DECREASING DELIRIUM THROUGH MUSIC IN CRITICALLY ILL OLDER ADULTS (DDM) PROTOCOL

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1. BACKGROUND:

One million adults in the United States receive mechanical ventilation for acute respiratory failure in the intensive care units (ICUs) annually and up to 80% of them develop delirium during their ICU stay. Presence of delirium predisposes older adults 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. In addition, ICU delirium is associated with long-term post-discharge complications such as development of cognitive impairment and dementia. Not only does the presence of delirium portend adverse patient-related outcomes; both delirium duration and delirium severity have also been identified as predictors of mortality and other adverse consequences. Research studies to date exploring pharmacological strategies to manage ICU delirium have not been successful in demonstrating efficacy. Additionally, receipt of sedative and opioid medications to treat other commonly co-occurring symptoms of pain and anxiety among the critically ill predisposes patients to further delirium propagation and persistence. Early implementation of a non- pharmacological intervention with the ability to manage pain and anxiety symptoms along with a reduction in harmful medications exposure holds great potential to reduce downstream delirium and its sequelae.

Music listening is one such intervention that holds promise for non-pharmacological management of delirium commonly experienced by mechanically ventilated patients. Music has been shown to break the harmful cycle of over-sedation in critically ill and can reduce anxiety and stress, factors that could predispose to ICU delirium. These findings are not surprising given that music results in a reduction in inflammatory cytokines, decreases cortisol production, and dampens central nervous system arousal through diminished norepinephrine release; pathways similar to those implicated in delirium. In a randomized clinical trial conducted by Dr. Chlan (MPI), a music intervention consisting of patient-directed, slow-tempo, relaxing music delivered during the latter portion of mechanical ventilator support was superior to usual ICU care in reducing anxiety and sedative exposure in critically ill patients. Even with such positive findings both at mechanistic and patient-outcome levels, music listening interventions are notably absent in routine ICU care. Further, there is a paucity of rigorous investigation of music's impact on ICU delirium, a significant knowledge gap.

We now propose an adequately powered randomized clinical trial to test the efficacy of a seven-day music intervention in reducing delirium and improving brain health among critically ill, mechanically ventilated older adults through the following specific aims:

2. RATIONALE and SPECIFIC AIMS:

Critically ill patients on mechanical ventilation are at high risk to develop delirium and need innovative, safe and scalable interventions to ameliorate it. The scientific premise of our proposal is that early slow-tempo music listening in the ICU setting will reduce delirium among older adults, which will lead to downstream beneficial effects on long-term cognition. Music has been shown to be beneficial in managing pain and anxiety symptoms through anti-inflammatory and cortisol mediated pathways, similar pathways that are disrupted and implicated in delirium development. Additionally, slow-tempo music could also reduce exposure to opioids and sedative medications ubiquitous in the ICU setting and associated with delirium. Hence it stands to reason that a music intervention will be efficacious in reducing ICU delirium. Even with the clinical rationale and aforementioned data, a rigorous trial testing the efficacy of music intervention on ICU delirium is notably lacking.

Primary Specific Aim: Test the efficacy of music intervention in *improving delirium/coma free days* among mechanically ventilated patients as compared to attention control. Hypothesis: Patients in the music intervention group will have higher number of delirium/coma free days as measured by the Confusion Assessment Method for the ICU (CAM-ICU) at seven days post randomization.

Secondary Specific Aim 1: Test the efficacy of music intervention in *improving delirium severity, pain and anxiety* among mechanically ventilated patients as compared to attention control. Hypotheses: Patients in the music intervention group will have lower delirium severity, pain and anxiety scores as measured by the CAM- ICU-7, Critical Care Pain Observation Tool (CPOT) and Visual Analogue Scale-Anxiety (VAS-A) respectively at seven days post-randomization.

Secondary Specific Aim 2*:* Test the efficacy of music intervention in *improving the long-term neuro-psychological outcomes* as compared to attention control. Hypotheses: Patients in the music intervention group will have higher cognitive scores as assessed by the Indiana University Telephone Based Assessment of Neuropsychological Status (IU-TBANS), and lower depression and anxiety scores on the Patient Health Questionnaire (PHQ-9) and Generalized Anxiety Disorder (GAD-7) scales at 3 months post hospital discharge.

3. STUDY DESIGN

Two-arm, randomized parallel-group, clinical trial with concealment of outcomes assessment to evaluate the efficacy of music intervention compared to a silence-track attention control in improving delirium/coma free days in mechanically-ventilated critically ill older adults. The total duration of the intervention will be 7 days from randomization unless a patient has died, discharged, or transferred out of the ICU.

4. INCLUSION/EXCLUSION CRITERIA

DDM Inclusion and Exclusion Criteria	
Inclusion Criteria	**Exclusion Criteria**
-Age 50 years or older -English speaking -Admitted to the intensive care unit (medical or surgical) -Expected mechanical ventilator support for ≥48 hours -Consentable through a legally authorized representative -Have access to a telephone	-History of dementing illnesses and other neurodegenerative diseases such as Alzheimer's disease or vascular dementia -Psychiatric illness which is not well controlled -Alcohol withdrawal symptoms/concern for withdrawal -Suspected or confirmed drug intoxication/overdose -Traumatic brain injury, ischemic or hemorrhagic cerebrovascular accident, or undergoing neurosurgery -Uncorrected hearing or vision impairment including legal blindness -Incarcerated at the time of study enrollment -Enrolled in another clinical trial which does not permit co-enrollment -Any medical condition precluding safe use of headphones such as: skin breakdown, burns, facial or skull fractures

5. ENROLLMENT and RANDOMIZATION

Clinical Settings and Study Population: Patients will be recruited from two Indianapolis Hospital systems: Eskenazi Health and Indiana University Health. Patients will also be recruited from Mayo Clinic Rochester.

Recruitment Targets: Final study sample will comprise 160 mechanically ventilated older adults ≥50 years of age.

