Family Automated Voice Reorientation Study: Reorientation Intervention for Delirium in the ICU

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ClinicalTrials.gov Identifier: NCT03128671

1. Protocol Title

Reorientation Intervention for Delirium in the ICU

2. IRB Review History

This minimal risk study received expedited review IRB approval from the University of South Florida IRB on September 30, 2016 and remains open following the last Continued Review on September 5, 2017. The contact number for the USF IRB is 813-974-5638. The USF IRB protocol number is Pro00027039. This study is funded by National Institutes of Health, National Institute of Nursing (1R01NR016702) and registered on ClinicalTrials.gov (NCT03128671).

3. Objectives

The primary specific aim of the proposed project is to test the effect of the Family Automated Voice Reorientation (FAVoR) intervention on delirium in critically ill, mechanically ventilated adults during hospitalization in the ICU. We hypothesize that subjects who receive FAVoR will have less delirium than control subjects who do not receive the intervention.

Secondary aims of this project are to: (1) explore if the effect of FAVoR on delirium is mediated by sleep, (2) explore if selected biobehavioral factors may potentially moderate the effects of FAVoR on delirium, and (3) examine the effects of FAVoR on short term (immediately after ICU discharge) and long term (1 and 6 months after hospital discharge) outcomes, including cognitive function and patient-reported health status.

4. Background

Delirium is an acute disturbance in attention (reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment), with additional change in cognition (memory, disorientation, or language disturbance).[1] Mechanically ventilated patients are especially at risk for cognitive dysfunction, and experience delirium at higher rates than patients who are not ventilated, with delirium occurring in as many as 80% of mechanically ventilated critically ill patients. It typically occurs within the first few days of intensive care unit (ICU) stay,[2] and results in significant negative outcomes.[2,3] A recent meta-analysis of 16 studies involving 6,410 patients confirmed that delirium has direct negative effects on ICU and hospital length of stay and mortality.[4] Number of days of delirium has been identified as an independent predictor of mortality in ICU patients.[5-7] Meta-analyses have confirmed that patients with delirium have longer duration of mechanical ventilation, greater incidence of complications including nosocomial pneumonia and higher hospital mortality than patients without delirium.[4]

Sleep disturbances in the ICU have been associated with risk of delirium,[3,8,9] and may also interact with interventions aimed at reducing delirium. A variety of other iatrogenic/environmental and biobehavioral factors (including environmental conditions, pharmacological therapies, disease severity and comorbid conditions, and demographic characteristics) are also theorized to affect the incidence of delirium.[10,11] However, empirical evidence of the relationships of these factors to the development of delirium and its treatments is limited.

Importantly, delirium in the ICU not only complicates the hospital course, but is also associated with lasting sequelae.[12-15] Data suggest that 25% to 78% of patients who have delirium in the ICU suffer clinically significant declines in cognitive function following their ICU stay.[16,17]

Cognitive dysfunction may persist for months or be permanent,[14,16,18] and is associated with impairments in daily function.[19] In recent studies, increasing duration of delirium was an independent predictor of worse cognition 3 months and 12 months after ICU discharge,[16,18] and this remained true even after adjusting for risk factors such as age, severity of illness, severe sepsis, and exposure to sedative medications in the ICU.[16] Reducing delirium in mechanically ventilated ICU patients may reduce both short and long term cognitive dysfunction and posthospitalization disability.

To date, the focus of delirium research has been on detection of existing delirium and on its pharmacologic treatment.[20] In contrast, our approach focuses on prevention of delirium using a nonpharmacologic intervention.

Significance

Delirium is a common manifestation of cognitive dysfunction in critically ill patients, which is associated with substantial negative outcomes both during and following hospitalization. Using the published estimates[22-24] that there are 5 million ICU admissions in the US each year, that approximately 40% of the critically ill require mechanical ventilation, and that delirium affects up to 80% of mechanically ventilated adult ICU patients, delirium likely affects an astonishing 1.6 million critically ill, mechanically ventilated ICU patients annually.

Delirium in critical illness is estimated to cost $4 to $16 billion annually[3] Delirium increases ICU cost, hospital cost, complications, and mortality. A recent meta-analysis concluded that compared to patients without delirium, delirious patients were six times more likely to experience complications, had 7.22 days longer duration of mechanical ventilation, 7.32 days longer ICU length of stay, and 6.53 days longer hospital length of stay.[4] Further, patients who experience delirium have problems with cognitive function and health status after hospital discharge, which have been documented at 3 and 12 months and may persist indefinitely.[18,25,26] Because of the extensive incidence and significant negative outcomes associated with delirium, identification of effective interventions to reduce delirium is critically important. The Society of Critical Care Medicine, in its most recent guidelines for managing pain, agitation, and delirium in the adult critically ill,[3] recommended routine assessment for delirium in the ICU and stated that the study of delirium in mechanically ventilated patients may lead to important advancements in the treatment of critically ill patients. A primary goal for the critically ill patient is to provide patient comfort while maintaining a level of arousal sufficient to follow commands. As a result of trends toward lighter sedation, most patients are aware of the ICU surroundings and require consistent and frequent reorientation to all aspects of their care.

Reorientation may enhance patients' feelings of security and comfort, allow them to more accurately interpret these stimuli, and ultimately reduce delirium. However, communication with sedated or non-responsive critically ill patients is often not optimal[27-29] and is often considered to be a low priority in the ICU setting.[30] A review of nurse-patient communication in the ICU found that nurses communicate poorly with patients, despite a high level of knowledge and skill with respect to communication. High stress levels and preoccupation with physical care and technology are potential explanations.[29] Although most critically ill patients are sedated and many appear nonresponsive, several studies have documented that patients hear, understand and respond emotionally to what is being said even when healthcare providers assumed they were not aware.[31,32] In interviews 48 hours after ICU discharge, patients were not able to recall their nurse's name, but did recall detailed explanations given to them by nurses.[31] Automated messages about the ICU environment will provide consistency of information, augment the

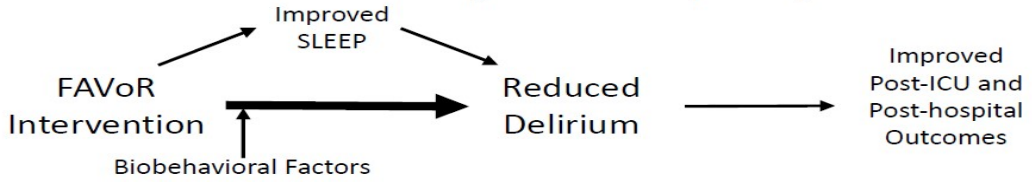
communication provided by nurses at the bedside, and may enhance the critically ill patient's feelings of comfort.

The scientific premise for the proposed project is that providing reorientation through scripted, automated, recorded messages in a family member voice familiar to the critically ill mechanically ventilated adult will mitigate the reduction of orientation to the environment which is a central feature of delirium, and reduce the occurrence of delirium. Several small studies have evaluated the effects of messages recorded by family on head injured comatose patients, although delirium was not assessed, and non-comatose patients have not been studied. Two small studies (12 subjects[33], and 10 subjects[34]) evaluated physiologic risks in comatose patients with head injury, and found no evidence of increased ICP or other physiologic derangements related to a single recorded family voice message. In a recent small RCT (n=40) of comatose patients with acute subdural hematoma, the group who received recorded family messages of encouragement twice a day for 10 days had better GCS scores on day 10 compared with a control group (p=0.0001), although the groups had equivalent GCS scores at baseline.[35] Use of a recorded family voice to improve orientation and reduce delirium is a novel approach which has not been previously described in the research literature nor considered in recent clinical guidelines, but our own preliminary data in a small randomized trial of 30 subjects (further described as preliminary study 2) supports beneficial effects of the intervention on reducing delirium occurrence and improving sleep in the ICU. Our own pilot work and small studies conducted by others support the scientific premise that scripted, automated, recorded messages in a family voice are not harmful, may benefit consciousness and improve cognitive orientation, and may reduce incidence of delirium. While promising, a more robust examination of the effects of this intervention, using rigorous methods in an adequately powered sample, as we propose, is warranted.

The cognitive reorientation intervention we have developed and pilot tested is a simple but potentially powerful strategy to provide structured information in a familiar voice to patients on a regular basis. Because the intervention has a strong nursing care focus, it has the potential to affect delirium in ways that are distinct from but synergistic with medical care, which has focused primarily on pharmacologic management of delirium. The FAVoR intervention we propose in this project holds promise for reducing delirium in critically ill adults, improving sleep in the ICU, and secondarily benefitting cognitive function post-ICU.

We will accomplish the objectives using a prospective, randomized, experimental design to achieve robust and unbiased results. Subjects (n=182) will be randomly assigned within 48 hours of ICU admission and intubation to one of two groups. In the intervention group, scripted audio messages recorded by the patient's family (FAVoR) will be played for the patient at hourly intervals during daytime hours. These messages will be personalized, delivered automatically, and provide information about the ICU environment. Subjects in the control group will not receive recorded audio FAVoR messages. The FAVoR intervention, a standardized protocol developed and tested in preliminary work, will be delivered by audio recording for 5 consecutive days (120 hours), or until ICU discharge if discharge occurs within the first 5 days. The number of episodes of delirium during ICU stay is the primary outcome measure. We will also collect data at 1 month and 6 months following ICU stay for secondary aim 3. A model of the study is presented in Figure 1.

