Early Cognitive Intervention in Delirium (ECID)

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1.0 Background

Delirium is a form of acute brain failure that afflicts 17% of older emergency department (ED) and 25% of older hospitalized patients.[1-4] Based upon our work and the work of others, delirium is associated with accelerated long-term cognitive decline particularly in patients with Alzheimer's disease and related dementias (ADRD).[5-17] Unfortunately, most delirium interventions have been ineffective in improving outcomes.[18-20]

Cognitive training and rehabilitation may be a feasible intervention to preserve long-term cognition in delirious patients.[21] Cognitive training's purpose is to prevent and restore cognitive deficits acquired during the delirium episode. Cognitive training is the "guided practice on a set of standard tasks designed to reflect particular cognitive functions."[22,23] Within a cognitive task, there is a range of difficulty levels that can be tailored to each individual, with the goal being to "stress" the abilities of individuals enough that they will be challenged but not overwhelmed.[23] Cognitive rehabilitation's goal is to improve performance in everyday life activities and in daily functioning rather than on cognitive tests.[24] It seeks to help individuals by establishing new cognitive activity patterns or compensatory mechanisms for impaired neurological systems. This is achieved by building on and extending the patients' existing cognitive strengths[25-28] and developing effective strategies to compensate for their newly acquired cognitive deficits.[26,29,30] Because GMT is also cognitively demanding, it may also help restore cognitive deficits[31] such as attention and working memory.[32]

Cognitive training/rehabilitation or any delirium intervention is unlikely to be effective in all delirious patients. Specific delirium phenotypes may be associated with a higher risk of accelerated cognitive decline and may benefit more from intervention. Delirium is a complex syndrome that can vary by psychomotor activity, arousal, severity, etiology, and pathophysiology. Based upon these observable delirium heterogeneity factors, overarching delirium phenotypes (or latent classes) may exist which can be uncovered using statistical techniques such as latent class analysis (LCA).[33]

2.0 Rationale and Specific Aims

Currently, there is no universally accepted delirium intervention that has been shown to prevent long-term cognition decline. Older adults who are acutely ill do not typically engage in cognitive activities especially when delirious, and this further hastens the cognitive decline during hospitalization.[34,35] Cognitive training during hospitalization and cognitive rehabilitation post-hospital discharge may attenuate delirium's deleterious effect on long-term cognition. The cognitive intervention, however, has not been rigorously evaluated in hospitalized older patients with delirium. Furthermore, its mechanisms also remain unknown. The cognitive intervention is also unlikely to be benefit all delirious patients; it may be more effective in a subset of delirious patients with a specific phenotype, but these phenotypes are not well-defined. To address this dearth of data, we propose this study which will enroll 350 older delirious patients with and without ADRD within 12 hours of ED presentation with the following specific aims and hypotheses:

Aim #1: Using a RCT design, determine if early (<24 hours) cognitive training performed twice daily during hospitalization and cognitive rehabilitation performed weekly for 12-weeks post-hospital discharge are associated with improved 4-month global cognition in older delirious patients with and without ADRD. *We hypothesize that early cognitive training and rehabilitation will improve 4-month global cognition in older delirious patients with and without ADRD compared with usual care.*

Aim #2: In a subset of 50 patients, determine if cognitive training and rehabilitation are associated with less disintegration of eloquent brain networks at 4-months as determined by functional magnetic resonance imaging (fMRI) compared with controls. *We hypothesize that*

cognitive training and rehabilitation will lead to improved network connectivity in the frontoparietal cortex compared with controls at 4-months.

Aim #3: Using LCA, identify novel delirium phenotypes (latent classes) based on psychomotor activity, arousal, severity, etiology, and pathophysiological plasma biomarkers (inflammation, endothelial dysfunction, and BBB injury), and explore if they modify early cognitive intervention's effect on 4-month global cognition. *We hypothesize that we will establish three novel delirium phenotypes using LCA and that one phenotype will benefit more from the early cognitive training and rehabilitation intervention.*

3.0 Inclusion/Exclusion Criteria

Table 1 lists the inclusion criteria for Aims #1, #2, and #3. Patients will be included in the study if they are 65 years or older, hospitalized from the ED, can receive cognitive training within 24 hours of ED presentation, and are delirious. We will enroll patients who are 65 years or older, because delirium disproportionately affects older patients, and they are most likely to benefit from our research. Comatose patients will be re-evaluated 1 to 2 hours later. If the coma is persistent, they will be excluded because delirium cannot be assessed for in these patients. Patients who are unable to follow simple commands prior to their acute illness are considered to have end-stage ADRD and may not benefit from our intervention. In addition, our delirium assessment has not been validated for these patients.

Inclusion Criteria	Exclusion Criteria
• 65 years or older • Admitted through the ED • Cognitive training can be initiated within 24 hours of ED presentation • Delirious at enrollment	• Comatose • Not able to follow simple commands or non-verbal prior to the acute illness (end-stage pre-illness ADRD) • Resides in a nursing home • Prisoner • Receiving hospice care • Lives > 100 miles away from the enrolling sites • Non-English speaking • Previously enrolled • Deaf or blind • Intravenous drug, crack or cocaine, or methamphetamine use within the past one year, or any condition that, in the investigator's opinion, makes them an unreliable trial patient or unlikely to complete the trial. • Psychotic disorder or suicidal gesture requiring hospitalization within the past one year • Discharged from the ED

Table 1. Inclusion and Exclusion Criteria for Aims #1 to 3

Additional exclusions exist for Aim #2 (fMRI). Patients who have absolute and relative contraindications to MRI will be excluded:

1) Metal foreign bodies such as shrapnel
2) Cardiac pacemakers or internal cardiac defibrillators
3) Cerebral aneurysm clips
4) Deep brain stimulator
5) Breast expander

6) Ocular, cochlear, and penile implants
7) Drug infusion devices (e.g., insulin pump)
8) Claustrophobia significant enough to require a sedative-hypnotic

In addition, patients will be able to opt-out of the MRI portion of the study. No sedation will be provided prior to the MRI acquisition.

4.0 Enrollment/Randomization

4.1. Screening, Recruitment, and Consent

Screening and recruitment for this study will be performed by clinical trials associates (CTAs) at Vanderbilt University Medical Center and the Tennessee Valley Healthcare System Veterans Affairs Medical Center. The CTAs will screen the electronic ED Whiteboards and admission logs which provide the patient's age, location, and length of stay. Patients who are $\geq$ 65 years old and can receive cognitive training within 24 hours of ED presentation will be approached to determine eligibility using the script in **Appendix A**. While CTAs will approach patients as early as possible, most will be approached after the initial clinical evaluation and management have been completed to prevent any delays in clinical care.