Screening and Enrollment: Research staff will review the electronic medical records of ICU patients daily for eligibility. Eligible patients' clinical teams will be approached if necessary to confirm eligibility. 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 approached for the study using the CAM-ICU-7. Once eligibility is confirmed, the research team will approach patients or their legally authorized representatives for consent depending on patients' clinical status. Patients consented through their legally authorized representative will be re-consented once clinically able.

Randomization: Using a computer-generated list of random numbers created by study statistician, participants will be randomized by permuted block with varying block sizes. Randomization will occur after consent in a 1:1 manner and will be stratified based on hospital location.

6. STUDY PROCEDURES

Interventions: For up to seven days, enrolled subjects will either receive 1) one-hour music listening sessions twice daily through noise-cancelling headphones, or 2) one-hour sessions consisting of a silence track twice daily through noise-cancelling headphones.

a. Music Intervention: Twice daily one-hour intervention will be delivered based on our extensive playlist created by our board-certified music therapist consultant and used in our previous studies. The playlist contains relaxing slow tempo instrumental music (60-80 beats/minute). Featured instruments in the playlist include piano, harp, reed, guitar and Native American flute. The mix features classical music and relaxing melodies and does not contain lyrics or spoken words.[71] In addition to the twice daily music intervention sessions, patients will be encouraged to self-initiate listening to slow-tempo music from the study playlist whenever desired as a means to engage in quiet time or listening enjoyment. Our iPad® app will efficiently log all of the 'as desired' music listening sessions by automatically capturing frequency, length, and music selections for both the twice daily music intervention sessions as well as the self-directed listening sessions. Variability in self-directed music listening duration and frequency will be used as a covariate in subsequent analyses.

b. Attention Control: A silence only track will be added to the study iPads® and will be activated in the form of an app similar to the music listening tracking app. Patients randomized to this arm will receive a noise cancellation headphone-applied condition identical to the music intervention experimental treatment; twice daily one hour-sessions. Likewise, patients will have the opportunity to use the silence app with headphones whenever desired. As with the music intervention, the app will track each session's length, frequency, and self-directed headphone application with the silence track.

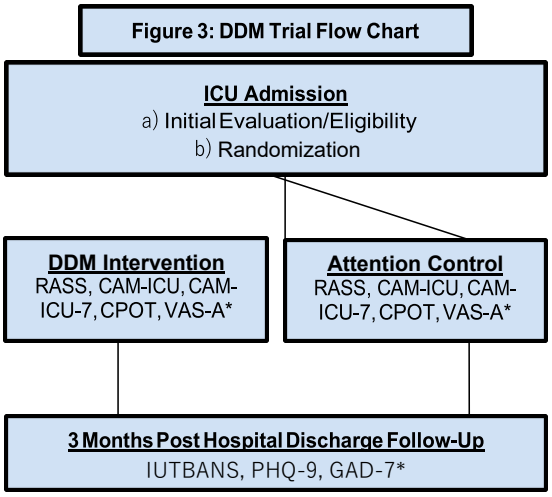
Delivery of the Intervention: The research manager will ensure good operating status of the iPad® music app, headphones and connectivity to the tracking portal prior to the initiation of the intervention. Both the experimental and the attention control conditions will be delivered through identical iPads® with our music tracking app and noise cancellation headphones to ensure blinding of group assignment when study staff perform assessments. All patients will receive two one-hour sessions daily between the hours of 0900 to 1200, and from 1300 to 2000. Nurses will receive training to minimize distractions at that time, such as turning off televisions and avoiding non-essential patient care. Patients will receive standard ICU care per local practices including the ABCDEF bundle,[21,22] which is part of routine care at participating ICUs. Patients will continue to receive clinical care for delirium based on their primary clinical team's discretion.

Blood Sample Collection

We will collect blood samples prior to first intervention session (up to 10ml in tubes containing anticoagulant), at day 3, and at the end of the intervention period (up to 10 ml in tubes containing anticoagulant). The samples will be transported to the CTSI lab, and will be prepared and stored using deidentified labels. Samples will be stored for future biomarker analysis which includes measurement of pro-inflammatory and anti-inflammatory cytokines, reactive oxygen species and DNA damage, proteomics, epigenetics, and protein-gene associations.

Blinding: Apart from the patient and research staff member assigning the music intervention, all study personnel and clinical staff interacting with the patient will remain blinded to each patient's intervention assignment throughout enrollment, follow-up and data analysis.

Study Flow: Eligible patients or their legally authorized representatives will be approached immediately after fulfilling the inclusion criteria. The intervention will start immediately post-enrollment depending on the time of enrollment. If enrolled prior to 1100, subjects will receive both one-hour music sessions on day of enrollment, if enrolled after 1200; they will receive a single one-hour music session on day of enrollment. If enrollment occurs after 2000, sessions will be started the following day. Study staff will assess for delirium, pain, and anxiety for the whole duration of ICU stay or until day 28 if the patient remains in the ICU. Cognition, depression and anxiety measures will be collected at three months post-hospital discharge in both intervention and control groups. See Figure 3 for study flow and outcomes assessment.



Outcomes Assessments: Trained and blinded research assistants will complete in-hospital and post- hospital outcomes assessments consisting of measures of delirium, cognition, pain, depression and anxiety. Data will be

collected using Research Electronic Data Capture (REDCap). We will employ multiple techniques to ensure concealment of outcomes assessment.[73,74] Our research assistants are trained not to inquire about study assignments. The research randomization staff member will deliver the intervention and the research assistants will not be aware of the intervention assignments. Subjects and their family members will be instructed not to discuss their intervention with the research assistants. All research staff undergoes a comprehensive training program with respect to outcomes assessments that has been employed in our prior trials. We will train the research staff on conducting sedation, delirium, delirium severity, pain, anxiety, depression and cognition assessments utilizing the same teaching methods. The PIs and Co-I will oversee the relevant training. Dr. Khan and Dr. Chlan will do the didactics and bedside teachings and certifications of all the research staff for sedation, delirium, pain, anxiety, and depression assessments. Dr. Unverzagt will train and certify the research staff on cognition assessments.