Figure 1. Relationship of study variables

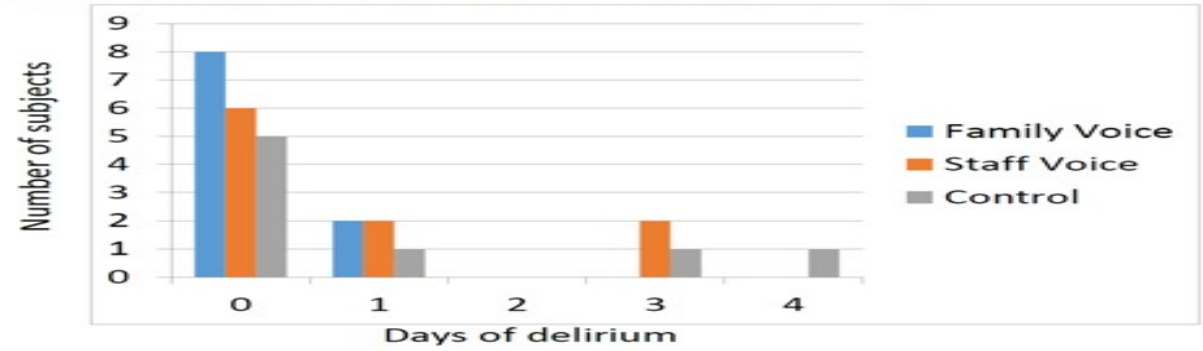


Preliminary Studies

1. Development of a reorientation intervention for critically ill adults. We conducted an early feasibility study to develop a reorientation intervention and test it in healthy volunteers in an ICU setting. A draft script of reorientation messages was developed based on published research by our team and others about patients' recall of ICU experiences.[38-40] The draft script was reviewed by 3 experts in critical care. We edited based on their feedback. The recorded message was then tested on 2 healthy nurse volunteers, simulating patients, in the ICU setting. Adjustments to message volume and length as well as location of the speaker were then made based on characteristics of the ICU environment (noise levels, ICU equipment placement, etc.). These data assisted in the development and testing of the proposed intervention in the ICU setting.

2. Reorientation Intervention for Cognitive Dysfunction in the Critically Ill: A Feasibility Study. We conducted a randomized, controlled, preliminary study to explore the effect of a cognitive reorientation intervention on delirium in a small sample (n=30) of critically ill adults. Thirty adult patients admitted to Tampa General Hospital ICUs were randomized to three groups. The sample was 63% male, ranged in age from 19 to 97 years old (mean 59.5, SD 17.0), and had a mean APACHE severity of illness score of 64 (SD 20.7). Using scripts developed in preliminary study 1, ten subjects were randomized to receive automated, scripted reorientation messages in a familial voice, ten subjects received the same messages in a nonfamilial voice (bilingual female research team member) and ten subjects did not receive a reorientation message. Delirium was evaluated by the Confusion Assessment Method (CAM)–modified ICU version. The family voice group had more delirium free days than the non-familial voice group, and significantly more delirium free days (Chi-Square, p= 0.0450) than the control group (see figure 2). During the three-day intervention period, mean days of delirium were 0.2 in the family voice group, 0.8 in the staff voice group, and 0.9 in the control group. Wrist actigraphy was recorded for a maximum of three consecutive days starting from the time of admission to the ICU. Actigraphy was successfully obtained in 76% (n=23) of the sample. Sleep efficiency was calculated from actigraphy data to evaluate sleep in the ICU. To explore the possible mediation effect of sleep in a longitudinal study setting, we fitted two linear mixed models: (1) the ICU-CAM score against the group assignment and (2) the ICU-CAM scores against the percent of sleep and Sobel's test was applied. Following the reorientation intervention, sleep efficiency increased from baseline in both intervention groups, but decreased in the control group. The mean sleep efficiency in the family voice group increased from 56% to 66%, and sleep efficiency also increased from 45% to 52% in the non-familial voice group, both compared with the control group (sleep efficiency decreased from 54% to 52%). While it was not statistically significant, there was a trend towards improvement of the sleep efficiency as measured by actigraphy in the two intervention groups. Based on the results of the preliminary study that indicated family voice was most effective, we focused the primary aim of this proposal on testing the effect of family voice on delirium.

Figure 2. Delirium frequency by intervention group



3. Oral care in mechanically ventilated adults. Over the past 2 decades, we have conducted research to provide definitive guidance for effective evidence-based oral care interventions for critically ill adults. Clinical practice recommendations for routine prescription of chlorhexidine (CHX) to reduce oral microbial colonization and risk of ventilator associated complications are based in part on the results of the first component of the program of research in oral care in mechanically ventilated adults (R01 NR07652)[37-41]. In the initial funding period, we examined the effects of tooth brushing three times a day and CHX twice a day, alone and in combination, on dental plaque and risk of VAP. We found that while CHX reduced risk, tooth brushing neither reduced risk nor enhanced the effect of CHX.[41] In the second funding period, we tested the addition of a pre-intubation application of CHX, and surprisingly, found that it did not reduce VAP risk beyond the protection afforded by adherence to post-intubation CHX application guidelines.[42] This was also important to clinical practice; since our data indicate that it is not essential to deliver the first dose of CHX prior to intubation, permitting providers to focus their attention on other critical pre-intubation activities. The current project will complete the essential evidence base for oral care delivered by nurses to critically ill patients. In the current funding period, we are determining optimal tooth brushing frequency, while considering individual-level variables that may influence both efficacy and risk of adverse events. Although we recognize that the proposed project addresses a different iatrogenic risk (delirium rather than ventilator associated complications), this series of projects is relevant to the proposed study because it established and refined our expertise in conducting intervention research in the challenging ICU environment, and demonstrates our commitment and ability to translate our findings to clinical practice.

Importance of the Knowledge to be Gained

The data obtained will provide empirical evidence that will enable us to evaluate the effect of the FAVoR intervention on delirium and holds promise to translate new knowledge into clinical decision-making about the management of delirium in the critically ill to ultimately improve patient outcomes, both in the ICU and as long-term survivors. We plan to publish the results of this study.

5. Inclusion and Exclusion Criteria

Since delirium in the ICU setting has a mean onset of 2.6 days (S.D.+/-1.7),[45] enrolling within 48 hours of initial intubation and ICU admission will initiate the FAVoR intervention prior to likely time of delirium onset. Male and female adults from all ethnic and racial backgrounds will be recruited.

For inclusion, mechanically ventilated subjects must be:

- at least 18 years old,

- within 48 hours of initial intubation and ICU admission,
- they or their legally authorized representative (LAR) must be able to provide informed consent in English or Spanish, and
- a family member able to speak English or Spanish must be available and willing to audio record scripted messages.

Exclusion criteria include:

- dementia (because it complicates planned longitudinal cognitive assessments),
- anticipation by the clinical provider of imminent patient death,
- medical contraindication to the intervention (for example, psychiatric history of auditory hallucinations, or profoundly deaf), and
- inability to speak either English or Spanish.

We will use the procedure described by our consultant, Dr. Ely, and his colleagues[45] to screen for pre-existing dementia as follows. The modified Blessed Dementia Rating scale (mBDRS)[47] will be used to screen for dementia using family interviews; it is a valid measure in ICU patients where direct patient assessment is not feasible.[48] Similar to Ely et al.,[45] we will include an additional family/surrogate question asking them to rate on a 5-point scale whether they believe the patient has dementia. We will also increase the sensitivity for detecting pre-existing dementia by excluding potential subjects with suspected dementia if they meet any of the following 3 criteria: (1) history of an expert diagnosis of dementia, (2) modified Blessed Dementia Rating scale score of at least 3, or (3) rating by the surrogate of at least 3 out of 5 as possibly having dementia.

Because the intervention scripts have been developed, IRB approved, and pilot tested in English and Spanish, patients who do not speak either English or Spanish, as identified by self or their family, will be excluded.

Inclusion of Adults Unable to Consent

In our experience in conducting clinical research in the critical care areas, we have found that potential subjects who are mechanically ventilated are generally sedated to some degree. In addition, since use of mechanical ventilation primarily occurs during periods of patient instability, the use of sedation at these times is extensive and compromises patient's ability to communicate effectively which is compounded by the presence of the endotracheal tube. As a result, we have always found it appropriate to contact the legally authorized representative for consent. However, there may be rare occurrences when potential subjects are adequately oriented and lucid to be able to provide informed consent. Therefore, we will use the 2-step procedure described by Fan et al.[76] to determine the patient's ability to provide informed consent. Step 1 is objective evaluation with the Richmond Agitation-Sedation Scale (RASS) and the Confusion Assessment Method for Intensive Care Unit (CAM-ICU). Patients who score -1, 0, +1 on the RASS indicating drowsy, alert, or restless respectively and are not delirious (CAM-ICU = No) will move to Step 2. Step 2 is assessment for competency using the MacArthur Competence Assessment Tool for Clinical Research: MacCAT-CR that evaluates all four capacity domains for consent (understanding, appreciation, reasoning, expression of a choice). Evaluation of Step 1 requires approximately 2-3 minutes, Step 2 requires approximately 15 minutes. Fan et al.[76] found in consent evaluations of 150 ICU patients that 89% were sedated/delirious, and unable to provide consent; our experience in previous research is similar. Therefore, we expect that few potential subjects will move to Step 2 while critically ill and mechanically ventilated. The LAR will be contacted for those who fail Step 1 or Step 2.