Because delirium is key inclusion and only occurs in 10% of patients,[36] its assessment will be incorporated to the screening process (prior to informed consent) in those who meet the other inclusion criteria and do not have any exclusion criteria. We will use the 4AT (**Appendix U**) for non-mechanically ventilated patients and the or Confusion Assessment for the Intensive Care Unit (CAM-ICU, **Appendix C**) for mechanically ventilated patients which are brief (<1 minute) and pose minimal risk. We have previously incorporated similar brief delirium assessments into the screening process in the DELINEATE study which similarly enrolled older patients with delirium.[37]

If the subject meets eligibility criteria, including the presence of delirium, the CTA will review the informed consent document with the patient and/or their legally authorized representative (LAR). They will describe the proposed study protocol in lay terminology and allow time for questions to be answered. Because patients with delirium may have cognitive impairment significant enough to affect capacity, there is a possibility that the patient may not be capable of providing informed consent. In these cases, informed consent will be obtained from the LAR. The determination of whether or not a patient can provide informed consent will be determined by the study team. They will be trained to determine who is not consentable through clinical judgment and direct patient interaction (**Appendix D**). Patients will be deemed capable of consenting if: 1) they are able to carry a normal adult conversation and 2) they are able to recall aspects of the consent (e.g. Can you tell me what the purpose and risks of the study are?"). The patient will be asked questions about the study to ensure they comprehend study procedures. If they are unable to adequately answer these questions, then consent will be obtained from a LAR.

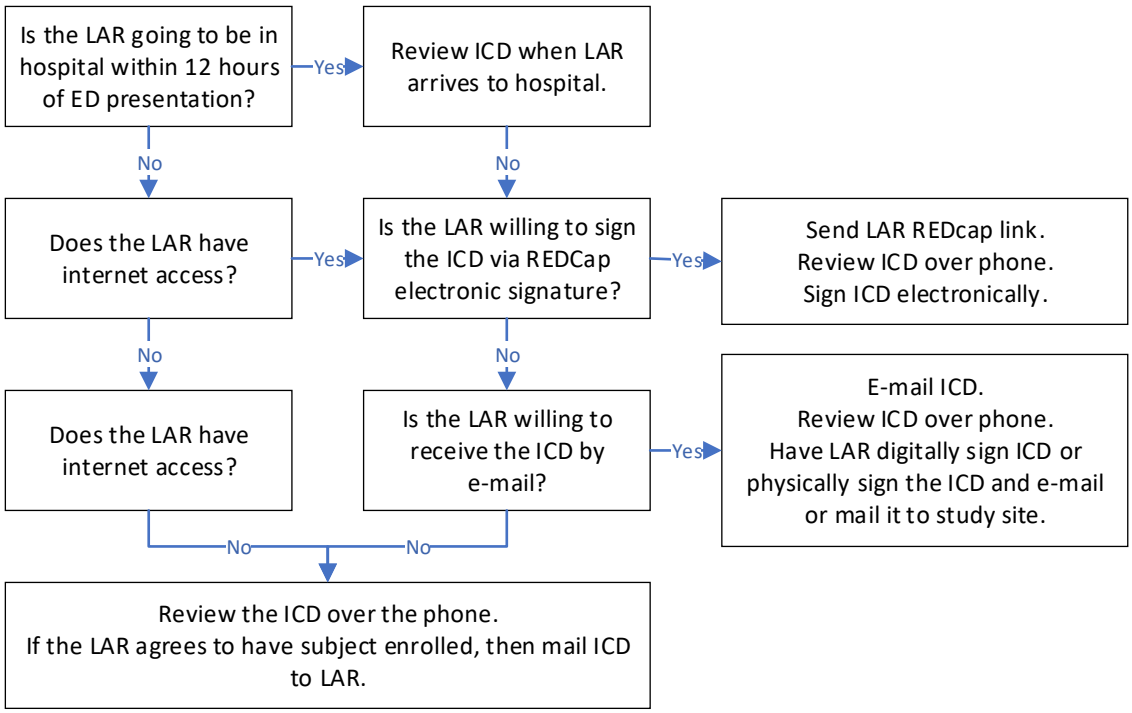
If a LAR is not available in the ED or hospital, then the CTAs will attempt to contact the LAR by phone. If phone contact is made, then CTA will use the LAR script in **Appendix A**. If the LAR is interested in having the patient participate, then we will follow the procedures listed in **Figure 1**. If possible, the research staff will electronically deliver the informed consent document to the LAR via REDCap or e-mail. After receipt, the research staff will review the informed consent document with the LAR. If the LAR agrees to have the patient participate in the study, then they will digitally sign the informed consent document. If they are unable to sign the informed consent document digitally, then they will physically sign the document and return it to Vanderbilt via e-mail or mail. If the LAR does not have internet access or does not want to receive the informed consent electronically, then the research staff will review the informed consent document with the LAR over the phone. If the LAR verbally agrees to have the patient

participate in the study, then the research staff will mail the informed consent document to the LAR with a self-addressed and stamped envelope.

For LARs who are not in the ED and unable to sign the informed consent document digitally, we are requesting an alteration by initiating the study procedures, including randomization, after the LAR verbally agrees for the patient to participate in the study over the phone. This is requested for several reasons:

1) The cognitive training intervention is time sensitive and must be started as soon as possible (<24 hours) to enhance its potency and maximize outcomes.
2) Cognitive intervention is a behavioral, non-pharmacological intervention that poses minimal risk for the patient.
3) Patients with LARs who are unable to come to VUMC within 12-hours of ED presentation and do not have internet access likely represent a vulnerable patient population. These are likely patients who come from disadvantaged socioeconomic backgrounds and/or low education attainment. These patients may most benefit from the intervention, and their exclusion may pose an ethical dilemma.

Every effort will be made for the LAR to sign the informed consent document. If the LAR does not sign the informed consent document, the patient may also sign if he/she regains capacity to provide consent. If no one is able to sign the informed consent document prior to hospital discharge, then all post-hospital study activities (e.g., cognitive rehabilitation at home and follow-up) will not be performed until the informed consent document is signed.