Outcomes Measures:

In-Hospital Outcomes:

1. Delirium/Coma Free Days: Delirium/coma free days will be the primary outcome for the trial. Delirium/coma free days are the number of days after randomization patients are alive free of delirium and not in coma during the seven-day study intervention phase. This outcome describes the duration of normal cognitive status where the patient is not comatose and does not have delirium and has been utilized in high impact studies.[14-17] We will utilize the Confusion Assessment Method for the ICU (CAM-ICU)[75] and the Richmond Agitation Sedation Scale (RASS)[76] for assessment of delirium and coma respectively. RASS score ranges from -5 to +4 with a score of -4 or -5 (lack of response to verbal or physical stimuli) characterized as comatose and ineligible for CAM-ICU assessments. RASS scores of -3 and -2 depict moderate and light sedation, -1 drowsiness, 0 alert and calm, and +1 to +4 various degrees of agitation. Patients with a RASS score of -3 to +4 will be considered eligible for CAM-ICU assessments. The CAM-ICU score will be determined by examining the patient for (a) acute or fluctuating changes in mental status, (b) inattention, (c) altered level of consciousness and (d) disorganized thinking. Patients will be considered delirious if they display (a), (b), plus (c) and/or (d). Trained research assistants will be performing CAM-ICU twice daily after the assigned intervention. Sedation status through RASS will be collected before and after the intervention delivery. After the 7-day study intervention phase, study staff will continue to assess RASS and CAM-ICU twice daily throughout the subject's hospital stay (up till day 28).

2. Delirium Severity*:* Delirium severity will be assessed twice daily by trained research assistants using the CAM-ICU-7 developed by Dr. Khan. CAM-ICU-7 is a seven-point scale (0-7), derived from the RASS and the CAM-ICU. The CAM-ICU-7 score ranges from 0-7; categorized as 0-2: no delirium, 3-5: mild to moderate delirium, and 6-7: severe delirium.[77] Trained research assistants will be performing CAM-ICU-7 twice daily after the assigned intervention. After the 7-day study intervention phase, study staff will continue to assess CAM-ICU-7 twice daily throughout the subject's hospital stay (up till day 28).

3. Pain: Pain will be assessed by trained research assistants utilizing the Critical Care Pain Observation Tool (CPOT), a valid and reliable instrument in critically ill patients with and without delirium,[78,79] recommended by the SCCM 2018 PADIS guidelines.[21] CPOT uses observable physiological and behavioral indicators of pain to determine whether pain is present and can be used in nonverbal patients. It contains 4 sections, each with different behavioral categories, including facial expressions, body movements, muscle tension, and either compliance with ventilator (intubated patients) or vocalization (non-intubated patients). The score ranges from 0-2 for each section with a total score range of 0-8 with higher scores indicating more pain. Trained research assistants will be performing CPOT four times daily before and after intervention delivery. We will continue to assess CPOT twice daily after the 7-day study intervention phase throughout the ICU stay.

4. Anxiety: Anxiety intensity defined as a heightened state of apprehension, agitation, and arousal,[80] will be measured four times daily before and after assigned intervention using a 100-mm Visual Analog Scale-Anxiety (VAS-A), which measures changing anxiety and is amenable to intervention.[81,82] The VAS-A will be presented to all patients vertically, like a thermometer, and will be anchored on the ends by 0 = not anxious at all and 100 = most anxious ever. The VAS-A is scored using a ruler from the 0 anchor to the mark placed by the patient, which yields the current level of anxiety from 0 to 100. The same ruler will be used to score all VAS-As for consistency. Dr. Chlan has used the VAS-A extensively in prior research studies, including a vertical orientation of the instrument that is sensitive and easier for critically ill patients to see, resulting in very little missing data on this important variable.[31,81-83] We will continue to assess VAS-A twice daily after the 7-day study intervention phase throughout the ICU stay.

Post-Hospital Discharge Outcomes:

1. Cognition: Cognition will be measured by 4 objective tests of memory, attention, information processing speed, and executive cognitive function (Auditory Verbal Learning Test [AVLT], Digit Span, and Symbol Digit Modalities Test [SDMT], and Controlled Oral Word Association test [COWA]) using a telephone-based administration format, the Indiana University Telephone-Based Assessment of Neuropsychological Status (IU-TBANS) at 3-months post hospital discharge. Previous research has demonstrated that these tests can be delivered reliably and precisely by telephone.[84] The AVLT is a 5-trial 15-item word list learning task that provides two scores: sum recall of the five learning trials and delayed recall. Digit Span measures working memory and the ability to repeat short random number sequences forward and backward. We will use the oral version of the SDMT. Participants will be mailed the SDMT response sheet prior to the assessment and told to keep the envelope sealed and at hand for the day of the assessment. At the day of the assessment, the participant will be instructed to open the envelope and the SDMT practice items will be completed. Total score is the number of correct numbers-symbol pairings called out in 90 seconds. The COWA is a measure of verbal fluency and executive cognitive function in which words are generated orally that begins with specified letters of the alphabet. Scores derived from these tests can be analyzed separately and also combined to form a single cognitive composite score. We will provide participants with pre-assessment instructions to structure the assessment to minimize distraction and interruption and maximize reliability and precision.

