7: 363-371
111. Davis N, Pohlman A, Gehlbach B, et al. Improving the process of informed consent in the critically ill. *JAMA* 2003; 289:1963-1968.
112. Garber, C.E., et al., Quantity and Quality of Exercise for Developing and Maintaining Cardiorespiratory, Musculoskeletal, and Neuromotor Fitness in Apparently Healthy Adults: Guidance for Prescribing Exercise*. Medicine and Science in Sports and Exercise*, 2011. 43(7): p. 1334-1359.
113. Nelson, M.E., et al., Physical Activity and Public Health in Older Adults: Recommendation from the American College of Sports Medicine and the American Heart Association*. Medicine and Science in Sports and Exercise*, 2007. 39(8): p. 1435-1445.

114. Seynnes, O., et al., Physiological and functional responses to low-moderate versus high-intensity progressive resistance training in frail elders*. Journals of Gerontology Series a-Biological Sciences and Medical Sciences,* 2004. 59(5): p. 503-509.
115. Pahor, M., et al., Effects of a physical activity intervention on measures of physical performance: Results of the Lifestyle Interventions and Independence for Elders Pilot (LIFE-P) study. *Journals of Gerontology Series a-Biological Sciences and Medical Sciences,* 2006. 61(11): p. 1157-1165.
116. Thompson, P.D., et al., Exercise and acute cardiovascular events placing the risks into perspective - A scientific statement from the American Heart Association council on nutrition, physical activity, and metabolism - In collaboration with the American college of sports medicine. *Circulation*, 2007. 115(17): p. 2358-2368.
117. Minns Lowe CJ, Wilson MS, Sackley CM, Barker KL. Blind outcome assessment: the development and use of procedures to maintain and describe blinding in a pragmatic physiotherapy rehabilitation trial. *Clin Rehabili*. 2011. 25(3):264-74
118. Boutron IS, Guittet L, Estellat C et al. Reporting methods of blinding in randomized trials assessing nonpharmacological treatments. *PLoS Med* 2007. 4(2): e61
119. Wechsler, D., *Wechsler Adult Intelligence Scale*–Fourth Edition. 2008, San Antonio, TX: Pearson.
120. Reitan, R.M. and D. Wolfson, The Halstead-Reitan Neuropsychological Test Battery: theory, and clinical interpretation. 1993, South Tucson, Arizona: Neuropsychology Press.
121. Golden, C.J., Stroop Color and Word Test. 1978, Chicago, IL: Stoelting.
122. Rey, A., L'examen psychologique dans les cas d'encephalopathie traumatique. Archives de Psychologie, 1941. 28: p. 286-340.
123. Hixson, J.E. and D.T. Vernier, Restriction isotyping of human apolipoprotein-e by gene amplification and cleavage with hhai. *Journal of Lipid Research*, 1990. 31(3): p. 545-548.
124. Chouraki V, Beiser A, Younkin L, et al. Plasma amyloid-beta and risk of Alzheimer's disease in the Framingham Heart Study. *Alzheimers Dement.* Mar 2015;11(3):249-257 e241.
125. Koyama A, Okereke OI, Yang T, Blacker D, Selkoe DJ, Grodstein F. Plasma amyloid-beta as a predictor of dementia and cognitive decline: a systematic review and meta-analysis. *Arch Neurol.* Jul 2012;69(7):824-831.
126. Charlson ME, Sax FL, MacKenzie CR, Fields SD, Braham RL, et al. Resuscitation: how do we decide? A prospective study of physicians' preferences and the clinical course of hospitalized patients. *J Am Med Assoc.* 1986; 255:1316-1322.
127. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med*. 1985; 13:818-829.
128. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged. The index of Adl: A standardized measure of biological and psychosocial function. *J Am Med Assoc.* 1963;185:914-919.
129. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist.* 1969; 9:179-186.
130. Jorm AF, Jacomb PA. The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): socio-demographic correlates, reliability, validity and some norms. *Psychol Med* 1989; 19:1015-1022.
131. Little RJA, Rbin DB. *Statistical Analysis with missing Data.* 2002, 2nd Edition. New York: John Wiley
132. Valenzuela M, Sachdev P. Can cognitive exercise prevent the onset of dementia? Systematic review of randomized clinical trials with longitudinal follow-up. *The American journal of geriatric psychiatry: official journal of the American Association for Geriatric Psychiatry.* Mar 2009;17(3):179-187

133. American College of Sports Medicine. (2017) *ACSM's guidelines for exercise testing and prescription 10th Edition*. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins Health.