If LAR provides consent for the subject to be enrolled, but does not return a signed ICD, then we will continue with the in-hospital data procedures. We will wait for the LAR to arrive to the hospital to sign the ICD. If the patient regains his/her ability to provide informed consent, we will obtain consent from the patient. If the patient or LAR are unable to sign the informed consent document before hospital discharge, then we will stop any further study activities.

Figure 1. Consent procedures if the legally authorized representative (LAR) is not available to sign the informed consent document (ICD) in the emergency department (ED). If the LAR requests to receive the ICD by e-mail, the script in **Appendix T** will be sent.

A subset of patients (25 cognitive intervention and 25 usual care) will be enrolled in Aim #2. Because of the 1:2 random allocation, one out of two controls will be randomly selected to participate in the fMRI aim. Patients will be able to opt-out of the fMRI portion of the study.

4.2. Randomization

After the patient or authorized surrogate provides informed consent, the cognitive training and rehabilitation intervention versus usual care will be randomly assigned at a 1:2 allocation ratio. Computerized randomization will occur after informed consent has been obtained using a permuted-block randomization scheme with varying block size. We will use adequate allocation concealment using a computer-generated, permuted-block randomization scheme with varying block size. The block size and randomization list will only be known to the independent biostatistician creating the randomization list and will not be shared with trial investigators or any other study personnel, as this information could make it easier to correctly guess the next treatment allocation. This list will be directly uploaded into REDCap's randomization module.[38]

5.0 Study Procedures

5.1 Cognitive Training and Rehabilitation Intervention

Cognitive training and rehabilitation will be administered by a Cognitive Intervention Specialist who will be trained and supervised by Dr. James Jackson (Co-PI). During hospitalization, enrolled patients assigned to the intervention arm will undergo two 20-minute cognitive training sessions daily, 7 days a week. The first session will occur within 24 hours of ED presentation. If an unanticipated delay with the initial cognitive training session occurs (e.g., patient leaves for a procedure or radiographic procedure), the cognitive training will be administered as soon as feasibly possible. The Cognitive Intervention Specialist will primarily administer the cognitive training Monday through Friday from 8A to 4P. If the Cognitive Intervention Specialist is not available (e.g., weekends), then cognitive training will be administered by trained CTAs.

Table 2. Cognitive training during hospitalization

Orientation exercise
Forward and backward digit span
Memory and problem solving
Reverse digit spans
Letters-numbers
Puzzles, games, hobbies

Table 3. Key Components of Goal Management Training

I. Slip-Ups	Overall Introduction; Psychoeducation; Define Goals and Absentminded Slips; Raise Awareness of Consequences of Slips.
II. Stop the Automatic Pilot	Define Automatic Pilot and How Leads to Errors; Learn how to "STOP" Automatic Pilot.
III. The Mental Blackboard	Define the Mental Blackboard; Learn How to "STOP" and Check Mental Blackboard.
IV. State your Goals	Define Goals; Learn How to State Goals; Practice "STOP" and "STATE."
V. Making Decisions	Define Competing Goals; Learn How to Split Goals; Practice "STOP-STATE-SPLIT."
VI. Splitting Tasks into Subtasks	Define Overwhelming Goals; Learn How to Split Goals; Practice "STOP-STATE-SPLIT."
VII. Checking (STOP)	Learn How to Recognize Errors in "STOP-STATE-SPLIT" Cycle; Review How to Use "STOP" to Monitor Daily Tasks; Wrap-Up.

The cognitive training program and its degree of difficulty will be tailored to the patient's current level of cognitive functioning. Patients will be asked to work through progressively more challenging exercises pertaining to orientation, attention, problem solving, and memory (**Table 2**). These cognitive training exercises will be significantly difficult, but when they can be completed easily (>85% mastery), their difficulty will be increased, and this process will be repeated as appropriate. They will also perform puzzles, games, or cognitive tasks related to

their hobbies (based on a brief survey that gauges patient's hobbies and interests) and will participate in simple second language learning (likely Spanish, unless already conversant).[39,40] For patients with severe delirium and are unable to fully engage in the cognitive task, the Cognitive Intervention Specialist will engage them with relatively simpler, less demanding tasks such as reorientation or following simple 1 or 2 step commands. For mechanically ventilated patients (<3% of our cohort), patients will provide written responses. If unable to write, they will be presented with a booklet from which to indicate correct answers for each exercise.[41] To assess uptake, the Cognitive Intervention Specialist will record what tasks were performed and session length for each interaction. The subject's cognitive deficits will also be recorded, especially after the delirium has resolved, to help tailor the cognitive intervention.

Cognitive rehabilitation, using GMT, will be administered in subjects randomized to the intervention arm within 1 week after hospital discharge at their place of residence. We will administer the cognitive rehabilitation in post-acute care facilities (~30% of enrolled subjects) by leveraging our existing relationships with over 40 skilled-nursing facilities from previous and current research studies. The Cognitive Intervention Specialist will administer GMT, representing a meaningful cognitive challenge, using the key components listed in **Table 3** once a week for 12-weeks; each session will last approximately one hour. In summary, GMT will (1) teach patients compensatory strategies such as "stop" techniques [e.g., to "stop and think" about consequences of a decision before making it]; (2) help them to take complex tasks and divide them into manageable subtasks to increase the likelihood of completing the task; and (3) enable them to learn to regain cognitive control when their behavior becomes incompatible with their intended goals. GMT is anchored in "sustained and vigilant attention theory," and it enables patients to actively attend to "higher order" goals critical to functioning. GMT is tailored to the individual needs of the patient. During the initial session, the Cognitive Intervention Specialist will meet with the subject and their family member or caregiver to identify these functional and cognitive deficiencies. Using this information and the cognitive deficits identified during hospitalization, Dr. Jackson and the Cognitive Intervention Specialist will tailor the GMT protocol to the subject's unique disabilities. Thereafter, each session will build on the previous one, so that a "dose" of rehabilitation is delivered. Between each session, patients (with assistance from their caregiver if needed) will also complete relevant homework assignments emphasizing real world applications of the techniques learned. The cognitive rehabilitation will be discontinued if the patient dies, is transitioned to hospice care, is persistently unable to follow simple commands after hospital discharge for 4 consecutive GMT sessions, or withdraws. If the patient is re-hospitalized, we will temporarily stop the intervention. After the subject is discharged from the re-hospitalization, we will reinitiate cognitive rehabilitation until the patient completes a total of 12 sessions.