Time-line of Data Collection and Outcomes Assessments

Variable	Method of Collection	ICU Phase			Hospital Discharge	Post-Hospital Discharge Phase
		Enrollment	Intervention Phase	Post-intervention Phase		3 months
Demographics (Age, race, gender, education, insurance)	EMR	X				
Clinical data (lab values)	EMR	X	Daily			
Comorbidities (Charlson)[a]	EMR	X				
Baseline cognitive function (IQCODE)[b]	Caregiver interview	X				
History of depression, anxiety	EMR	X				
Diagnoses	EMR	X			X	
Severity of Illness[c] (APACHE II, SOFA)	EMR	X (APACHE)	Daily (SOFA)			
Functional Status[d] (ADL, IADL)	EMR	X				
Medications[e] (sedatives, analgesics, anxiolytics, antipsychotics)	EMR, patient, caregiver	X	Daily	Daily	X	X
Duration of Mechanical Ventilation, Length of ICU and Hospital Stay	EMR				X	
Mortality	EMR				X	X
Discharge Disposition	EMR				X	
ABCDEF bundle adherence	EMR, Nursing reports	X	Daily	Daily		
Intervention characteristics	iPad App and Web Portal	X	X			
Physiologic Parameters (respiratory rate, heart rate, blood pressure)	EMR	X	4XDaily	Daily		
Delirium, Pain, Anxiety[f] (RASS, CAM-ICU, CAM-ICU-7, CPOT, VAS-A)	Direct Assessment		2XDaily (CAM-ICU, CAM-ICU-7) 4XDaily (RASS, CPOT, VAS-A)	2XDaily		
Cognition (IUTBANS)[g]	Direct Assessment					X
Mood symptoms[h] (GAD-7, PHQ-9)	Direct Assessment					X
Healthcare Utilization	EMR, INPC					X

[a]Chronic comorbidities measured through Charlson Comorbidity Index[89]; [b]IQCODE: Informant Questionnaire on Cognitive Decline in Elderly[90]; [c]Severity of Illness measured through APACHE II[91] and SOFA[92]; [d]Functional Status measured through Katz and Lawton Scales[93,94]; [e]Anlgesic and sedative exposure is defined as aggregate measure of pain and sedation intensity and the drug frequency in a 24 hour period. We will aggregate dose frequency and dosing intensity by each enrollment day. A dose frequency analysis will be used[95-97]. [f]RASS: Richmond-Agitation Sedation Scale[76],CAM-ICU: Confusion Assessment Method in the ICU[75],CPOT: Critical Care Pain Observation Tool[78],VAS-A: Visual Analog Scale-Anxiety[81]; [g]IUTBANS: Indiana University Telephone-Based Assessment of Neuropsychological Status[84]; [h]PHQ-9: Patient Health Questionnaire[85], GAD-7, Generalized Anxiety Disorder Scale[87]; [i] Captured through Indiana Network for Patient Care (INPC)

2. Depression and Anxiety: We will use the Patient Health Questionnaire–9 (PHQ-9)[85,86] and Generalized Anxiety Disorder Scale (GAD-7)[87,88] to determine the impact of the music intervention on ICU 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, test–retest reliability as well as construct, criterion, procedural and factorial validity for the diagnosis of major depression and general anxiety disorder.[85-88] Research staff will collect PHQ-9 and GAD-7 over the phone at 3 months post-hospital discharge.

Other Data Measures: The table above shows other data measures including physiologic parameters of respiratory rate, heart rate, blood pressure (collected four times daily before and after assigned intervention during the 7-day intervention phase; daily afterwards during ICU stay) and timeline of data collection. We will also collect the post-extubation ICU Recall Prior to/around Discharge. The Intensive Care Experience (ICE) questionnaire will be administered to all subjects and contains 25 total questions in four main categories: awareness of surroundings, frightening experiences, recall of experiences, and satisfaction with care.

2. REPORTING OF ADVERSE EVENTS

Safety: Patients will be monitored for adverse events on a daily basis. Adverse events will be reported to the Institutional Review Board (IRB), data safety officer and contact MPI Dr. Khan immediately. In our prior work, we have not experienced any adverse events related to the study protocols. All infection control guidelines will be followed based on each hospital's policy. Patient risks will be minimized through use of quality electronic devices, regular cleaning and maintenance. Lastly, given the high-intensity nature of the ICU, all patients will receive benefit from frequent monitoring in the ICU as part of routine care.

Study Withdrawal/Discontinuation: Participants who wish to withdraw from the study will notify the study team verbally during study interactions or via letter as outlined in the HIPAA authorization document.

3. STATISTICAL CONSIDERATIONS

Statistical Analyses: We will compare baseline patients' demographic characteristics (age, gender, race and levels of education) between the intervention and control group using two sample t-tests for continuous variables and Chi-square tests for categorical variables to determine whether the two groups are balanced in these variables. Variables that are found to be unbalanced will be included as covariates in all models comparing outcomes between the two groups. Intention to treat approach will be used in all analyses.

a. Primary Specific Aim: Delirium/coma free days by day 7 will be compared using analysis of covariance (ANCOVA) model with group (intervention versus control) as the independent variable while adjusting for the baseline patients' demographic variables not balanced between the two groups. For patients discharged before day 7, the days from discharge to day 7 will be counted as delirium/coma free. For patients who died before day 7, 0 delirium/coma free days will be counted from date of death to day 7. We have used the same approach in our previous trials and this approach is able to appropriately handle potential missing data due to discharge or death of patients before day 7.[17]

Secondary Specific Aim 1: Mixed effects models will be used to compare delirium severity (CAM-ICU-7), pain (CPOT) and anxiety scores (VAS-A) measured twice daily from randomization to day 7, time of death or discharge. In each of the models, repeated CAM-ICU-7, CPOT or VAS-A scores will be the outcome variable respectively. Group, time, group and time interactions will be included as independent variables while adjusting for potential baseline covariates. Significant group and time interactions will indicate differences in changes of these outcomes between the two groups. Post-hoc analyses will be conducted to determine the earliest times when significant differences between these outcomes can be detected. We will compare various variance covariance structures including autoregressive (AR) and variance components blocked by time of the day (am versus pm) using the likelihood ratio tests to determine the most appropriate covariance structure. We will also examine potential non-linear trajectories of change in these outcomes by including quadratic time in the models and by fitting spline models.

b. Secondary Specific Aim 2: ANCOVA models will be used to compare IU-TBANS, PHQ-9, and GAD-7 collected at three months post hospital discharge with group as the independent variable while adjusting for potential baseline covariates.