We will evaluate the potential subject's level of orientation and response to our discussions of the study on a daily basis during the hospital phase, and if the potential subject is able to respond in a manner that is clearly understandable, we will use the potential subject's own consent to continue participation. However, in any instance where the potential subject's ability to comprehend and communicate his/her desires is in question, we will seek consent for continued participation from the LAR and will invite the research subject to provide his/her assent. Verbal consent to continue participation and for post-hospital follow up will be obtained from the subject as soon as their medical condition permits. We will follow UM IRB, JMH, and UMH Policies and Procedures.

Inclusion of Pregnant Women

The study carries no added risk to pregnant women and the well-being of their unborn child. Therefore, pregnancy is not an exclusion for participation in the study.

Inclusion of Children

Children less than 18 years of age will not be included in this study, because delirium presents differently in children and is dependent upon developmental level, cognitive reorientation would require adjustment for developmental level, and adequate power for each pediatric developmental level would be prohibitive and could not be obtained during the proposed study period.

Inclusion of Prisoners

Prisoners are a vulnerable population because of the many unique conditions associated with confinement that compromise their ability to exercise free choice. Due to the added vulnerability in their ability to exercise free choice in addition to their critical illness, prisoners will not be recruited.

6. Number of Subjects

We will recruit 182 subjects in the adult intensive care units at University of Miami Hospital and Jackson Memorial Hospital.

7. Study Timelines

Duration of Intervention and Data Collection Procedures. Following consent, the duration of participation includes data collection over a maximum of 120 hours (5 days) of the ICU stay, overnight data collection at least 24 hours following ICU discharge, and overnight data collection during home visits at 1 and 6 months following hospital discharge. Multiple subjects (up to a maximum of 4) will be actively enrolled in this study as inpatients and outpatients, using research equipment obtained for this study (multiple wireless speakers, Sleep Profilers, and actigraphy watches) to achieve the collection of key variables in Table 1.

As of March 2020, per the updated guidance regarding research continuity from the University of Miami IRB and research administrations, we are complying with the COVID-19 safety recommendations to protect our subjects, research personnel, students, and faculty members.

As of June 2020, we will resume new enrollments at UMH; temporary pause of enrollments at JMH continues. We will deliver interventions and collect face-to face data at UMH. We will not collect data that can only be collected face-to-face during follow up visits. We will schedule and conduct follow-up visits by phone or video conference calls, and we will substitute NIH PROMIS measures (including PROMIS Global Health, PROMIS-SD, PROMIS-SRI, PROMIS-CF,

PROMIS-CFA) for the Sleep Profiler and Actigraphy measures, until it is safe to resume face-toface interactions with subjects at follow-up.

Please refer to the updated Table 1 for a detailed list of which data will be collected remotely via the electronic medical record and from the subject over the phone or via video conference.

Table 1. Key Variables and Data Collection

Concept	Measure	Data Collection Time Points						
		24 hours Pre-Study	Study Admission	ICU Days 1-5	ICU Days 6-7	24-72 hours Post-ICU Discharge	1 Month Post-Hospital Discharge	6 Months Post-Hospital Discharge
Delirium								
ICU delirium	CAM-ICU		*	*	*			
Post-ICU delirium	CAM					*	***	***
Provider report of delirium	Documentation of delirium	**	**	**	**	**		
Activity/Sleep	Actigraphy		*	*		*	*	*
	SP-PSG		*	*		*	*	*
Iatrogenic, Environmental, and Biobehavioral Factors								
Ambient light	Actigraphy		*	*		*	*	*
Pharmacological therapies affecting sleep and/or cognition	Drug type and cumulative sedative dose	**	**	**	**	**	***	***
Disease severity and comorbid conditions	APACHE IV			**				
	STOP-BANG			*			***	***
	SOFA			**	**	**		
Demographic characteristics	Age, sex, race/ethnicity		*					
Patient-reported Health Status	PROMIS Global Health					*	***	***
Patient-reported Sleep Quality	PROMIS-SD					*	***	***
	PROMIS-SRI					*	***	***
Patient-reported Cognitive Function	PROMIS-CF					*	***	***
	PROMIS-CFA					*	***	***
Cognitive Function	NIH Toolbox Cognition Battery					*	*	*

Note:
* = Data collection in person (measures shaded in grey are temporarily paused)
** = Data collection from the electronic medical record
*** = Data collection via telephone or video conference visit (measures highlighted in yellow are telephone- or video-collected substitutes for in-person visits)

We plan to review approximately 350 medical records in order to achieve our sample size of 182 enrollments during the 4-year study. The data collection schedule is shown in Table 2.

Table 2. Study Timeline

Activity	Year	Year 1			Year 2			Year 3			Year 4		
	Months	1-4	5-8	9-12	1-4	5-8	9-12	1-4	5-8	9-12	1-4	5-8	9-12
Hire/train personnel													
Database refinement													
Subject recruitment and enrollment													
Subject 1 and 6 month follow up													
Data collection													
Data management													
Analysis of final results													
Final results manuscript													
Final grant report													

8. Study Endpoints

Primary Endpoint. To test the effect of the Family Automated Voice Reorientation (FAVoR) intervention on delirium in critically ill, mechanically ventilated adults during hospitalization in the ICU, we plan for 95% power respectively to detect an effect size (W) of 0.35 using a 2 degrees of freedom Chi-Square Test with a significance level (alpha) of 0.05.

Secondary Endpoint. The recently completed BRAIN-ICU descriptive study of ICU survivors reported a 43% attrition from the inpatient sample to a 12 month follow up time point.[18] Given that a secondary aim of the proposed project plans 1month and 6 months post-hospital discharge follow up, we conservatively planned for a 40% attrition rate, which is a sample size of 182 total (91 in each group).

Primary and Secondary Safety Endpoints. The FAVoR intervention will be interspersed with the care team's activities, and at no time will the study personnel delay or interfere with critical care procedures; if the needs and activities of providers are such that the study personnel are unable to access the subject to provide audio reorientation, the subject will be withdrawn from the study. At all times, we will place the subject's need for medical treatment, and avoidance with interference with treatment, foremost.

To reduce skin irritation from applied devices, the Sleep Profiler and ActiWatch will not be placed on skin that is not intact or damaged in any way. The Sleep Profiler and ActiWatch will be removed as soon as data collection is complete (up to 120 hours) and skin assessments will be conducted daily. If the skin shows any signs of irritation, the sleep monitoring devices will be discontinued.

If a 20% or larger fluctuation in vital signs (heart rate and blood pressure) during the recorded message occur, research staff will turn off the recorded message. The clinical nurse assigned to the subject will be immediately notified, and the clinical medical provided will be notified as well. The message will be restarted when the critical care nurse or physician indicates the patient is stable. If the 20% or larger fluctuation in vital signs re-occurs, the intervention will be discontinued and the in-hospital data only up to that point will be included in the study.

Prior to beginning the NIH Toolbox Cognition Battery testing and questionnaires, the subject will be told if they feel excessively frustrated or anxious during the test, they may stop. There is no alternative therapy. However, subjects may elect not to participate and may withdraw from the study at any time without affecting the care they receive.

9. Procedures Involved

Research Design

We will use a prospective, randomized, experimental design to accomplish the specific aims. Subjects (n=182) will be randomly assigned within 48 hours of intubation and ICU admission to one of two groups. The intervention group will receive the FAVoR intervention over a 5-day period (120 hours) or until discharge from the ICU, if discharged within 5 days. The control group will receive standard ICU care, but will not receive the FAVoR intervention. All subjects will receive standard clinical care for mechanically ventilated patients, as per clinical guidelines and clinical agency guidelines. Standard clinical care includes all components of the IHI ventilator care bundle.[37]

Sample. Because delirium occurs with a greater frequency in those who are mechanically ventilated,[43] this study will focus on subjects who are mechanically ventilated. The sample of 182 subjects will be drawn from all patients over the age of 18 years admitted to the Intensive Care Units at University of Miami Hospital (UMH) and Jackson Memorial Hospital (JMH) who are newly intubated (within 48 hours of initial intubation at time of study recruitment) and have a family member available to record the scripted intervention message. Subjects will be randomized to group according to a permuted block design[44] developed by Dr. Ji such that after every k subjects, balance will be maintained between the groups. In order to fully enroll the study during the requested 4-year funding period, we will target enrollment of 7 subjects per month.

Group Assignment. The Project Director and Research Assistants will recruit, enroll, and assign subjects to groups. Subjects will be randomly assigned to one of two study groups (FAVoR intervention or control) using randomization processes described in the Sample section above.

1) Intervention Group: Subjects in the intervention group will receive personalized digitally recorded reorientation messages administered for up to 2 minutes every hour over an 8hour daytime period (beginning at 9 am daily) recorded in the voice of a family member. Subjects in the intervention group will continue to receive the intervention for up to a total of 5 days (120 hours), or until ICU discharge if ICU discharge occurs within the first 5 days. Since in the ICU setting delirium has a mean onset of 2.6 days (S.D.+/-1.7), and a mean duration of 3.4+/-1.9 days,[49] a 5-day period for the study intervention is appropriate and includes the period prior to delirium onset as well as when delirium has been shown to occur most frequently.
2) Control Group: The control group will consist of usual care, and will not receive audio reorientation messages. Subjects will remain in the study for five days or until ICU discharge if discharged before five days.