To assess uptake and fidelity of the cognitive training and rehabilitation, we will record the number of sessions, time taken per session, and what tasks were completed. The Cognitive Intervention Specialist will also assess patient engagement at hospital discharge and at the end of the cognitive rehabilitation intervention using the ***Hopkins Rehabilitation Engagement Rating Scale (Appendix E).***[42] All sessions may be audiotaped (with patient consent). Dr. Jackson will listen to selected cognitive training and GMT sessions within one week of their completion to (1) ensure the continued validity of the intervention of interest and (2) ensure high levels of consistency among all individuals delivering the intervention. Dr. Jackson will provide feedback if the intervention administration appears suboptimal. Initially, Dr. Jackson will review all recorded sessions early in the study. Once the Dr. Jackson feels that the Cognitive Intervention Specialist develops mastery with cognitive training and rehabilitation protocols, spot checks will occur (~5% of recorded sessions). He will also review recorded sessions that may had issues or been problematic.

Due to COVID-19 pandemic, patients may not feel comfortable with face-to-face evaluations even after the pandemic is over. As an alternative, the cognitive training and rehabilitation intervention may be done over videoconferencing (e.g., Skype, Zoom, WebEx, FaceTime, etc.). In addition, patients or their families may not feel comfortable with research staff coming into their place of residence. Patients will have the option to come to the medical center to have their cognitive rehabilitation completed. Post-acute care facilities may also restrict visitation, even after the pandemic is over. We will attempt to do the intervention via videoconferencing in the post-acute care facility case. If not feasible, then cognitive rehabilitation will start after the patient is discharged home. These alternatives will be available to the subject for the entirety of the study. Even when the pandemic is over, some may patients or families or skilled nursing facilities may continue to have these concerns.

5.2. Prospective Data Collection – The data collected prospectively in the ED, hospital, 12-weeks post-hospital discharge, and 4-months are summarized in **Table 4**.

Prospective Data Collection	Source	Duration	ED	Hospital	12-weeks post-discharge*	4-months follow-up
Brief Confusion assessment Method (bCAM, Appendix B)	Patient	1 min	X	X		
Confusion Assessment Method for the Intensive Care Unit (CAM-ICU, Appendix C)	Patient	1 min	X	X		
Delirium Assessment Battery (Appendix G)	Patient	5 min	X	X		
Richmond Agitation Sedation Scale (RASS, Appendix H)	Patient	Observ-ation	X	X		
Delirium Motor Subtyping Scale-4 (DMSS-4, Appendix I)	Patient	Observ-ation	X	X		
Confusion Assessment Method Severity (CAM-S, Appendix J)	Patient	Observ-ation	X	X		
Blood and urine[#]	Patient	5 min	X	X		
Demographics, education, substance abuse, sensory impairment, recent hospitalization, region of residence, highest occupation, height, weight, hospitalization in past 6-months.	Patient / Informant	5 min	X			
Quick Dementia Rating Scale (QDRS, Appendix K)	Informant	3 min	X			
Everyday Cognition (eCOG, Appendix U)	Informant	5 min	X			
Montreal Cognitive Assessment (Appendix V)	Patient	5 min	X	X[o]		X
Older American Resources and Services Activities of Daily Living Scale (OARS ADL, Appendix L)	Patient / Informant	5 min	X			X
Mini-Nutritional Assessment (Appendix M)	Patient / Informant	2 min	X			
Clinical Frailty Scale (Appendix N)	Patient	Observ-ation	X			X
Hopkins Rehabilitation Engagement Rating Scale (Appendix E)	Patient	Observ-ation		X*	X*	
Life Space Assessment (Appendix F)	Patient/ Informant	5 min	X			X
Repeatable Battery for the Assessment of Neuropsychological Status (RBANS, Appendix O)	Patient	30 min				X

DKEFS Proverbs (Appendix P)	Patient	4 min				X
DKEFS Color-Word Interference (Appendix Q)	Patient	3 min				X
DKEFS Category Switching (Appendix R)	Patient	3 min				X
Trails A and B (Appendix W)	Patient	5 min				X
EQ-5D-5L (Appendix S)	Patient / Informant	5 min				X
Death, nursing home placement, or rehospitalization	Patient / Informant / Medical record	2 min				X
Brain MRI	Patient	45 min				X
Propositional density	Patient writing sample^	None	X			

Table 4. Prospective data collection schedule. °MOCA to be performed at 120 hours or at hospital discharge, whichever comes first. $hospital discharge only. *To be performed at hospital discharge and after the cognitive rehabilitation sessions are completed. #, Blood and urine will be collected at enrollment and 72 hours; 120 hour blood and urine is optional. ^Home writing samples will be used to calculate propositional density. "Observation" in the "Duration" column indicates that these measures are obtained by observing the patient during routine research activities.

5.2a. Delirium will be assessed for in the ED at screening and 3-hours, and once daily throughout the hospitalization if enrolled for 10 days and at discharge, whichever comes first. Trained CTAs will perform the ***modified Brief Confusion Assessment Method (bCAM, 1 minute, Appendix B***) in non-mechanically ventilated patients or the ***Confusion Assessment Method for the Intensive Care Unit (CAM-ICU, Appendix C)***. The modified bCAM can be reliably performed by our non-physician research staff. It is 82% to 86% sensitive and 93 to 96% specific for delirium with a kappa of 0.87 indicating excellent interobserver reliability.[43] The CTAs will also perform the ***Delirium Assessment Battery*** *(**Appendix G, 5 minutes**)* to capture additional delirium assessments such as the CAM, 3D-CAM, and 4AT for our sensitivity analyses.[44-47]

5.2.b. Delirium Heterogeneity Factors

Delirium heterogeneity factors will be collected once daily in the ED and hospital to help identify delirium phenotypes using LCA (Aim #3). These heterogeneity assessments do not require any additional patient interaction and arousal, psychomotor activity, and severity can be observed while performing the delirium assessments. ***Arousal*** will be determined with the ***Richmond Agitation Sedation Scale (RASS, Appendix H)***[48,49] Patients will be categorized as having delirium with normal arousal (RASS = 0), decreased arousal (RASS < 0) or increased arousal (RASS > 0). ***Psychomotor activity*** will be assessed by using the ***Delirium Motor Subtyping Scale-4 (DMSS-4, Appendix I).***[50] This observational scale is an abbreviated version of the more complex 11-item Delirium Motor Subtyping Scale (DMSS) with very good agreement (κ = 0.63 to 0.92).[50,51] Patients will be categorized into hypoactive, hyperactive, mixed, and no psychomotor subtype delirium. ***Delirium severity*** will be determined by the short form ***Confusion Assessment Method Severity (CAM-S, Appendix J)*** and will be categorized as none (0 points), low (1 point), moderate (2 points), or severe (3 to 7 points).[52]