c. Missing Data: We expect up to 20% of patients who may not complete the primary outcome at day 7 due to death in the ICU or discharge before day 7. We will conduct sensitivity analyses with varying assumptions for the patients with missing outcomes to determine the robustness of our findings. The mixed effects model we propose for Secondary Aim 1 is robust to the missing at random assumption and is unbiased if we include all relevant covariates in the model. We will also compare baseline characteristics of patients with 3-month

assessment and those who are lost to follow-up and adjust for the variables associated with missing data to ensure unbiased estimation and inference.

d. Sex as a Biological Variable: Both male and female patients will be included in the trial. We do not anticipate treatment efficacy will differ by sex. We will include sex as a covariate in each analysis to

determine whether estimated treatment effects differ by sex.

e. Sample Size and Power: Sample size estimation is based on the observed effect size from our pilot data where the intervention group had higher delirium/coma free days from the control group with estimated effect size of 0.52. Using two sample *t*-test, we estimate that we will need 128 total patients with complete data to detect an effect size of 0.5SD or higher at α=0.05. For robustness of results, we also estimated power if we assume Poisson distribution for mean delirium/coma free days with a total 128 patients observed at day 7, we will have 98.7% power to detect group difference at α=0.05 using the nonparametric Wilcoxon test. Allowing up to 20% attrition rate for patients dropping out before day 7, we will enroll 160 total patients for this trial (80 per group).

For Aim 2, for anxiety measured by VAS-A, we estimated power using results published by Chlan et al[31] where the author reported (1) changes in VAS-A in both the music and control groups appear linear; and (2) the music group showed an average difference of 11 points (SD=6.48) in VAS-A scores between the two groups and the noise canceling headphones group had no-significant change over time. Assuming 128 total patients complete anxiety evaluation by day 7, a daily decrease of 0.03SD on VAS-A in the music group and no decrease in the control group, we will have 83.5% power in detecting a group and time interaction in the repeated measure model at α=0.05 assuming a first order autoregressive correlation structure with 0.4 for measurements one day apart. For pain, assuming a baseline mean of 0.54 for both groups (SD=0.63), a daily decrease of 0.2SD on CPOT in the music group and no decrease in the attention control group, we will have 80.6% power to detect a group and time interaction in a mixed effect model. We will also have 80.6% power to detect a significant interaction assuming similar trajectories for CAM-ICU-7 in the two groups. For Aim 3, we will have 80% power to detect an effect size of 0.5SD between the two groups using two sample *t*-test at α=0.05. The power estimates were conducted using the Power and GLMPower procedures in SAS 9.4.

3. PROTECTION OF HUMAN SUBJECTS

1. Risks to Human Subjects:

1.a. Human Subjects Involvement, Characteristics, and Design**:** 80% of older adults develop delirium during their ICU stay. Presence of delirium predisposes older adults 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. In addition, ICU delirium is associated with long-term post-discharge complications such as development of cognitive impairment and dementia. Our team is proposing to conduct a randomized clinical trial called "Decreasing Delirium through Music (DDM) in Critically Ill Older Adults" to evaluate the efficacy of a seven-day slow-tempo music intervention on the primary outcome of delirium/coma free days among mechanically-ventilated older adults admitted to the ICU.

The target population will be English-speaking; mechanically ventilated adults aged 50 and older who have been admitted to the intensive care unit in either Eskenazi Health or Methodist Hospital in Indianapolis or the Mayo Clinic in Rochester. The intervention comprises slow-tempo relaxing music versus a silence track attention control delivered twice daily for seven days. The primary outcomes will be delirium/coma free days. The enrolled population will also include women and minorities who meet the inclusion criteria. Subjects will be excluded as follows: [1] History of dementing illnesses and other neurodegenerative diseases such as Alzheimer's disease or vascular dementia; [2] Psychiatric illness which is not well controlled [3] Alcohol withdrawal symptoms/concern for withdrawal; [4] Suspected or confirmed drug intoxication/overdose, [5] Traumatic brain injury, ischemic or hemorrhagic cerebrovascular accident, or undergoing neurosurgery; [6] Uncorrected hearing or vision impairment including legal blindness; [7] Incarcerated at the time of study enrollment, [8] Enrolled in another clinical trial which does not permit co-enrollment

After obtaining approval from the local institutional Review Board (IRB) and the ICU leadership at each hospital, subjects or their legally authorized representative will be approached for participation into the study. After enrollment the subjects will be randomized into two groups, slow-tempo music intervention and silence track attention control. The interventionist research staff will initiate the study intervention. The research staff will perform blinded outcomes assessment including delirium/coma free days, delirium severity, pain, and anxiety during the ICU stay. After discharge, at 3 months, research assistants will perform cognition assessment, and will collect depression and anxiety measures over the phone.

1.b. Sources of Materials**:** During the hospital stay, research assistants will review the medical records and conduct delirium, coma, pain, and anxiety assessments. The blinded research assistants will also be collecting information on physiologic status (blood pressure, height, weight, heart rate, respiratory rate). The assessors will also conduct a medical record review to assess subject's chronic conditions (Charlson comorbidity index) and severity of medical illness (APACHE II index, SOFA). Study specific blood specimens will provide biomarker data.

All data gathering is done initially with subjects or their legally authorized representatives in the ICU and afterwards at the 3 months post hospital discharge follow-up. 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. Case Report Forms (CRFs) will be stored in locked filing cabinets at Regenstrief Institute or Mayo Clinic and all data will be entered into electronic case report forms (eCRFs) in a secured password-protected database. All study data will be entered via a password-protected, study specific REDCap (Research Electronic Data Capture) database website. REDCap was developed specifically around HIPAA- Security guidelines and 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.project-redcap.org).

1.c. Potential Risks**:**

(1) *Fatigue, anxiety, stress, or embarrassment from the assessments.* 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.