Subjects in both groups will be reoriented by care providers as part of usual care practices. Data will be collected from the medical record daily. Both groups (intervention and control) will undergo longitudinal cognitive and patient-reported health status evaluations concurrently with 24-hour sleep profiler-polysomnography and actigraphy at three different points in time. The first time point is inpatient, at least 24 hours after ICU discharge, then outpatient with two home visit data collection events at 1 month and 6 months post hospital discharge.

Description of Intervention. The FAVoR intervention includes a set of 8 recorded messages which were developed in preliminary study 1, and were tested and refined in preliminary study 2. Based on the feasibility data (preliminary study 2) each message is scripted, is no longer than

2 minutes long, is a personal message using the subject's name, uses simple terms, and is written at a 5th grade reading level. Messages include information about the critical care environment, the visual and auditory stimuli to be expected, and the availability of providers and family. The messages call the patient by name (preferred name as recommended by the patient's family); we believe the use of the patient's name may create greater attention to the message.

Each message indicates that it is daytime (to provide general time orientation), states that the message is a recorded message, and tells the subject that he/she will hear messages frequently throughout the day to help him/her understand that he/she is in the ICU. Other than the patient's name, the recorded message is generic in nature, and not specific to any one patient condition, procedure, or family situation. Topics for message scripts were developed in response to patients' recollections of the ICU experience.[38-40] The 8 recorded messages will vary randomly in order each day, reducing message repetition, which may eventually annoy or be ignored by the subject.

The messages will be recorded by a family member of the family's choice using a standardized script, in either English or Spanish, based on the family member's decision regarding which language would be most meaningful to the subject. Family members are not human subjects in this project; no data will be collected about the family members. The messages will be digitally recorded using audacity software and stored on the study computer's hard drive as a standard Microsoft wave files. The wave files are loaded onto a small, wireless, digital audio player with a wireless speaker, protected inside a disposable plastic bag, placed near the subject's ear, and set to shuffle play. Shuffle play is a mode of audio playback in which messages are played in a randomized order that is decided upon for all tracks at once and prevents repeated tracks, which makes it distinct from random playback. Shuffle play randomly selects the order of the messages to be played in the patient's room every hour for 8 hours during the daytime, beginning at 9:00 am. The digitally recorded messages will continue at the predetermined daytime intervals each day for a total of 5 days (120 hours), or until ICU discharge if ICU discharge occurs prior to 5 days. All intervention "doses" will be administered during the hours of 9:00 am and 4:00 pm for each of the 5 days, with intervention beginning at the earliest available time following completion of family recording. The research personnel will document the time and number of recordings each day so that a message "dose" can be documented. Research personnel will monitor the subject and the recorded messages regularly to document if the subject was not in the unit (for procedures off the unit etc.) so that those off-unit times can be included in the dose calculation.

The timeframe chosen for intervention delivery coincides with usual waking hours; no message will be played outside of this timeframe so as not to disturb sleep or interrupt family visits in the evening hours. Further, early morning hours are typically times of patient care intensity and additional stimulation at that time may not be appropriate. Based on our preliminary studies we found that by placing the speaker near the patient's ear, the recorded message is able to be heard at a volume that is loud enough for the patient but not so loud as to be noxious or interfere with care providing activities; the message will be loud enough for the patient to hear comfortably but not loud enough to be excessively stimulating or irritating to the normal listener. Although the use of earphones to deliver the message might focus the subject's attention on the message, we chose not to use earphones as these would also block out other stimuli and potentially result in greater disorientation. In addition, earphones could impair understanding of communication to the subjects from providers or family.

Sources of Materials

Data will be obtained both inpatient and outpatient from the patient's medical record, noninvasive physiologic monitoring, cognitive testing (delirium assessment and NIH Toolbox Cognition Battery), and observation. Data will include patient's gender, age, race, ethnic background, reason for admission to the ICU, pharmacological therapies affecting cognition and sleep, laboratory data to calculate the APACHE III, SBM and SOFA, wrist actigraphy, sleep profiler-polysomnography, cognitive testing (delirium and NIH Toolbox Cognition Battery) scores and PROMIS global health scores. Only study personnel who are responsible for enrolment and data collection will have access to individually identifiable information. Each subject will be assigned an arbitrary study identification number, and no individually identifiable private information will be entered into the study database.

Key Variables and Their Measurement

Please refer to Table 1 for a detailed list of which data can only be collected in person. To protect human subjects, we are closely following the COVID-19 safety recommendations.

Therefore, we will pause data collection for the following 4 measures at JMH until enrollment resumes, and during followup visits:

1. CAM-ICU (substituted by CAM)
2. Actigraphy
3. SP-PSG (substituted by PROMIS-SD and PROMIS-SRI)
4. NIH Toolbox Cognition Battery (substituted by PROMIS-CF and PROMIS-CFA)

Delirium. The primary outcome measure for this project is delirium free days. We will quantify delirium using the Confusion Assessment Method for the ICU (CAM-ICU).[45] CAM-ICU scores for each subject will be obtained by study personnel twice daily at 9 am and 4 pm (coinciding with the schedule for initiation and conclusion of messages each day in the FAVoR intervention group, and at identical times for the control group). CAM-ICU scores will also be recorded at the same times for two days following the completion of the intervention period. The Confusion Assessment Method (CAM) will be used during study visits after transfer from the ICU (post ICU, 1 month, and 6 month follow up periods) for comparison.

We will also collect documentation by providers in the medical record of episodes of delirium occurring outside of the CAM-ICU data collection conducted by research personnel. Only days without any instances of delirium will be counted as delirium free days. The CAM-ICU is recognized in the Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit as a valid, reliable, and feasible tool to detect delirium in ICU patients[3] with pooled sensitivity of 75.5% and specificity of 95.8%.[50]

Sleep/Activity. Sleep patterns in the critically ill are highly disorganized, with fragmentation, a predominance of light sleep, and reduction in deep sleep and rapid eye movements.[8] We will use the FDA approved Sleep Profiler system (Advanced Brain Monitoring, Carlsbad, CA) to obtain continuous polysomnography data (SPPSG). The Sleep Profiler has been successfully utilized in mechanically ventilated and sedated patients and provides three frontopolar electroencephalographic (EEG) signals (AF7/AF8, AF7/Fpz and AF8/Fpz).[51-54]

A wrist actigraph (ActiWatch Spectrum, Philips Respironics, Bend, OR) will be placed on the wrist to measure patient activity and ambient light levels. We have extensive experience with

the use of actigraphy. In our previously published work[55-57] and the preliminary study, we used actigraphy as a surrogate measure of sleep, as have other ICU researchers[58]. Wrist actigraphy also has been found by our research team to be a reliable method of assessing activity and agitation in the ICU.[55-57,59]

Iatrogenic/Environmental and Biobehavioral Factors. Critical illness and its treatment predispose patients to delirium through several mechanisms which are poorly understood. Factors may include patient characteristics, predisposing conditions, and iatrogenic/environmental factors.

Ambient light. Although the FAVoR intervention does not involve manipulation of ambient light levels, environmental conditions have been hypothesized to influence risk of delirium and may affect sleep in the ICU.

Pharmacological Therapies Affecting Cognition and Sleep. We will collect data regarding specific pharmacologic therapies. For sedatives and narcotics, we will determine equivalent doses to facilitate analysis. To provide sedative and analgesic dose equivalents for analysis, doses will be converted as described in Cammarano et al.[60]

Disease Severity and Comorbid Conditions

Acute Physiology and Chronic Health Evaluation (APACHE) IV. There is strong evidence that severity of illness on admission to the ICU, assessed by APACHE score [61-65], is a risk factor for delirium.[4,11]

Sequential Organ Failure Score (SOFA). To determine daily severity of illness we will use the SOFA[66], which was developed to quantify severity of illness based on the degree of organ dysfunction, serially over time. The SOFA score has good reliability and accuracy,[67] accurately reflects the daily severity of organ dysfunction, predicts prognosis[68] and is able to predict ICU mortality.[69]

STOP-Bang Model (SBM) Assessment. Obstructive sleep apnea (OSA) underlies numerous co-morbidities and is linked with cardiovascular and neurovascular diseases, metabolic disorders, and impaired neurocognitive function.[70-72] The STOP-Bang Model (SBM) questionnaire will be used as an OSA screening tool for baseline data collection.

Subject Demographics. Subject characteristics that may affect the development of delirium will be collected at admission to the study, including age, race, ethnicity and gender.[11]

Additional Subject Descriptive Data. In order to completely describe the study population, we will also collect the type of ICU (reflecting type of critical illness and population; i.e. surgical, medical ICU). In addition, because visual or auditory deficits may affect measurements and/or delirium, information about these will be recorded including if patients wore corrective lenses (glasses, bifocals, or contacts) or hearing aids prior to ICU admission. Families or significant others will also be asked if the patient had any documented impairment in vision or hearing.
Patient-Reported Health Status. The Patient-Reported Outcomes Measurement Information System (PROMIS) global health instrument will be used to document subjects' perceptions of their health status.[73,74].The PROMIS Sleep Disturbance (PROMIS-SD) and Sleep Related Impairment (PROMIS-SRI) instruments will be used to document subjects' perception of their sleep quality following transfer out of the ICU and during 1 month and 6 month visits. Both

PROMIS measures are validated and available in English and Spanish on the NIH website.
Cognitive Function. The NIH Toolbox Cognition Battery[75] testing will be used to measure cognitive function after transferring out of the ICU and at 1 month and 6 months following hospital discharge.
The PROMIS Cognitive Function (PROMIS-CF) and PROMIS Cognitive Function Abilities (PROMIS-CFA) instruments will be used to document subjects' perception of their cognitive function following transfer out of the ICU and during 1 month and 6 month visits. Both of these assessments can be completed remotely, over the phone or by video conference. Both PROMIS measures are validated and available in English and Spanish on the NIH website.