5.2.c. Establishing Pre-Illness Cognition and Intelligence

To account for ***pre-illness cognition***, we will obtain the **Quick Dementia Rating Scale (QDRS, Appendix K)** and **Everyday Cognition (eCOG, Appendix U)** scales from a qualified informant (caregiver, offspring, spouse, sibling, or having known the patient >5 years)***.*** A qualified informant is present in 97% of delirious ED patients. ***Pre-existing ADRD*** will be defined as a

QDRS > 5.0, ADRD documented in the medical record, or prescribed an acetylcholine esterase inhibitor (galantamine, donepezil, and rivastigmine) before randomization.

We will also account for ***pre-morbid intelligence***, which is considered a measure of cognitive reserve, by calculating ***propositional density*** using the patient's writing samples written prior to the acute illness. Propositional density is the number of propositions per 10 words, and its measurement early and late in life has been shown to be strongly associated with future dementia status.[53,54] We will use the Computerized Propositional Idea Density Rater (CPIDR version 3.2, Athens, GA) to calculate propositional density automatically.[55,56] While propositional density remains stable over time even in patients with dementia,[57] We will attempt to collect the earliest writing samples available. Based on our pilot study, approximately 90% of older ED patients with a qualified informant will have writing samples available for analysis.

5.2.d. Additional prospective data collected at enrollment.
To ascertain ***pre-illness function***, we will collect the ***Older American Resources and Services Activities of Daily Living (OARS ADL, 2 min, Appendix L)*** at enrollment from the patient or qualified informant.[58] Scores range from 0 (completely dependent) to 28 (completely independent. ***Nutritional status*** will be determined by the ***Mini-Nutritional Assessment (MNA, Appendix M).***[59] The MNA ranges from 0 (malnourished) to 14 (normal nutritional status). We will also determine ***pre-illness frailty*** using the ***Clinical Frailty Scale (Observational, Appendix N)*** which is based upon comorbidities, functional status, and cognition. This scale ranges from 0 (no frailty) to 9 (terminally ill). ***Patient demographics***, including age, race, sex, marital status, years of education, highest occupation, weight, height, and place of residence will be recorded. Hospitalization within 6 months, substance abuse history, and hearing or visual impairment will also be obtained.

Medical Record Variable	Description
Elixhauser comorbidity index[61]	Summarizes the prognostic significance of 31 predefined comorbidities. Higher scores represent higher comorbidity.
Acute Physiology Score (APS) of the Acute Physiology and Chronic Health Evaluation (APACHE II)[62]	The APS is based upon the initial values of 12 routine physiologic and laboratory measurements. Higher scores indicate higher severity of illness.
ADRD documented in the medical record or prescribed an acetylcholine esterase inhibitor (galantamine, donepezil, and rivastigmine) prior to randomization.	This data will be used to help define pre-existing ADRD.
Drug Burden Index (DBI)[63]	Characterizes the patient's home exposure to anticholinergic and sedative medications. The DBI incorporates the principles of dose-response and maximal effect.[63]
Medications given in the ED and hospital	Daily benzodiazepines, opiates, and medications with anticholinergic properties given in the ED and hospital will be recorded.[64-66]
Interventions received in the ED and hospital	Interventions such as physical, occupational, and speech therapies, consultations (psychiatry, geriatrics, or neurology), surgeries or procedures, and treatment for delirium etiologies will be recorded.
ED, ICU, and hospital length of stay	The length of stay in the ED, ICU, and hospital will be quantified by hours.
Hospital discharge disposition	The patient's hospital discharge disposition will be classified as discharged to home, assisted living, post-acute care facility, nursing home, or expired.

Table 5. Variables to be collected during medical record review.

5.3. Medical Record Review for Index Hospitalization

Delirium etiology during index hospitalization will be determined using the ***Delirium Etiology Checklist (Appendix T)*** which classifies delirium etiologies into 13 categories.[60] Using medical record review, delirium etiology will be independently determined by two physician reviewers who have expertise in delirium; any disagreements will be adjudicated by a third physician reviewer. If the inter-rater reliability between the emergency physician and physician reviewers is good (kappa > 0.60), then the emergency physician's delirium etiology rating will be used for the LCA. For the purpose of our analysis, delirium etiologies will be collapsed into the following categories based upon our preliminary data: (1) CNS, (2) metabolic, (3) systemic infection, and (4) other. The physician reviewers will also record what treatments were provided and determine if the delirium etiologies were treated adequately.

Additional data will be collected from the medical record and is summarized in **Table 5**.

	Outcome Variable	Description	Source	Length
Primary Outcome	Repeatable Battery for the Assessment of Neuropsychological Status (RBANS, Appendix E)[67]	A neuropsychological battery for global cognition which evaluates immediate and delayed memory, attention, visuospatial construction, and language. It has been validated in subjects with mild cognitive impairment, moderate to severe traumatic brain injuries, vascular dementias, and Alzheimer's disease.[67-71] Scores range from 40 to 160, and the population mean (SD) is 100 (15).	Patient	30 mins
Secondary Outcomes	Delis–Kaplan Executive Function System (D-KEFS) Proverbs subscale (conceptual flexibility, Appendix F), the DKEFS Color Word Interference (inhibition, Appendix G), and DKEFS Verbal Fluency Category Switching subscale (monitoring, Appendix H)[72]	This neuropsychological battery will be used to quantify executive function. It assesses conceptual flexibility, inhibition, and monitoring which are the cornerstones of executive function.[72] An executive function composite score will be calculated from these three DKEFS subscales.	Patient	10 mins
	Older American Resources and Services Activities of Daily Living Scale (OARS ADL, Appendix I)[58]	It is based upon 7 basic and 7 instrumental activities of daily living. Scores range from 0 (completely dependent) to 28 (completely independent).	Patient or informant	5 mins
	EQ-5D-5L (Appendix J)[73-75]	EQ-5D-5L characterizes quality of life and contains 5-dimensions ("5D") related to everyday living: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D-5L asks patients to grade their current global health status from 0 (worst health you can imagine) to 100 (best health you can imagine).	Patient	5 mins

	Rehospitalization and nursing home placement	While attempting to contact the subject or surrogate, we will determine if the patient was rehospitalized or placed in a nursing home.	Patient or informant	1 min
	Death	To be ascertained via medical review, subject or surrogate contact, obituary searches, and National Death Index.	Informant, electronic health record	1 min

Table 6. Four-month outcome variables to be collected.