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

(3) *Discomfort with music delivery.* There is potential for discomfort, infection, and irritation with use of the headphones. Another potential risk is that a subject could have an adverse emotional response to a certain piece of music. The potential risk for an adverse emotional response to music is thought to be low in regards to the music planned for our study playlist. Our music therapist consultant has extensive professional experience with ICU patients receiving mechanical ventilation. *Depression and suicidal ideation.* The duration of the study intervention is limited to the ICU; therefore adverse events related to the intervention occurring after the date of discharge are unlikely. Because research staff will continue to collect data from participants for 3 months after discharge, and because psychological complications have been described in ICU survivors, study staff will recognize worrisome conditions such as suicidal ideation or other emergent concerns of clinical conditions (chest pain, etc) during any study interaction. Study personnel will follow a scripted protocol to notify the appropriate medical personnel and the PI so that appropriate notification and clinical follow-up is ensured. The PI or delegated study personnel will notify the appropriate provider or emergency personnel depending on the severity of the presentation. Even in depression trials conducted by Regenstrief investigators with clinically depressed patients, this is only an occasional event, and in the present study we expect it to be rare. Nonetheless, we will train study personnel in the recognition and communication of such events to ensure prompt response to emergent reports if they occur.
Risks related to blood sample collection will be minimized by use of clinical nurses for sample collection, use of existing intravascular devices for drawing blood whenever possible, and transport of the samples using lab best practices, and labelling the samples with deidentified labels.
(4) Subjects may have pain, bruising or very rarely get an infection from the blood draw. To minimize these problems, blood will be drawn by trained staff using sterile procedures.

2. Adequacy of Protection Against Risks:
2.a. Recruitment and Informed Consent: Eligible subjects will be identified through the intensive care units census to which they are admitted. A waiver of consent documentation will be obtained for recruitment purposes only. Study personnel will consent the patient or their legally authorized representative (if the patient is unable to consent for themselves).

2.b. 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. Research staff 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.
(2) *Exposure of confidential information.* Indiana University requires certification of training in protection of human subjects in research. The investigators, interventionist, 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. We will also utilize these rigorous protocols to protect confidentiality of biomarker analyses which include genetics and epigenetics associations. Our 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.
(3) *Discomfort with music delivery.* Patients will be monitored for adverse events on a daily basis. Adverse events will be reported to the Institutional Review Board (IRB), data safety officer, and PIs immediately. In our prior work, we have not experienced any adverse events related to the study protocols. All infection control guidelines will be followed based on each hospital's policy. Patient risks will be minimized through the use of quality electronic devices, their regular cleaning and maintenance. If patients endorse discomfort from headphones, they will be switched to another set. In case of an adverse emotional response to music, subjects will be informed that they are free to withdraw from the study at any time they so desire without affecting their care. In previous work by the PI in which subjects listened to music from a discrete collection, no adverse emotional responses to music has occurred, thus we believe our plan here will be equally effective.
(4) *Depression and suicidal ideation*: During follow-up assessments it is possible that participants endorse

suicidal ideation on the PHQ-9. We have handled them extensively in our prior m-CCRP and IMPROVE trials and have developed a suicide response protocol. A positive PHQ-9 will be followed by the Columbia Suicide Severity Rating Scale (C-SSRS) questions. If a participant answers yes to any C-SSRS question, the PI (Dr. Khan) will be notified immediately who will contact the family member to arrange transfer to the ER. If the participant does not answer yes to any C-SSRS question, the RA will still notify Dr. Khan who will contact the PCP of the patient and will arrange for an urgent follow-up.
(5) Subjects may have pain, bruising or very rarely get an infection from the blood draw. To minimize these problems, blood will be drawn by trained staff using sterile procedures. Existing intravascular devices for drawing blood will be used whenever possible.

3. Potential Benefits of Proposed Research to Human Subjects and Others: Participants may experience short-term benefits such as improve delirium/coma free days, lower delirium severity, pain, anxiety, depression and improved cognition. The intervention may also reduce potential harms from short-term, and possibly long- term use of opioids and benzodiazepines, recognized as potentially inappropriate medications according to the American Geriatrics Society Beer's Criteria. Discontinuation of medications with adverse cognitive effects may improve short- and long-term cognitive performance. The improvement in cognitive function may or may not be noticeable to study participants. This research could also provide a non-pharmacological approach for delirium management in ICU patients.

The intervention proposed in this study builds upon 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. While risks associated with this proposed study are thought to be low, findings have the potential to be applied to the million patients who receive mechanical ventilatory support each year in the United States. If the findings from this investigation support the research hypothesis, mechanically ventilated patients who listen to music would experience fewer of the side effects documented to occur with these symptom management regimens that rely solely on potent sedative medications. This in turn may lead to patients being weaned quicker from mechanical ventilation, which would decrease the suffering and burdensome symptoms associated with mechanical ventilation such as fewer ventilator-associated pneumonias which could lead to reduced complications and costs for ICU medical care.

4. Importance of Knowledge Gained: Up to 80% of ICU patients develop delirium and currently there are no effective and scalable treatment modalities. Our proposed intervention may provide a conceptual and scalable recovery model to remediate or treat ICU delirium and its deleterious effects on cognition.

4. DATA AND SAFETY MONITORING PLAN

The MPIs (Dr. Khan, Dr. Chlan) and a safety officer will monitor the study.

~~1.~~ **Qualifications and responsibilities of the Safety Officer:** The safety officer for this trial will be a clinical researcher experienced in running intervention studies. The safety officer will review the reports sent by the study manager to determine whether there is any corrective action, trigger of an ad hoc review, or stopping rule violation that should be communicated to the study primary investigator, the Indiana University IRB, and the NIH. In addition, the safety officer may comment on whether the study investigators need to report any specific out of range data to the participant and/or her physician. As with our prior trials, the safety officer will receive a monthly report of all events that occurred during the month.