Inpatient. Once consent is obtained and the subject is enrolled, baseline data will be collected from medical records. In randomized assignment to the intervention group, the family member selected by the family to record scripted FAVoR messages will be contacted, and taken to a quiet area to complete the recording on the assigned computer. FAVoR will be delivered through a wireless speaker, which will be placed near the patient's head. Delivery of the intervention to subjects randomized to receive it will begin as soon as possible during 9 am and 4 pm; if the FAVoR messages cannot be recorded before 4 pm, the intervention will begin on the following morning at 9 am. Data recording devices (SP-PSG and ActiWatch) will be applied to the subjects receiving the intervention immediately prior to the onset of the FAVoR intervention, and to control subjects as soon as feasible following consent. Actigraphy and SPPSG will continue throughout the 120-hour period beginning with the intervention delivery and continuing until the same time 5 days (120 hours) later. Data collection will resume and continue after at least 24 hours of ICU discharge. The subject will complete the NIH Toolbox-Cognition Battery, and the PROMIS Global Health instrument, and actigraphy and SP-PSG will be obtained.

We will follow University of Miami Hospital and Jackson Memorial Hospital infection control policies and procedures for cleaning portable equipment before and between patients, which include appropriate germicidal or bleach agents and single use disposable equipment covers.

As of June 2020, we will resume data collection at UMH for the following measures: CAM-ICU, Actigraphy, SP-PSG, and the NIH Toolbox Cognition Battery. Data collection remains paused for these measures at JMH.

Outpatient. There will be two outpatient data collection events at 1 month and 6 months posthospital discharge. During the 1 month home visit, research staff will travel to the subject's home (or other location agreed upon) to administer the NIH Toolbox-Cognition Battery testing and the PROMIS Global Health assessment, PROMIS-SD, PROMIS-SRI, PROMIS-CF, PROMIS-CFA questionnaires. While face-to-face interaction is not permitted, the subjects will not be asked to wear the SP-PSG and ActiWatch (for acquisition of sleep and activity data) overnight. Identical data collection processes will be used at the 6 month visit.

Procedures for telephone or video conference:

Per protocol, research staff will collect data on subjects' hospital discharge dates. There are two outpatient data collection time points: 1 month post-hospital discharge, and 6 posthospital discharge. Research staff will call the phone number that the subject or subject's LAR provided for outpatient follow-up visits.

During this phone call, we will verbally notify the subject that we have modified procedures to enable remote visits to protect all enrolled subjects and our research personnel.

The subject will be asked to complete the visit entirely by phone or by Zoom-enabled video conference. If the subject agrees to a Zoom-enabled video visit, then we will provide two options for accessing the Zoom video link: 1) email address as provided by the subject and/or the subject's LAR, or 2) text message to a phone number as provided by the subject and/or the subject's LAR. If the subject does not have access to video capability, or does not wish to conduct the visit by video, then the visit will be conducted entirely by phone.

The CAM, STOP-BANG, PROMIS Global Health, PROMIS-SD, PROMIS-SRI, PROMISCF, and PROMIS-CFA can all be completed over the phone or by video call; each instrument will be administered by the research staff. Subjects may choose not to complete any measure if unwilling, and may end the call at any time.

Compensation

Upon the hospital discharge date, a gift card in the amount of $25, along with a note of thanks to the participant and their family, will be mailed to the home address of the participant. A second gift card valued in the amount of $25 will be hand delivered if the visit is face-to-face during the second (and final) home visit, approximately 6-months after the hospital discharge date. If the visit is done by phone or video call, the second gift card will be mailed.

10. Data Management

All data will be downloaded into research electronic data capture (REDCap), a secure web application database, which will be accessed by a secure UM web connection with authentication and data logging. The Project Director will review all data for completeness and appropriate entries before it is entered into the study database. At the beginning of the data entry process a minimum of 1 in every 10 participant records will be checked against the original medical record for data errors. Records for review will be randomly chosen by the data manager. As the study progresses, the frequency of monitoring will be based on the results of the previous data review. If the error rate is unacceptable then the monitoring will increase until the error rate is acceptable (less than 5% of all data). The Data Manager in consultation with the Principal Investigator will develop reports that will help in the coordination and management of the project and also allow project staff to monitor the quality of the data and the progress of the study. Furthermore, only a unique identifier, assigned by the Principal Investigator or Data Manager, in the database will identify each subject. The data files will be backed up daily during the data entry process and once a week during other times by the Project Director. All data files will be housed on the university server which is backed up every 24 hours and copies are stored off-site for additional security. Access to the database will be password protected and limited to the investigators, Project Director, and Data Manager.

Data Analysis Plan

The primary specific aim of the proposed project is to test the effect of the Family Automated Voice Reorientation (FAVoR) intervention on delirium in critically ill, mechanically ventilated adults during hospitalization in the ICU. We hypothesize that subjects who receive the FAVoR intervention will have less delirium than control subjects who do not receive the intervention.

Secondary aims of this project are to: (1) explore if the effect of FAVoR on delirium is mediated by sleep, (2) explore if selected biobehavioral factors may potentially moderate the effects of FAVoR on delirium, and (3) examine the effects of FAVoR on short term (immediately after ICU discharge) and long term (1 and 6 months after hospital discharge) outcomes, including cognitive function and patient-reported health status.

There will be two parts of the data analysis: Part I: A traditional statistical data analysis for randomized controlled trials for the Primary Specific Aim, and Part II: Pathway analytic model analyses to address the secondary aims. Dr. Ji will work closely with the Data Manager to perform all the planned data analyses for this study.

Part I: We will follow the research and regulatory guidelines for statistical analysis of clinical trials including the ICH Guideline[77] and the CONSORT guidelines[78]. First, descriptive statistics will be performed to describe and compare the characteristics of the intervention and the control groups. Descriptive statistics will be reported as means +/- standard deviation for continuous variables and as frequencies and percentages for categorical variables. Shapes of the data distributions, missing data and outliers will be examined by both graphics and statistical tests. Any data issues identified will be discussed with the PI and other investigators and addressed before formal data analysis. For example, skewed variables may be transformed so that their distributions are close to the Normal Distribution. Outliers may be excluded or included in two separate analyses. Missing data may be imputed or handled by other missing data techniques. Distributions of continuous variables and categorical variables will be compared between the intervention and the control group by using the t-test or Wilcoxon rank sum test and the Chisquare test, respectively. Any baseline covariate that is differentially distributed in the two groups will be adjusted in the subsequent analysis for testing the intervention effect. Assuming the randomization produces well balanced intervention and control groups, a Chi-square test for a 2x2 table with the number of delirium free days and the treatment assignment will be performed to test the primary hypothesis. If there are unbalanced covariates, then covariance adjustment will be performed by using logistic regression that includes both the treatment assignment and the unbalanced covariates. If there are missing values in the primary outcome, then multiple imputation will be performed using SAS PROC MI for missing at random (MAR) data.[79,80] Sensitivity analysis for potentially not missing at random data will be performed using the Yau and Little[81] Intent-to-Treat Analysis for Longitudinal Studies with Dropouts.

Part II: Given the large number of variables measured for activity/sleep, disease severity, environment and demographics and the potential complex pathways among these variables, we plan to use partial least square structural equation models (PLS-SEM) to analyze the relative importance and the pathways of these variables.
Partial least squares (PLS) is a predictive modeling method that can predict high dimensional outcomes from high dimensional, correlated predictors. The variance importance in projection (VIP) measure in PLS models can be used to compare the relative importance of different predictors which is a useful tool for variable selection in high dimensional data.[82] In recent years, PLS-SEM was developed to use PLS fit pathway models with both manifested and latent variables.[83-86] PLS-SEM is implemented in the R package semPLS. We will perform the predictive PLS using SAS PROC PLS for variable screening so that important predictors from the high dimensional raw data (such as the sleep measure) will be identified. Then we will fit PLS-SEM using the R package semPLS to the mediation effect of sleep and other empirically or theoretically hypothesized pathways. Specifically, for secondary aim 1, we will perform meditation analysis within multilevel SEM; for secondary aim 2, we will test moderation in PLSSEM to test the biobehavioral factors as multiple moderators; and for secondary aim 3, we will fit path analytic models from the FAVoR intervention to the short-term and the long term cognitive function and patient-reported health status measures, respectively.

11. Provisions to Monitor the Data to Ensure the Safety of Subjects

In addition to the Data Safety and Monitoring plan described below, the study will be monitored under the quality assurance procedures of the SONHS which includes a review of the regulatory binder, review of consents upon enrollment of the first 5 participants and every 6 months thereafter until human subjects activities are completed.

Data Safety and Monitoring Plan

Purpose:

The purpose of the DSM Plan is to:

1. Assure monitoring of the progress of the trial and the safety of participants
2. Assure compliance with reporting requirements for adverse events
3. Assure data accuracy and protocol compliance.

