1. Administrative Information

Title	Early Cognitive Intervention in Delirium (ECID)
Trial Registration	https://clinicaltrials.gov/study/NCT04740567
Principal Investigators	Jin H. Han, M.D., M.Sc. and James C. Jackson, PsyD
Biostatisticians	Cathy A. Jenkins, MS and Guanchao Wang, MS
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2. Introduction

This is the Statistical Analysis Plan (SAP) for the study titled "Early Cognitive Intervention in Delirium (ECID)" randomized trial. This study was sponsored by the National Institute on Aging (5R01AG065249).

3. Background and Rationale

Delirium is a form of acute brain failure that afflicts 17% of older emergency department (ED) and 25% of older hospitalized patients.[1-4] 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] but to our knowledge, has not been rigorously evaluated in older hospitalized patients with delirium.

4. Objectives

To address this dearth in knowledge, we conducted a randomized trial with the following objective:

> 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 structured usual care.*

5. Study Population

Table 1 lists the inclusion criteria for ECID randomized trial. Patients were included in the study if they were 65 years or older, hospitalized from the ED, can receive cognitive training within 24 hours of ED presentation, and are delirious. We enrolled patients who were 65 years or older, because delirium disproportionately affects older patients, and they were most likely to benefit from our research. Comatose patients were re-evaluated 1 to 2 hours later. If the coma was persistent, then they were excluded delirium cannot be assessed for in these patients. Additionally, they must be arousable for the cognitive intervention to be administered. Patients who were unable to follow simple commands prior to their acute illness were 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 as determined by the 4AT[22]	• 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 ECID randomized trial.

6. Treatment arms

Hospitalized patients with delirium were randomized in 1:2 ratio using permuted block randomization to either cognitive training and rehabilitation intervention or structured usual care defined as follows:

- **Intervention:** Two daily 20-minute cognitive training sessions were administered during hospitalization with the first session occurring within 24 hours of ED presentation. The level of difficulty of the training was tailored to the patient's current level of cognitive functioning. Cognitive rehabilitation was administered in the patient's home within 1 week after hospital discharge. Patients received cognitive rehabilitation once a week for 12 weeks with each session lasting approximately 1 hour.
- **Usual care:** Daily delirium assessment without cognitive training occurred during hospitalization. No cognitive rehabilitation was performed in the usual care arm.

7. Outcomes

7.1. Primary outcome at 4-months

The primary outcomes for ECID was global cognition at 4-months, as determined by a comprehensive neuropsychological assessment. Global cognition was assessed for using the ***Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)***. The RBANS is a comprehensive neuropsychological battery for the evaluation of global cognition

and has been validated in subjects with mild cognitive impairment, moderate to severe traumatic brain injuries, vascular dementias, and Alzheimer's disease.[23-27] In addition to providing a score for global cognition, it also provides individual scores for immediate and delayed memory, attention, visuospatial construction, and language. Scores range from 40 to 160, with higher scores indicating better cognition.

7.2. Secondary Outcomes at 4-months are listed in Table 2.

Study Assessment	Description
Executive function score	Based on the Delis–Kaplan Executive Function System (D-KEFS) Proverbs subscale (conceptual flexibility), the DKEFS Color Word Interference (inhibition), and DKEFS Verbal Fluency Category Switching subscale (monitoring).[28] Scores range from 1 to 18, with higher scores indicating better executive function.
Older American Resources and Services Activities of Daily Living Scale (OARS ADL)[29]	Assesses functional status and is based on 7 basic and 7 instrumental activities of daily living. Scores range from 0 (completely dependent) to 28 (completely independent).
EQ-5D-5L [30-32]	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. EQ-5D-5L index values, validated for the US population, were calculated, and higher scores represented better quality of life.[33] An index value score of 1.0 indicates perfect quality of life, whereas a score <0.0 indicates quality of life worse than death. The EQ-5D-5L also asks patients to grade their current global health status from 0 (worst health you can imagine) to 100 (best health you can imagine).
Montreal Cognitive Assessment[34]	This is a brief test of global cognition based on attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. Scores range from 0 to 30, with higher scores indicating better global cognition.
Mortality	Collected by medical record review or informant interview.
Permanent nursing home placement	Collected by patient or informant interview.

Table 2. Secondary outcomes for ECID.