5.4. Outcome Variables for Aim #1 (randomized control trial)

Four months (3 to 7 months) after randomization, subjects will return to the local site for outcome ascertainment. For those who are unable to travel, a member of the neuropsychological team will travel to the patient's home. The primary and secondary outcome variables to be collected at 4-months (range 3 to 7 months) are listed in **Table 4**. We will also investigate the effect of cognitive training on ***index hospital outcomes*** as part of our secondary analyses. We will collect delirium duration using the modified bCAM, and hospital length of stay, ICU length of stay, and post-discharge disposition (e.g., skilled nursing facility) to be collected via medical record review. Based upon the neuropsychological raters' observations, they will also determine the Clinical Frailty Scale (Appendix N). They will also collect the ***Mini-Nutritional Assessment (Appendix M)*** for covariate adjustment.

5.5. Outcome Variables for Aim #2 (MRI)

Functional magnetic resonance imaging (fMRI) will be performed at 4 (range 3 to 7) months after randomization at the Vanderbilt University Institute of Imaging Science (VUIIS). Because of the 1:2 random allocation, one out of two controls will be randomly selected to participate in the fMRI aim. Patients will be scanned using dual-channel body coil radiofrequency transmission and SENSE-array 32-channel reception with the following protocol:

a. *Functional MRI.* Whole-brain gradient echo blood oxygenation level-dependent (BOLD) fMRI will be performed using a single-shot EPI multiband (factor=2.0) readout with spatial resolution=2x2x2 mm^3 and TR/TE=1000/35 ms. The acquisition will be performed during a face/scene delayed matching task[76] during fMRI acquisition using standard seed-based as well as minimum spanning tree (MST) analysis. This face/scene delayed matching task evaluates selective attention and working memory, and is designed to target medial temporal lobe and frontal and parietal cortices.[77]
b. *Perfusion imaging*. We will perform pseudo-continuous arterial spin labeling (pCASL) to obtain quantitative perfusion maps (ml blood / 100g tissue / min). Here, we will apply Hanning-windowed block pulse labeling (pulse-train duration=1600 ms) followed by post-labeling delay=1800 ms with TR=4.1s. Labeling will occur 90 mm inferior to the AC/PC line. We will apply a 3D GRASE readout (spatial resolution=3x3x5 mm^3; SENSE (Phase)=3; SENSE (Slice)=2; turbo direction=slice) with background suppression. A TR=20s equilibrium magnetization (M_0) image with identical geometry as pCASL but with labeling removed will also be acquired.
c. *Anatomical.* T_1-weighted (MPRAGE; spatial resolution=1.0x1.0x1.0 mm^3; TR/TE=8.2/3.7 ms), T_2-weighted FLAIR (spatial resolution=0.9x1.1x3.0 mm^3; TR/TI/TE=11000/2800/120 ms), T_2*-weighted (spatial resolution=0.5x0.5x1mm^3; $TR/TE_1/\Delta TE$=31/7.2/6.2 ms), and intracranial and extracranial time-of-flight MR angiography (TOF-MRA; intracranial: spatial resolution=0.5x0.8x1.4 mm^3, TR/TE=18.6/3.2 ms; extracranial: spatial resolution=0.9x0.9x3.0 mm^3; TR/TE=18.6/3.2 ms).

The brain MRI data will be interpreted by Dr. Donahue's staff at the Vanderbilt University Institute of Imaging Science using the following approaches:

a. *Functional MRI.* BOLD data will be corrected for motion, baseline drift, and slice-time and will be analyzed using standard seed-based functional connectivity and more novel MST following previously-reported standard procedures in eloquent functional networks known to be affected by delirium.[78,79] Individual-subject t- and z-statistic connectivity maps will be calculated, along with betweenness centrality and degree (from MST analysis); maps will be warped using FSL FLIRT and FNIRT[80] to a 2 mm MNI atlas using a T_1-weighted anatomical image as an intermediate template.
b. *Perfusion imaging.* pCASL data will be corrected for motion and baseline drift, surround-subtracted,[81] and normalized by M_0 to generate a difference magnetization map ($\Delta M/M_0$); these values will subsequently be converted to CBF in absolute units upon application of the flow-modified Bloch equation[82] and transformed to the standard atlas using identical procedures as outlined for BOLD.
c. *Anatomical.* Tissue volume will be quantified from the T_1-weighted images using Freesurfer and quantitative metrics of tissue volume in all brain lobes will be recorded.

5.6. Plasma biomarkers of *inflammation* (*IL-6 and CRP), endothelial dysfunction (PAI-1), and BBB injury (S100B)* using blood specimens collected at enrollment. Within 1 hour of blood draw, the blood will be centrifuged, processed, and stored in a -80^o Celsius freezer. These plasma biomarkers will be batch measured in years 3 and 4 at the Lorraine Ware Laboratory using Electrochemiluminescent assays (IL-6, CRP, and PAI-1, Meso Scale Discovery; Rockville, MD) and sandwich ELISAs (S100B; Millipore; Billerica, MA). Plasma biomarkers will be measured in blood collected at enrollment and 72 hours. Additional blood may be collected at 120-hours for future analyses, but will be optional; some patients no longer have routine blood draws by 120-hours. Additional blood will be collected at enrollment for future genetic analysis. Urine will also be collected at baseline, 72-hours, and 120-hours for future analyses.