Required elements:

a. Monitoring entity or who will monitor the study: The project involves minimal risk and will be conducted at a single site. The PI and an independent Safety Monitoring Committee (SMC) will have responsibilities for monitoring the study. The PI, Dr. Munro, will be directly responsible for ongoing data and safety monitoring of the study. An independent Safety Monitoring Committee (SMC) will be responsible for oversight of the safety of participants, including but not limited to review of adverse events. The SMC will be composed of 3 members who are not directly associated with the project. A statistician will serve as chair; two PhD nurse researchers with expertise in research in critical care settings will serve as members.

b. Procedures for

1) monitoring study safety to include monitoring schedule, auditing selected cases for compliance with IRB requirements, conformance with informed consent requirements, verification of source documents, and investigator compliance: Enrollment, study fidelity, and safety data will be reviewed regularly at study team monthly meetings. The SMC will convene after data collection has been completed for the first 20 subjects and every six months thereafter to review monitoring plan data, including safety and adverse events data. The monitoring plan, including data sources and reporting intervals, is summarized in the accompanying table below. Written minutes of monthly team meetings will be kept and will include reports detailed in the monitoring plan table. Written minutes of SMC meetings will be forwarded to the IRB and NIH as part of the annual reporting process.

2) minimizing research-associated risk: We anticipate minimal additional physical and psychological risks associated with this study. Reorientation is routinely provided to critically ill patients by bedside nurses as part of clinical care. The intervention will be interspersed with the care team's activities, and at no time will the study personnel delay or interfere with clinical care; if the needs and activities of providers are such that the study personnel are unable to access the subject to provide interventions, the subject will be withdrawn from the study. At all times, we will place the subject's need for medical treatment, and avoidance with interference with treatment, foremost. Because these subjects are receiving clinical care in the hospital, the attending clinical nursing and medical providers will be promptly informed of any adverse effects to the subjects; if an adverse event occurs, necessary interventions will be determined and delivered by the clinical providers.

3) protecting the confidentiality of participant data: In order to reduce risks to privacy of individuals or confidentiality of data, we will not include personally identifiable data in the

database files. All computers and data files will be password protected, and data will be stored on the University server, with access only to study personnel, under the direct supervision of the PI, Dr. Munro. Each subject will be assigned an arbitrary code number to conceal the identity of the research data, and no identifiable private information will be associated with any data files. All data will be collected on laptops in the clinical setting; these laptops will remain in the possession of study personnel at all times (unless locked in a cabinet in the locked research office), and all study-related files will be password protected. At the conclusion of each segment of the subject's participation (ICU, hospital discharge, 1 month post-hospital, 6 months posthospital), that subject's data will be transferred from the laptop computer to a secure, password protected file on the UM server, under the direct supervision of Dr. Munro, with access limited to study personnel. Study information obtained will be kept strictly confidential, and it will not be possible to identify any participant from the reports that may result from this research.

c. Procedures for identifying, reviewing, and reporting adverse events and unanticipated problems to the IRB and NINR (FDA not applicable): Research staff will report any unusual occurrence or possible adverse event immediately to the PI, and will provide the PI with a detailed written description of the circumstances, the event, and immediate actions taken to reduce harm to subjects or others. The PI will review the situation, using UM IRB policy HRP024 (https://eprost.med.miami.edu/eProst/Doc/0/HL7O55VBRRQ4BAAQ5NVBGFT62B/HRP-024%20-%20SOP%20-%20New%20Information_rev04.29.2016.pdf) and OHRP guidance (http://www.hhs.gov/ohrp/policy/advevntguid.htmland) to determine required reporting. All adverse events will be reported to the SMC, IRB and to NINR following institutional and NIH guidelines. All unusual occurrences and adverse events will be reviewed in monthly study team meetings. The PI will report any unanticipated problems (including those that are serious adverse events and those involving risks to subjects or others) to the IRB immediately upon becoming aware of the problem, in accordance with UM policy. In addition, a summary of adverse events will be included in biannual reports to the SMC and annual progress reports to the UM IRB and to NINR.

Because we anticipate that the study involves minimal risk, if any serious adverse events or unanticipated problems occur (i.e., those that suggest that the research places subjects or others at greater risk of harm than previously known) we will halt accrual and engage the SMC to conduct a complete review of eligibility, monitoring, assessments, and intervention. Resumption of accrual will occur only following SMC recommendation and IRB approval of any required changes to the study to reduce future risks to subjects (or IRB determination that no changes are required and accrual may resume).

d. The study will be conducted at a single site (not a multi-site study).

e. An assessment of external factors or relevant information (i.e., developments in the literature, results of related studies) that may have an impact of the safety of participants or on the ethics for the research study: The PI will conduct monthly reviews of related projects in recently published literature and Clinicaltrials.gov, and assess the relevance for subject safety and ethics to this project. Identified issues will be discussed in monthly study team meetings, and communicated to the IRB and NINR as appropriate.

f. No interim analysis nor futility analysis is planned.

Format

The format for the DSM Plan will consist of:

1. Continuous, close monitoring by the principal investigator, including regularly scheduled research team staff meetings;
2. Review of and action on reports by study team, SMC, and others at scheduled intervals and as needed (see monitoring plan table below); and
3. Reporting by the principal investigator to the IRB and NIH in compliance with institutional and NIH policy.

Safety Monitoring Plan

Report	**Purpose**	**Report elements**	**Prepared by**	**Report interval**	**Distributed to**	**Action**
Accrual update report	Monitor enrollment to ensure that accrual goals are met in a timely manner Monitor inclusion of women and racial/ ethnic diversity to ensure adequate representation	For current month, and cumulative, reported by ICU unit and total: -Number screened -Number eligible for inclusion -Number not enrolled (subcategories for reason) -Number enrolled -Gender -Race -Ethnicity	Project Director, Data Manager	Monthly	PI, Study team	Review at team meeting Corrective action plan as required

Monthly progress report	Summarize status of subjects Assess progress on the study	For current month, and cumulative, reported by ICU unit and total: -Number of subjects completed intervention - Number of subjects with intervention completed, data collection continuing - Number of subjects off study (by reasons) - Number of subjects lost to follow-up (by reason) - Inclusion/ exclusion violations	Project Director, Data Manager	Monthly	PI, Study team	Review at team meeting Corrective action plan as required
Data completeness report	Identify missing data elements Minimize missing data Remedy data collection issues	Data collection forms	Data Manager	Monthly for first year, then quarterly	PI, Study team	Review at team meeting Corrective action as required

Protocol deviation log	Document deviations Facilitate regulatory reporting Protect safety of human subjects	- Detailed description of protocol deviation	Project Director, PI	Monthly	Study team	Review at team meeting Corrective action and report to IRB as required

AE report	Protect safety of human subjects	Detailed description of the adverse event, incident, experience, or outcome -Explanation of the basis for determining whether the adverse event, incident, experience, or outcome represents an unanticipated problem -Description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.	PI	As stated in UM HRP-024	UM IRB	As determined by UM IRB
				Urgent communication as needed to address issue	Study team	-Corrective action as required to protect subjects - As determined by UM IRB
				Annual summary (or more frequent as directed by UM IRB)	NIH	Include in annual progress report
Intervention fidelity and Protocol compliance report	To maintain intervention fidelity and compliance with protocol	-Performance testing of GRAs to ensure that all critical elements of each procedure are included - Audit of randomly selected research records for protocol compliance	Project Director, Data Manager	Quarterly	PI, Study team	Review at team meeting Corrective action as required during performance testing

SMC monitoring data report	Monitoring and oversight of human subject safety	Past 6 months and cumulative summary reports of: -Accrual update report -Monthly progress report -Data completeness report -Protocol deviation log -AE report -Intervention fidelity and Protocol compliance report -Other data as requested by SMC	PI, Biostatistician	First 20 subjects, then every 6 months, and as needed to respond to urgent issues	SMC	Recommend corrective action as required to protect subjects Recommend early stopping of the trial for reasons of participant safety

12. Withdrawal of Subjects

From our experience in clinical research with critically ill patients, we anticipate changes in the circumstances of subjects that no longer make them eligible to continue the study (i.e. exclusion criteria - anticipation by the clinical provider of imminent patient death). We will closely monitor for changes in circumstance that impact eligibility (i.e., orders for Care Measures Only or terminal extubation) and consider the study complete for the subject. We will use all information collected up to the completion point for inclusion in analysis. We will proceed with the following study completion procedures:

- Stop collecting research data.
- Remove all research equipment.
- Mail Thank You card with $25 gift card to subject's home address. Redact PHI from Enrollment Tracking Log.

In the event the subject (or their LAR) withdraws from the study, we will consider the study complete for the subject and use all information collected up to the point of study withdrawal. The same study completion procedures above will be followed.

13. Risks to Subjects

The risks of participation in the study are minimal. Risks of the intervention may include transient changes in vital signs from stimulation caused by the recorded message. Other risks include skin irritation from the actigraphy watch and sleep profiler-polysomnography, as well as frustration or anxiety with the NIH Toolbox Cognition Battery testing or any of the questionnaires (see Table 1). None of these risks were observed to occur in preliminary study #2.

Following consent and study enrollment, risk of breach of confidentiality is also possible since identifying information will be collected in an electronic enrollment tracking list, on a password

protected server limited to project director and research assistants, to track the location of subjects as inpatients and contact information for follow up home visits.

There is no alternative therapy. However, subjects may elect not to participate and may withdraw from the study at any time without affecting the care they receive.