7.3. Exploratory Outcomes at 4-months are listed in Table 3.

Study Assessment	Description
Individual RBANS subscale domains	Scores for each RBANS individual cognitive will be reported - Immediate and delayed memory, attention, language, visuospatial construction.
Individual D-KEF domains	Individual scores for each DKEF Subscale that make up the Executive Function Composite Score will be reported - Proverbs (conceptual scale flexibility), Color Word Interference (inhibition), and Verbal Fluency Category switching (monitoring).
Clinical Frailty Score[35]	Characterizes frailty and is based on comorbidities, functional status, and cognition. This scale ranges from 0 (no frailty) to 9 (terminally ill).
Life Space Assessment[36]	Characterizes mobility and physical activity by asking 9 questions characterizing the patient's movement within his/her environment over the past 3 days.
Rehospitalization	Collected by medical record review or informant interview.

Table 3. Exploratory outcomes at 4 months.

7.3. Index hospital exploratory outcomes

- Delirium duration was defined as the total # of days a patient was delirious or comatose. Delirium was measured daily using the bCAM[37] (non-mechanically ventilated) and CAM-ICU[38] (mechanically ventilated). We chose the bCAM and CAM-ICU because of their high specificity (>=95%).
- Mean delirium severity throughout hospitalization using the Confusion Assessment Method Severity (CAM-S) scale.[39]
- Maximum delirium severity throughout hospitalization using the CAM-S
- In-hospital death
- Total number of parenteral (intravenous and intramuscular) doses benzo/antipsychotic medications given during hospitalization adjusting for days in the hospital:
- Hospital length of stay
- ICU length of stay
- Post-discharge disposition in those who survived hospitalization

8. Statistical Methods

8.1. *Descriptive Analysis*

To characterize the study sample, demographic, clinical, and lab data will be described overall and by treatment arm. Categorical variables will be described using frequencies and proportions; continuous variables will be described using means and standard deviations as well

as medians and interquartile ranges (IQR) when appropriate. For the proportional odds logistic and logistic regression models, odds ratios (OR) with their 95% confidence intervals (95%CI) will be presented.

8.2. Primary outcome analysis:

Our primary analysis will be an intention-to-treat comparison of 4-month global cognition between those who receive and do not receive the cognitive training and rehabilitation intervention. The association of 4-month global cognition with the cognitive intervention vs usual care will be assessed using proportional odds logistic regression adjusting for a priori defined covariates as listed below in order of priority depending on the degrees of freedom available for each outcome:

Priority	Variable	Description
1	Pre-illness cognition	Quick Dementia Rating System is a10-item questionnaire ranges from 0 to 30, with higher scores representing greater cognitive impairment. .[40,41]
2	Pre-illness ADRD	Defined as a QDRS > 6,[40-42] past history of ADRD in the electronic health record, or prescribed a home acetylcholine esterase inhibitor (i.e., donepezil) with ≥ 1 ADL impairment in the pre-illness OARS ADL.[43]
3	Age	Age in years at the time of enrollment
4	Pre-illness function	Older American Resources and Services Activities of Daily Living (OARS ADL) scale which is assesses 7 basic and 7 instrument ADLs.[29]
5	Severity of illness	Acute Physiology Score of the Acute Physiology and Chronic Health Evaluation II (APACHE II) which is based on 12 laboratory, vital sign, and GCS.[44]
6	Comorbidity burden	Elixhauser comorbidity burden based on 31 comorbid conditions[45]
7	ADRD*treatment assignment interaction	To determine if cognitive intervention
8	Pre-illness Frailty	Clinical Frailty Scale (CFS) range from 0 (no frailty) to 9 (terminally ill) and is based on patient's comorbidities, and baseline cognition and function.[35,46]
9	Years of education	
10	Central nervous system etiology	Determined by 2 expert physician raters. Any disagreement was adjudicated by a third expert physician rater.
11	Race (Black vs non-Black)	
12	Sex	

Table 4. Covariates considered for the multivariable regression models in order of importance.

The number of covariates incorporated will depend on the number patients with completed 12-month RBANS. We will have one degree of freedom available for every 10 to 15 patients with completed outcome measurements.[47] If the number of RBANS completed (our primary outcome) is lower than expected, then we will reduce the number of covariates incorporated into the model to minimize overfitting. We will evaluate if the covariates are highly correlated with

each other; if two variables are highly correlated, the lesser priority covariate will be removed. We will not adjust for site (VUMC vs Nashville VA), because the proportion of patients enrolled in the Nashville VA is anticipated to be < 10% of those enrolled. Post-randomization covariates (e.g., interventions provided during hospitalization) will not be adjusted for because they may potentially be affected by the randomized intervention and be on the causal pathway. Unadjusted and adjusted medians with their interquartile ranges (IQR) will be reported for the intervention and usual groups. Unadjusted and adjusted odds ratio (aOR) with their 95% confidence intervals (95%CI) will also be reported.