2. Monitoring and Reporting: The frequency of data reviews for this study differs according to the type of data and can be summarized in the following table:

Data Type		**Frequency of Review**	
	Each Occurrence	Q 6 months	Annual
Subject accrual (adherence to inclusion/exclusion); drop-out rates; randomization		X	
Adverse event rates	X	X	
Subjects' Complaints		X	
Compliance to Interventions		X	
Protocol Violation/Non-compliance	X	X	
Risk Benefit Ratio Assessment			X
Stopping Rules Report			X

The study coordinator and biostatistician will generate reports for PI, and safety officer that will contain:

- Summary of adverse events and an explanation of how each event was handled,
- Summary of complaints and how each complaint was handled,
- Subject retention, including the number and reasons of participant withdrawals,
- Intervention compliance (session attendance), and
- Summary of protocol violations and how each was handled. All reports will be submitted to IU IRB at time of continuing review.

3. Measurement and reporting of adverse events: Adverse event rates associated with music intervention are low. Therefore, adverse event rates are expected to vary little between the treatment and control groups. We will present blinded adverse event data to the statistician and PI throughout the trial. We plan to present unblinded adverse events data to the safety officer throughout this trial and as requested by the safety officer and at annual meetings. If there is evidence of elevated adverse events, the safety officer will consult with the statistician and PI. The study staff will use an adverse event form to report adverse events caused by the intervention.

4. Possible Adverse Events: Adverse events will be monitored on an ongoing basis by the study coordinator. The PI will be notified within 24 hours of any adverse events. Serious adverse events will be reported within 5 business days to IU IRB, Safety Officer, and NIH. Non-serious adverse events will be reported weekly to the safety officer and at time of continuing review to IU IRB. In cases where there is any question regarding the level of adverse events or attributable cause, we will consult with the safety officer.

The information collected will include the following:

- Description of the AE.
- Time and Date of onset and eventual date of resolution or death, if available.
- Frequency: intermittent, single occurrence, or continuous.
- Severity of the event.
- Action taken, including use of any concomitant treatment or medication.
- Outcome.
- Relationship to study treatment regimen or other causality.

5. Stopping Rules: It is unlikely that the study would be stopped early due to important favorable differences in the intervention group compared to control group because of the short-term nature of the intervention. However, the study could be stopped early due to adverse events. The NIA will make the final decision on whether or not to accept the safety officer's recommendation about discontinuation of any component of the study.

6. Limits of Assumptions: It is possible that baseline differences between the groups, excessive study dropouts and/or missing data by the interim measurement time point (midway point to targeted enrollment) will limit the value of data analysis. Baseline differences will be evaluated after the first measurement time point and effects on the power to detect differences in the primary outcome will be evaluated and communicated to the PI, safety officer, and NIA. Given the monitoring plans outlined elsewhere in this document, it is exceedingly unlikely that there will be baseline differences between groups of any magnitude to threaten the validity of the study.

Dropout rates higher than 15% would be of concern, so we propose to monitor the dropout rate quarterly. Alert points are set at dropout rates of 15% (low alert), 25% (mid-alert), 35% (high alert) and 45% (extreme alert).
With early alerts to problems, action would be taken to avoid higher-level alerts; if a higher-level alert should arise, more drastic remedial action would be invoked.

The actions taken at each level of alert are given below:

- Mid-level alert = Conference call between study investigators to discuss approaches to minimize further losses to follow-up/dropouts.

- High-level alert = Conference call between investigators and safety officer to determine further alterations of study protocol to complete the study with no further losses.

- Extreme-level alert = In the unlikely event of a 45% dropout rate occurs prior to the six-month measurement time point, study investigators, the safety officer, and the NIA program official would convene on a conference call to discuss the usefulness of continuing the study.

Additional Protocol Materials based on Supplemental Funding

Changes added with protocol amendment 5/22/2023

1. ***Add baseline(prior to/around hospital discharge) and longitudinal outcomes assessment (month 6, month 12) data collection timepoints***

   A. Cognition: Cognition will be measured by 4 objective tests of memory, attention, information processing speed, and executive cognitive function (Auditory Verbal Learning Test [AVLT], Digit Span, and Symbol Digit Modalities Test [SDMT], and Controlled Oral Word Association test [COWA]) using a telephone-based administration format, the Indiana University Telephone-Based Assessment of Neuropsychological Status (IU- TBANS) **prior to/around hospital discharge**, at 3-months post hospital discharge**, 6 months post-hospital discharge and 12 months post-hospital discharge**.

   Previous research has demonstrated that these tests can be delivered reliably and precisely **in** person or by telephone.[84]

   B. Depression and Anxiety: Research staff will collect PHQ-9 and GAD-7 over the phone **or in person prior to/around hospital discharge**, at 3 months post-hospital discharge**, 6 months post-hospital discharge and 12 months post-hospital discharge.**

2. ***Add Blood Sample Collection Time points (month 3, month 6, month 12).***

   During hospitalization we will collect blood samples prior to first intervention session (up to 10ml in tubes containing anticoagulant), at day 3, and at the end of the intervention period (up to 10 ml in tubes containing anticoagulant). ***Samples will also be collected at the month 3, month 6 and month 12 post hospital discharge visits (up to 10ml in tubes containing anticoagulant) in the clinic***. ***This will be a total of up to 4 tablespoons of blood collected.*** The samples will be transported to the CTSI lab, and will be prepared and stored using deidentified labels.

3. ***Exploratory Aims added (1,2)*:**

   Exploratory Aim 1: Test the efficacy of the DDM treatment in slowing the rate of post-ICU cognitive decline in mechanically ventilated patients as compared to attention control. Hypothesis 1a: Patients in the DDM intervention group will have slower cognitive decline compared to the attention control group as measured by the IU-TBANS completed at 6- and 12-months after hospital discharge. Hypothesis 1b: This difference in cognitive trajectories between the DDM intervention group versus the attention control group will be due, in part, to the DDM treatment decreasing the duration and severity of ICU delirium during the index ICU stay.