Protections Against Risk

The FAVoR intervention will be interspersed with the care team's activities, and at no time will the study personnel delay or interfere with critical care procedures; if the needs and activities of providers are such that the study personnel are unable to access the subject to provide audio reorientation, the subject will be withdrawn from the study. At all times, we will place the subject's need for medical treatment, and avoidance with interference with treatment, foremost.

Following study enrollment, we will keep an active list of enrolled subjects (FAVoR Study Enrollment Tracking List) that require study procedures as inpatients at UMH and JMH and follow up home visits to be performed. All identifying information is redacted from this list as each subject's participation is complete. The enrollment tracking list will be maintained on a password protected server, with limited access to only the project director and research assistants. The enrollment tracking list will be completely destroyed upon the last subject's completed participation.

No personal protected information (none of the HIPAA elements) are ever recorded in study forms or in the study database. The information obtained will be kept strictly confidential, protecting the identity of participants in all reports or publications that may result from this research. Each participant will be assigned an arbitrary code number to conceal their identity on all research data, and all research data will be maintained in locked file cabinets under the direct supervision of the PI.

To ensure confidentiality, each participant will be assigned an arbitrary study identification number to conceal their identity on all research data. All hard copy research material (i.e., consent forms) will be maintained in locked file cabinets, electronic data will be kept on password protected computers under the direct supervision of the PI. Study information obtained will be kept strictly confidential, protecting the identity of participants in all reports or publications that may result from this research. To ensure privacy, all interactions with subjects and LARs will be conducted in the subject's hospital room or a private area of the ICU.

To reduce skin irritation from applied devices, the Sleep Profiler and ActiWatch will not be placed on skin that is not intact or damaged in any way. The Sleep Profiler and ActiWatch will be removed as soon as data collection is complete (up to 120 hours) and skin assessments will be conducted daily.

If a 20% or larger fluctuation in vital signs (heart rate and blood pressure) during the recorded message occur, research staff will turn off the recorded message. The clinical nurse assigned to the subject will be immediately notified, and the clinical medical provided will be notified as well. The message will be restarted when the critical care nurse or physician indicates the patient is stable. If the 20% or larger fluctuation in vital signs re-occurs, the intervention will be discontinued and the in-hospital data only up to that point will be included in the study.

Prior to beginning the NIH Toolbox Cognition Battery testing and questionnaires, the subject will be told if they feel excessively frustrated or anxious during the test, they may stop. There is no alternative therapy. However, subjects may elect not to participate and may withdraw from the study at any time without affecting the care they receive.

As of March 2020, per the updated guidance regarding research continuity from the University of Miami IRB and research administrations, we are complying with the COVID-19 safety recommendations to protect our subjects, research personnel, students, and faculty members.

14. Potential Benefits to Subjects

Subjects in the intervention group may benefit from this study if delirium is reduced by the FAVoR intervention. The data obtained will provide empirical evidence that will enable us to evaluate the effect of the FAVoR intervention on delirium and holds promise to translate new knowledge into clinical decision-making about the management of delirium in the critically ill to ultimately improve patient outcomes.

15. Vulnerable Populations

Cognitively Impaired Adults

In our experience in conducting clinical research in the critical care areas, we have found that potential subjects who are mechanically ventilated are generally sedated to some degree. In addition, since use of mechanical ventilation primarily occurs during periods of patient instability, the use of sedation at these times is extensive and compromises patient's ability to communicate effectively which is compounded by the presence of the endotracheal tube. As a result, we have always found it appropriate to contact the legally authorized representative for consent. However, there may be rare occurrences when potential subjects are adequately oriented and lucid to be able to provide informed consent. Therefore, we will use the 2-step procedure described by Fan et al.[76] to determine the patient's ability to provide informed consent. Step 1 is objective evaluation with the Richmond Agitation-Sedation Scale (RASS) and the Confusion Assessment Method for Intensive Care Unit (CAM-ICU). Patients who score -1, 0,
+1 on the RASS indicating drowsy, alert, or restless respectively and are not delirious (CAM-ICU = No) will move to Step 2. Step 2 is assessment for competency using the MacArthur Competence Assessment Tool for Clinical Research: MacCAT-CR that evaluates all four capacity domains for consent (understanding, appreciation, reasoning, expression of a choice). Evaluation of Step 1 requires approximately 2-3 minutes, Step 2 requires approximately 15 minutes. Fan et al.[76] found in consent evaluations of 150 ICU patients that 89% were sedated/delirious, and unable to provide consent; our experience in previous research is similar. Therefore, we expect that few potential subjects will move to Step 2 while critically ill and mechanically ventilated. The LAR will be contacted for those who fail Step 1 or Step 2.

We will evaluate the potential subject's level of orientation and response to our discussions of the study on a daily basis during the hospital phase, and if the potential subject is able to respond in a manner that is clearly understandable, we will use the potential subject's own consent to continue participation. However, in any instance where the potential subject's ability to comprehend and communicate his/her desires is in question, we will seek consent for continued participation from the LAR and will invite the research subject to provide his/her assent.

Subjects will be withdrawn if they appear to be unduly distressed. For example, if a 20% or larger fluctuation in vital signs (heart rate and blood pressure) during the delivery of the recorded message occur, research staff will turn off the recorded message. The clinical nurse assigned to the subject will be immediately notified, and the clinical medical provider will be notified as well. The message will be restarted when the critical care nurse or physician indicates the patient is stable. If the 20% or larger fluctuation in vital signs re-occurs, the intervention will be discontinued and the in-hospital data only up to that point will be included in the study.

Verbal consent to continue participation and for post-hospital follow up will be obtained from the subject as soon as their medical condition permits. We will follow UM IRB, JMH, and UMH policies and procedures. The consenting process for Spanish patients, family members, and/or LAR's will be the same process only with the addition of an individual UMH or JMH Spanish translator or by use of the UMH translation language line phone service, which is available 24 hours a day, 7 days a week.

Pregnant Women
This minimal risk study carries no added risk to pregnant women and the well-being of their unborn child.

16. Sharing of Results with Subjects

Individual subject results will not be shared with subjects or others (i.e., health care providers) during the study. De-identified study group results will be made available through publications and summarized on clinicaltrials.gov.

17. Setting

Subject recruitment, enrollment, and interventions will be conducted in the adult intensive care units (Cardiac Care, Medical, Neuro, Surgical, and Specialty critical care) at University of Miami Hospital (UMH) and Jackson Memorial Hospital (JMH), both in Miami, Florida. UMH is licensed for 560 beds that includes 52 critical care beds. JMH is a 1,500 bed facility that includes 194 critical care beds and is the primary teaching hospital for the University of Miami Miller School of Medicine. Miami-Dade County is comprised of approximately 67.7% minority population. In our current and completed projects, we have established excellent research relationships and have been successful in meeting target enrollments in critical care. We will use mechanisms established in previous and current studies for providing staff in-services, unit meetings, and frequent communication about the study for nurses, physicians, and other ICU team members at UMH and JMH.

18. Resources Available

This 4-year R01 study is funded by National Institutes of Health, National Institute of Nursing Research. We have substantial experience, which enhances the likelihood that we can successfully accomplish the specific aims. We have conducted preliminary work to develop and refine important components of the project, including the intervention, study measures, and data analysis. We have completed a small RCT, which provided suggestive support for the proposed study’s primary aim and informed decisions about the research plan. We have been active in funded research related to care of critically ill adults for over 2 decades, and have successfully conducted multiple RCTs in the critically ill population. We have direct and extensive experience

in time-sensitive recruitment and enrollment of critically ill subjects; delivering and maintaining intervention fidelity of interventions in intensive care settings, including oral care interventions; obtaining, measuring, and analyzing systemic and oral biomarker data; quantifying complications, including HAIs; and controlling for confounding variables in critically ill subjects. Our results have had direct impact on clinical practice, including contributing to national guidelines for care of mechanically ventilated adults.[37] Dr. Zhan will support regulatory compliance, data interpretation and analysis, preparation of presentations and publications and will be a co-author in dissemination of study results and methodologies. Dr. Ji will serve as the senior statistician and provide expertise to achieve maximum rigor in research design and methodology, develop the data analysis plan, final data analyses, as well as preparing reports and manuscripts. Staffing resources are presented in Table 4.

Table 4. Staffing Resources

Name and Title	**Responsibility**	**Address**	**Phone**
Cindy Munro, PhD, RN, ANP-BC, FAAN, FAANP, FAAAS UM School of Nursing and Health Studies, Dean and Professor	Principal Investigator	UM SONHS 5030 Brunson Drive P.O. Box 248153 Coral Gables, FL 33124-3850	305-284-2107
Zhan Liang, RN, PhD University of Miami School of Nursing and Health Studies, Assistant Professor	Co-Investigator	UM SONHS 5030 Brunson Drive P.O. Box 248153 Coral Gables, FL 33124-3850	305-284-5468
Ming Ji, PhD USF College of Nursing, Professor of Biostatistics	Co-Investigator	USF 12901 Bruce B. Downs Blvd., MDC22 Tampa, FL 33612-4766	813-396-9073
Maya Elias, PhD, RN University of Miami School of Nursing and Health Studies Post-Doctoral Associate	Post-Doctoral Associate	UM SONHS 5030 Brunson Drive P.O. Box 248153 Coral Gables, FL 33124-3850	407-925-4916
Karel Calero, MD USF College of Medicine, Assistant Professor Pulmonary Critical Care, Sleep Medicine	Consultant	USF 2 Tampa General Circle Suite C, 6th Floor Tampa, FL 33606	813-259-0619
Wes Ely, MD Vanderbilt University School of Medicine, Professor	Consultant	6109 Medical Center East Vanderbilt University School of Medicine Nashville, TN 37232-8300	615-936-3395
Xusheng Chen University of Miami School of Nursing and Health Studies	Data Manager	UM SONHS 5030 Brunson Drive P.O. Box 248153 Coral Gables, FL 33124-3850	305-284-2243
Cristobal Padilla Fortunati, MSN, BSN University of Miami School of Nursing and Health Studies	Research Assistant	UM SONHS 5030 Brunson Drive P.O. Box 248153 Coral Gables, FL 33124-3850	305-284-2243

TBN	Research Assistant	UM SONHS 5030 Brunson Drive P.O. Box 248153 Coral Gables, FL 33124-3850	305-284-2243
TBN	Research Assistant	UM SONHS 5030 Brunson Drive P.O. Box 248153 Coral Gables, FL 33124-3850	305-284-2243
TBN	Research Assistant	UM SONHS 5030 Brunson Drive P.O. Box 248153 Coral Gables, FL 33124-3850	305-284-2243
TBN	Research Assistant	UM SONHS 5030 Brunson Drive P.O. Box 248153 Coral Gables, FL 33124-3850	305-284-2243

Conflict of Interest. None of the investigators will benefit from subjects' participation in this project or completion of the project in general.