5.7. Database management

This study will use REDCap for data collection, transmission, and storage. REDCap is a secure, web-based application for building and managing online databases. Vanderbilt University Medical Center, with collaboration from a consortium of institutional partners, including the Vanderbilt Institute for Clinical and Translation Research (VICTR) Informatics Core, developed and manages a software toolset and workflow methodology for electronic data collection and management of research and clinical trial data. All study data will be entered via a password-protected, study unique REDCap database website. REDCap servers are housed in a local data center at Vanderbilt University Medical Center, and all web-based information transmission is encrypted. REDCap was developed specifically around HIPAA-Security guidelines and is recommended by both the Vanderbilt University Medical Center Privacy Office and Institutional Review Board. REDCap has been disseminated for use locally at other institutions and currently supports > 140 academic/non-profit consortium partners and 11,000 research end-users (www.projectredcap.org).

Whenever possible, data will be directly entered into electronic case report forms (eCRFs) within REDCap. When paper-based surveys or forms, such as the RBANs, are collected, these forms will be entered or uploaded into REDCap. The paper CRFs will only have the patient's unique identification number and initials. These case report forms will then be stored in a locked cabinet in a secure office space. All paper case report forms will be kept according to Institutional Review Board (IRB) policies.

All research materials will only be accessible by IRB approved research personnel. Principal investigators, co-investigators, study coordinators, Cognitive Intervention Specialist, CTAs, and neuropsychological raters will have access to individually identifiable private information. Such access is necessary for conducting medical record review and follow-up. The rest of the study team (e.g., biostatisticians) will only have access to de-identified data.

5.8. Reimbursement

We will provide $75 for patients to complete the ED, hospital, and 12-week post-discharge assessments. We will also provide participants financial compensation ($75) the 4-month follow-up. Patients will receive an additional $50 in they participate in the brain magnetic resonance imaging (MRI) study. For patients who develop significant functional impairment or are unable to travel (~30% of cohort), the neuropsychologists will go to their homes to conduct the long-term cognitive and secondary outcomes assessments. These patients will be reimbursed $25.

6.0 Risks

There are several risks associated with this R01:

1) Risks associated with the collection of protected health information. Collection of protected health information for research involves a small risk of the loss of patient confidentiality. To minimize this risk, at no time will we reveal subject identities in any manner, whether in presentation, description, or publication of the research for scientific purposes. Most data will be directly entered into a HIPAA compliant REDCap electronic database. These data will be stored on a secure network on Vanderbilt's computer servers. While data will be entered electronically whenever possible, paper-based case report forms may still be used to collect neuropsychological data (e.g., figure drawing and recall). The paper-based case report forms will have the patient's study identification number and initials only; no other patient identifiers will be present. All paper-based case report forms and questionnaires will be stored in a locked cabinet in office space only accessible to the study team. All case report forms will be kept for 3 years as per Vanderbilt's IRB policy; afterward, all paper documents will be shredded.
2) Fatigue, frustration, and distress. Subjects will undergo cognitive training, cognitive rehabilitation, and a neuropsychological examination that can take up to 45 minutes to perform. Some of the tasks related to the cognitive intervention and testing are also cognitively demanding. Therefore, there is a small risk that the patient may become fatigued, frustrated, or distressed during the cognitive intervention or assessments. In these cases, we will immediately stop the assessment or tasks, and allow the patient to rest. Afterward, we will ask the patient and their families if we can continue with the study assessments or cognitive training or rehabilitation session, or if we should come back later in the day or the next day. Occasionally, patients and their families may get visibly frustrated and distressed if the patient is unable to perform the cognitive tasks. We will reassure them that these tasks can be difficult to perform and that such difficulties are common. If the patient or his / her family continues to be distressed after this reassurance, we will skip that task or stop the assessment altogether.
3) Phlebotomy. All participants will have blood drawn for research purposes. As almost all participants will have intravenous lines placed for clinical purposes, the risk of blood draws is essentially nil, as blood can be easily obtained from these lines. In the rare case an intravenous line is not present, the risks of drawing blood are uncommon and include bleeding and bruising. Commonly, drawing blood is painful, and rarely, drawing blood can lead to infections at the site of the blood draw. To minimize this risk, we will prep the phlebotomy site with chlorhexidine (antiseptic fluid) and use the smallest gauge needle possible. We will also minimize the number of attempts.

4) Distress secondary to fMRI. A subset of 50 patients will undergo fMRI examination which can take 45 minutes to perform. There is a small risk of distress secondary to claustrophobia. To minimize this risk, patients will have an opportunity to opt-out of the fMRI portion, especially if they are claustrophobic. If the subject is in the MRI scanner and cannot tolerate it, then the MRI will be stopped immediately. We will ask the subject if they will be able to proceed with the MRI. If they are unable to continue, we will withdraw the patient from this portion of the study.

7.0 Safety Monitoring, Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

Because the cognitive training and rehabilitation is a non-pharmacologic intervention, the intervention poses minimal risk to the patient. Therefore, we will not have a formal DSMB. However, Dr. Babar Kahn (Indiana University) will independently serve as the data and safety monitor; he is not part of the study team and will not participate in any study or publication activities related to this R01. He will also review all data relevant to safety (including all clinical outcomes, SAEs, and unexpected AEs) in once a year during prospective enrollment. He will have access to unblinded data in order minimize potential for bias while maintaining appropriate safety monitoring. After this safety review, Dr. Kahn will provide a written report to the PIs. The PIs will provide this to the Vanderbilt IRB and the National Institute on Aging.

8.0 Study Withdrawal/Discontinuation

If patient or caregiver declines participation at the outset or does not meet inclusion criteria, they will not be included in the study. If patients wish to discontinue taking part in the study, they will be instructed to contact principal investigator or the research staff and let them know that they wish to withdraw. At that time, no further data will be collected on the patient. All health data previously collected before they withdraw their consent will still be used for reporting and research quality.