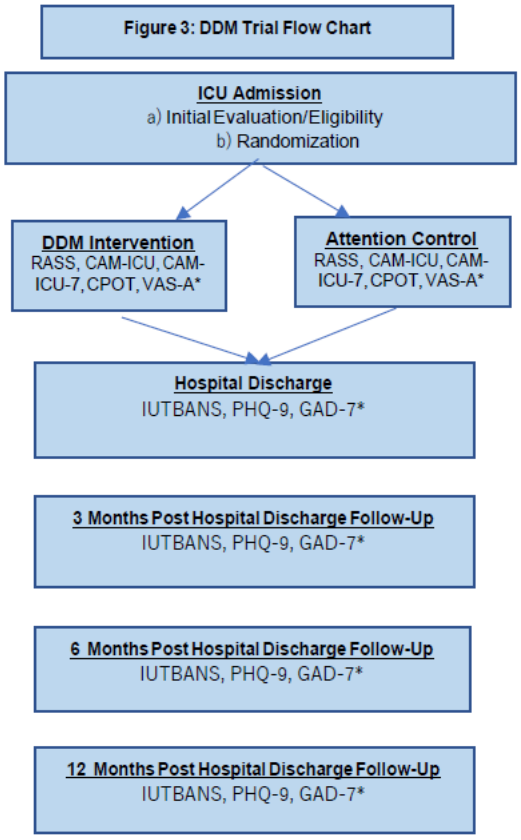
   Exploratory Aim 2: Determine whether the DDM treatment is associated with slower progression of ADRD pathology in older adult ICU survivors as compared to attention control. Hypothesis 2a: Patients in the DDM treatment group will have slower progression in measures of neurodegeneration (lower level of neurofilament light (NfL), phosphorylated tau-181 (p-tau 181), glial fibrillary acidic protein (GFAP), and S100B), AD pathology (higher levels of Aβ42/Aβ40), vascular pathology (lower levels of C-reactive protein (CRP))[8] and inflammation (lower levels of interleukins (IL)-1, 6, and 8) as measured by blood-based biomarkers collected in the ICU and 3, 6 and 12 months after hospital discharge, compared to those in the attention control group. Hypothesis 2b: These differences in progression of ADRD pathology between the DDM treatment versus control group will be due, in part, to the DDM treatment decreasing the duration and severity of ICU delirium during the index ICU stay.

4. Exploratory Aims Statistical Considerations added (1,2)

Exploratory Aim 1: Mixed effects models will be used with repeated IUTBANS scores (collected at baseline, 6 months and 12 months as the outcome measures), group, time, and a group and 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 between the two groups.

Exploratory Aim 2: Changes in the biomarkers 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. Mixed effects models will be used to explore the association between oxidative stress biomarkers at ICU admission and those collected at 3, 6-, and 12- months post discharge.

***5.* Revised Figure 3: DDM Trial Flow Chart**



6. Revised Table Time-line of Data Collection and Outcomes Assessments

Time-line of Data Collection and Outcomes Assessments								
Variable	**Method of Collection**	**ICU Phase**			**Hospital Discharge**	**Post Hospital Discharge**		
		Enrollment	**Intervention Phase**	**Post-intervention phase**		**3 months**	**6 months**	**12 months**
Demographics (Age, race, gender, education, Insurance)	EMR	X						
Clinical Data (lab values)	EMR	X						
Comorbidities (Charlson)[a]	EMR	X						
Baseline Cognitive function (IQCODE)[b]	Caregiver Interview	X						
History of depression, Anxiety	EMR	X						
Diagnoses	EMR	X			X			
Severity of Illness[c] (APACHE II, SOFA)	EMR	X (APACHE)						
Functional Status[d] (ADL, IADL)	EMR	X						
Medications	EMR, patient, caregiver	X	Daily	Daily	X	X	X	X
Duration of Mechanical Ventilation, Length of ICU and Hospital stay	EMR				X			
Mortality	EMR				X			
Discharge Disposition	EMR				X			
ABCDEF bundle adherence	EMR, Nursing reports	X	Daily	Daily				
Intervention characteristics	iPad App and Web portal	X	X					
Physiologic Parameters (respiratory rate, heart rate, blood pressure)	EMR	X	4X Daily	Daily				
Delirium, Pain, Anxiety[f] (RASS, CAM-ICU, CAM-ICU-7, CPOT, VAS-A)	Direct Assessment		2X Daily (CAM-ICU, CAM-ICU-7), 4X Daily (RASS, CPOT, VAS-A)	2X Daily				
Cognition (IUTBANS)[g]	Direct Assessment				X	X	X	X
Mood Symptoms[h] (GAD-7, PHQ-9)	Direct Assessment				X	X	X	X
ICU Experience, Music preference[j and k]	Direct Assessment				X			
Specimen collection	Direct Assessment	X	X	X		X	X	X
Healthcare Utilization[i]	EMR, INPC							X

[a]Chronic comorbidities measure through Charlson Comorbidity Index[89],[b]IQCODE: Informant Questionnaire on Cognitive Decline in Elderly[90],[c]Severity of Illness measured through APACHE II[91] and SOFA[92], Functional Status measured through Katz and Lawton Scales[93,94],[c]Analgesic and sedative exposure is defined as aggregate measure of pain and sedation intensity and the drug frequency in a 24 hour period. We will aggregate dose frequency and dosing intensity by each enrollment day. A dose frequency analysis will be used [95-97]. [f]RASS: Richmond-Agitation Sedation Scale[76],CAM-ICU: Confusion Assessment Method in the ICU[75],CPOT: Critical Care Pain Observation Tool[78], VAS-A: Visual Analog Scale-Anxiety[81],[g]IUTBANS: Indiana University Telephone-Based Assessment of Neuropsychological Status[84],[h] PHQ-9: Patient Health Questionnaire[85], GAD-7: Generalized Anxiety Disorder Scale[87],[i] Captured through Indiana Network for Patient Care (INPC),[j] Intensive Care Experience Questionnaire, Music Preferences Questionnaire. [k]We will obtain the Richard-Campbell Sleep Questionnaire around time of extubation (once patient can communicate), at hospital discharge, and at 3-, 6-, and 12-months.