Multiple imputation for missing covariates based on predictive mean matching will be performed. As with our previous studies, multiple imputation will also be performed for RBANS with partially missing cognitive domains.[9,48,49] If $\leq$ 5% of the RBANS is partially missing, then single imputation using a model-based approach will be used to calculate the RBANS global score. If > 5% of RBANS is partially missing, then multiple imputation will be performed to calculate the RBANS global score. Patients who had completely missing RBANS were removed from the statistical analysis.

8.3. Sensitivity analyses for Primary Outcome:

Several sensitivity analyses will be performed to assess the robustness of our findings:

1) We will perform a modified per-protocol analysis will be performed where we will determine if the total duration of cognitive training and total duration of cognitive rehabilitation is associated with our primary outcome. Participants in the usual care group will be assigned cognitive training and cognitive rehabilitation durations of 0.
2) We will also see if the intervention is effective in a subset of patients who are only positive for other delirium assessments (bCAM, CAM, 3D-CAM) by repeating the primary analysis on subsets of those positive for each of the listed delirium assessments.
3) To account for the potential differences in survival between the intervention and usual care groups, we will treat death as the worst outcome in those who died before the 4-month follow-up and assign these patients an RBANs score of 39.
4) To determine how multiple imputation impacted our findings, we will do a complete case analysis of patient who had missing RBANS.

We will re-run the proportional odd logistic regression models using the same covariates as our primary analysis.

8.4. Heterogeneity of treatment effect analysis for primary outcome:

Because detecting a statistical interaction may require significantly greater statistical power than detecting a main effect, a p-value for the interaction term < 0.20 will be considered as the threshold by which effect modification is potentially present. We will evaluate effect modification of the following variables:

1) Age
2) Severity of illness as defined by APS of the APACHE II
3) Years of education
4) Enrollment delirium severity (CAM-S)
5) Enrollment psychomotor subtype (hypoactive, hyperactive, mixed, normal)

6) Enrollment level of arousal (normal, decreased, increased)
7) Enrollment etiology (drug, infection, metabolic/endocrine, organ dysfunction, CNS)
8) Time from ED presentation to randomization, which is a surrogate to time to first cognitive intervention
9) Hopkins Rehabilitation Engagement Rating Scale (HRERS), which is a measure of patient engagement with the cognitive intervention. Patients in the usual care arm will be assigned a score of 0.

For the heterogeneity of treatment effect analysis, we will re-run the proportional odd logistic regression models using the same covariates as our primary analysis.

8.5. Analyses for Secondary Outcomes: All secondary outcomes analyses will be intention-to-treat using the same approach as our primary outcome.

1) Multivariable proportional odds logistic regression will be performed for executive function composite score, MoCA, OARS ADL, and EQ-5D-5L at 4-months using the same covariates.
2) For 4-month mortality, multivariable logistic regression will be performed. If there are less than 30 events, only a univariate analysis will be performed.
3) For nursing home placement, multivariable logistic regression will be performed. If there are less than 30 events, only a univariate analysis will be performed.

We will adjust for the same covariates as the primary analysis. However, the number of covariates incorporated will depend on the number patients and events for the proportional odds logistic regression and logistic regression models, respectively. For our proportional odds logistic regression model, we will have one degree of freedom available for every 10 to 15 patients with completed outcome measurements.[47] For our multivariable logistic regression models, we will have one degree of freedom available for every 10 to 15 outcomes for our multiple logistic regression models.[47] We will incorporate the covariates in order of importance. Proportions and medians with their IQR will be reported for the intervention and usual groups for categorical and continuous outcomes, respectively. Unadjusted and adjusted odds ratio (aOR) with their 95% confidence intervals (95%CI) will also be reported.

8.6. Analysis for Exploratory Outcomes (4-month and index hospitalization): All exploratory outcomes analyses will be intention-to-treat. For these outcomes, unadjusted comparisons using the Wilcoxon Rank-sum tests or chi-squared test will be performed for continuous and categorial variables, respectively. Unadjusted odds ratios will be reported. A p-value < 0.05 will be considered statistically significant.

8.7. Power and Sample Size

To estimate our sample size, we used half a standard deviation (SD) of that particular test to define the minimum clinically important difference (MCID) threshold. Based on our preliminary study,[9] the SD for the RBANS was 12.4, and we considered a 6.0 point difference to be the MCID threshold. Based upon a two-sided alpha of 0.05 and 80% power, we will need outcome data in a total of 153 patients (51 intervention and 102 usual care) to detect a 6.0 difference in 4-month RBANS. Using a conservative death and lost-to-follow-up rate or withdrawal estimate

of 30% and 22%, respectively, we estimated that 282 patients would have to be enrolled to achieve this sample size.

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