9.0 Statistical Considerations

Aim #1 Formula

$$\text{4-month global cognition} = \text{Cognitive training / rehabilitation intervention} + \text{premorbid cognition} + \text{premorbid intelligence} + \text{covariates} + \text{pre-existing ADRD*cognitive intervention}$$

9.1. Data analysis for Aim #1 (cognitive training/intervention RCT and 4-month global cognition): The primary analysis for Aim #1 will be an intention-to-treat comparison of 4-month global cognition between those who receive and not receive the cognitive training and rehabilitation intervention. Though randomization theoretically accounts for group imbalances and possible confounding, adjusting for strong risk factors for outcomes reduces measurement error, which may increase statistical power.[83] Therefore, we will use multivariable linear regression using the formula below and adjust for pre-illness cognition and other covariates listed in **Table C8.1.a**:

Covariates that occurred after randomization (e.g., interventions provided during hospitalization) will not be adjusted for because they may potentially be affected by the cognitive intervention and be on the causal pathway. We will also determine if pre-existing ADRD modifies any association between cognitive intervention and 4-month outcomes by incorporating a two-factor interaction (pre-illness ADRD*cognitive intervention) into the model. In the event of significant missing covariate data, multiple imputation will be used.[84-86] After the initial analysis has been completed, we will also evaluate if there is any **effect modification** of baseline severity of illness (APS), race, sex, and initial delirium psychomotor, arousal, severity, etiology, and pathophysiological subtypes. To determine if using a delirium assessment affects our conclusions, we will also perform a **sensitivity analysis** where the multivariable linear

regression model is re-run in a subset of patients who are positive for other delirium assessments (CAM, 3D-CAM, 4AT).[44-47]

Secondary analyses will also be performed. We will perform a per protocol analyses; for the multivariable linear regression model, the dose of the interventions (total duration of cognitive training and total duration of cognitive rehabilitation) will be the primary independent variables instead of treatment assignment (cognitive training/rehabilitation versus placebo). We will determine if early cognitive training and rehabilitation are associated with our 4-month secondary endpoints such as the individual RBANS cognitive domains (immediate and delayed memory, attention, language, and visuospatial construction), executive function, functional status, rehospitalization, nursing home placement, and death. We will also determine if early cognitive training reduces delirium duration, hospital length of stay, and discharge to a post-acute care facility. We will also explore if there are specific interventions that potentiate the cognitive intervention's effect such as time-to-cognitive training, discharge to a post-acute care facility, and physical activity during cognitive rehabilitation (mean Life Space questionnaire scores). We will explore if these factors modify the association between the cognitive intervention and 4-month global cognition.

Primary Independent	**df**
Cognitive intervention	1
Pre-illness Cognition / Intelligence	
Pre-illness ADRD	1
Pre-illness QDRS	1
Propositional density	1
Other Baseline Covariates	
Sex	1
Race	1
Education	1
Pre-illness function (OARS ADL)	1
Severity of illness (APS)	1
Comorbidity Burden	1
Interactions (Maximum)	
ADRD* Cognitive intervention	1
Total Degrees of Freedom (df)	11

Table C8.1.a. Covariates and interaction terms for multivariable linear regression.

9.2. Data analysis for Aim #2 (fMRI). To test if frontoparietal network connectivity, as characterized by BOLD fMRI, improves with cognitive training/rehabilitation compared with controls, we will apply the co-registered z-statistic maps in a mixed effects model to evaluate regions that differ in activation between the two groups, after separately modeling age, sex, and pre-illness QDRS. Group-level z-statistics and corrected p-values will be reported. As a supplementary analysis, we will also explore whether (i) regional tissue volumes at the imaging MRI time point vary between groups and (ii) cortical perfusion quantified from pCASL varies between groups. For these comparisons, a Wilcoxon rank-sum test or Student's t-test will be applied. With a sample size of 50 (25 per group), we will have sufficient power to detect a 30% improvement in frontoparietal cortex network connectivity with 80% power and a two-sided alpha of 0.05.

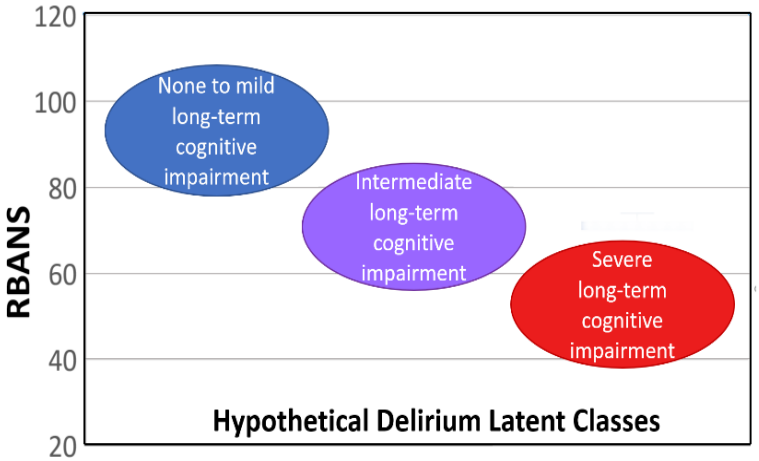


Figure C8.3.a. Three hypothetical latent classes or phenotypes for delirium.

9.3. Data Analysis for Aim #3 (identify novel delirium phenotypes using LCA): Aim #3 will use LCA to identify hidden groups based on the observed delirium subtypes

(arousal, psychomotor, severity, etiology, and pathophysiology) and separate them into mutually exclusive classes. This technique can be used to obtain phenotypes of delirium and determine if these novel phenotypes are associated with 4-month global cognition. Based upon our preliminary study (**Section C1.5**), pre-existing ADRD may strongly influence these delirium latent classes and will be considered for the LCA. The "best" number of latent classes is usually determined a priori by the researcher and we hypothesize that the cohort will be represented by three delirium phenotypes (**Figure C8.3.a**): no or mild, moderate, or severe 4-month cognitive impairment. The sensitivity of this hypothesis, model fit, and identification of the correct number of unique delirium phenotypes will be evaluated by comparing the models assuming different number of classes using the bootstrapped likelihood ratio test, which is a parametric bootstrap method that uses bootstrap samples to estimate the distribution of the log likelihood difference test statistic.[87]

Once the latent classes have been identified, we will explore if the delirium phenotypes identified by LCA modify the association between the cognitive training and rehabilitation intervention and 4-month global cognition using multivariable linear regression as described in **Section C8.1a** using the formula below:

Aim #3 Formula
4-month global cognition = **Cognitive training / rehabilitation intervention** + **Phenotypes identified by latent class analysis** **+ premorbid cognition + premorbid intelligence + covariates + cognitive intervention*phenotypes**

The multivariable linear model for Aim #3 will be adjusted for the covariates listed **Table C8.1.a.**

10.0 Privacy/Confidentiality Issues

The patient's information, without identifiers, may be shared with other institutions or universities. Dr. Han, his co-investigators, and their staff will comply with any and all laws regarding the privacy of such information. There are no plans to pay the patient for the use or transfer of their de-identified information or specimens.

11.0 Follow-up and Record Retention

The duration of this study is approximately 4 years. We will try to enroll 500 patients during this time. Data collected will be retained indefinitely.

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