Personnel Training. Before subjects are enrolled in the study, a comprehensive study manual will be developed describing all study procedures. Under the supervision of the PI, the Project Director will train all research assistants (RAs) on all aspects of the study, including intervention delivery, use of all study equipment (SP-PSG, actigraphy), use of the electronic medical record, and data collection and entry, documentation, and regulatory compliance. Training will include completion of the Collaborative Investigator Training Initiative (CITI) education in human subject protections. Training will continue until RAs have achieved 100% accuracy of all procedures and data collection processes, assessed by return demonstrations on all study procedures. Training reviews will occur regularly, and each RA will also be directly observed by the Project Director every 3 months throughout the study period to ensure that all critical elements of the study continue to be correctly performed. The Project Director will retrain RAs immediately if any critical element is found to be omitted or inaccurate.

19. Prior Approvals

Approval from the UMH Ancillary Committee and Jackson Health System (JHS) Clinical Research Review Committee are required.

20. Recruitment Methods

As of March 2020, to protect human subjects, we are closely following the COVID-19 safety recommendations. We have resumed enrollments at UMH as of June 2020, but continue temporarily suspending new enrollments at JMH.

Pre-Screening, Recruitment, and Enrollment. Subjects will be recruited from all patients admitted to the adult UMH and JMH ICUs including Cardiac Care, Medical, Neuro, Surgical, and Specialty critical care, who speak English or Spanish, are expected to remain in the ICU at least 48 hours, have no history of dementia, and have a family member able to speak English or Spanish who is available and willing to audio record scripted messages. Subjects will be

enrolled in the study within 48 hours of intubation and ICU admission. Male and female adults from all ethnic and racial backgrounds will be recruited.

A waiver of HIPAA Authorization is being requested for pre- screening and recruitment purposes only. It would be difficult to determine eligibility of potential participants without the waiver. Each patient and/or the nurse would have to be approached without the waiver, which could cause confusion for the patient and waste the time of the nurse in the event of ineligibility in the highly stressful, life-threatening, critical care environment. No identifying information will be collected or retained from the pre-screening and recruitment processes. Signed authorization will be obtained along with informed consent upon enrollment of subjects in the study.

Pre-screening process:

1. Project Director or RAs will make daily rounds in the adult ICUs to evaluate patients as potential subjects for the study.
2. Selection of medical records to review for eligibility and exclusion criteria will be based on the ICU census boards that reflect patient admissions.
3. Eligibility and exclusion criteria found on the consent checklist may be used as a prescreening aid while reviewing the medical record.
4. If the patient does not meet study criteria, no identifying information will be retained.
5. If the patient meets all study criteria, then the Project Director or RA will move on to the recruitment process.

Recruitment process:

1. If a patient meets all study criteria in the pre-screening process, the bedside nurse will be approached regarding availability of a family member to record scripted reorientation messages.
2. If the family member is found not to be available at bedside, the Project Director or RA will contact healthcare proxy or family member using the phone number found in patient's medical record, and will follow the Recruitment Script to speak with the family member regarding interest in study participation.
    a. In our experience, finding family members at the bedside during the eligibility window of 48 hours from admission or intubation has been a unique challenge in Miami hospitals. Many family members avoid staying in the hospital setting and visit infrequently or for short periods of time; some of the hospital units we recruit from have strict limitations on visitation time (15 minutes at a time, for example). Placing a call directly to family members would allow for family to be invited directly to discuss possible study participation.
3. If family is present at the bedside, the Project Director or RA will follow the Recruitment Script to address both the potential subject and family member regarding interest in study participation.
4. If the patient does not have a family member available and/or willing to record the scripted reorientation messages, the patient is not eligible for study enrollment. No identifying information will be retained.
5. If the patient has a family member available and willing to record the scripted reorientation messages, then the Project Director or RA will move on to the enrollment process.

Enrollment process:

2. The potential subject's capacity to consent will be determined (see section 18. Consent Process).
    a. In our experience, potential subjects who are critically ill, especially during the first 48 hours of intubation, are always sedated to some degree, and their ability to communicate effectively may be compromised by endotracheal intubation; in

these cases, consent has been obtained from the legally authorized representative (LAR).

3. If the potential subject or their LAR is not interested in consenting to participate in the study, no identifying information will be retained.
4. If the LAR is contacted by phone or HIPAA compliant Zoom:
    a. Review of the consent forms will be completed over the phone or by Zoom by the Project Director or RAs, as is done in person.
    b. Verbal consent will be obtained over the phone or by Zoom.
    c. Waiver of wet signature will be documented by the person obtaining consent.
5. All consent, HIPAA, and Audio Recording forms will be collected using a secured email server.
6. The family member willing to record the scripted reorientation messages will be required to sign the Authorization for Audio Recording in Research form if recording in person. If the family member is recording by phone or Zoom, verbal consent to record will be obtained and documented by the person obtaining consent.
7. UM IRB, JMH, and UMH policies and procedures for clinical research participant enrollment and tracking will be followed.

Since this study involves continuous data collection over 120 hours, the Project Director and RAs will be involved in the pre-screening, recruitment, and enrollment of subjects, along with collection of all data. We have successfully trained RAs to pre-screen, recruit, enroll, and collect complex data processes in the ICU environment in several previous studies. Although data collection will occur continuously for 120 hours, in our experience with continuous data collection, we have found that providing support for automated data collection (for example, actigraphy) approximately 10 hours per day (i.e. 8a – 6p) in person results in collection processes which run exceptionally well in the hours when study personnel are not present. In addition, we will conduct extensive education for the unit staff about the project, although no study activities will be required from them. Study personnel will also be on call by telephone during all study hours, so that hospital staff can contact us if they have any questions about the equipment (SP-PSG and ActiWatch).

21. Local Number of Subjects

We plan to review approximately 350 medical records in order to achieve our sample size of 182 enrollments.

22. Confidentiality

To ensure confidentiality, each participant will be assigned an arbitrary study identification number to conceal their identity on all research data. All hard copy research material (i.e., consent forms) will be maintained in locked file cabinets, in a locked room, electronic data will be kept on password protected computers under the direct supervision of the PI for 5 years after the final report has been submitted to the UM IRB. Study information obtained will be kept strictly confidential, protecting the identity of participants in all reports or publications that may result from this research. After the 5-year storage period, all documents will be destroyed by UM after the Project Director places these documents inside the locked HIPAA bins for destruction.

23. Provisions to Protect the Privacy Interests of Subjects

To ensure privacy, all interactions with subjects and LARs will be conducted in the subject's hospital room or a private area of the ICU. The information obtained will be kept strictly confidential, and it will not be possible to identify any participant from the reports of publications that may result from this research. Participants will be assigned an arbitrary code number to conceal their identity on all research data, and all research data will be maintained in locked file cabinets in a locked room under the direct supervision of the PI for 5 years after the final report has been submitted to the UM IRB. After the 5-year storage period, all documents will be destroyed by UM after the Project Director places these documents inside the locked HIPAA bins for destruction.

24. Compensation for Research-Related Injury

Since injury is unlikely in this minimal risk study, there is no compensation for research-related injury.

25. Economic Burden to Subjects

There is no cost to subjects participating in the study.

26. Consent Process

Following IRB approval of the partial HIPAA waiver, the trained Project Director or RAs will review the potential subject's medical record, and if there are no exclusions, the subject will be invited to enroll. The subject and the subject's LAR will be provided with an oral explanation of the nature of the study and study information, in writing. The information will include all elements required for informed consent, and will include all pertinent contact information as well as information about withdrawal from the study. Written consent will be obtained if the consent process is conducted in person. If the LAR is contacted by phone or HIPAA compliant Zoom, review of the consent forms will be completed over the phone or by Zoom by the Project Director or RAs, as is done in person. Verbal consent will be obtained over the phone or by Zoom. Waiver of wet signature will be documented by the person obtaining consent.

If at any time the subject or LAR does not wish to continue to participate in the study, no additional interactions with the subject will take place, no follow-up data will be collected and that subject's data forms will be destroyed. Dr. Munro (study PI) has extensive experience in obtaining consents from family members of critically ill adults. The study staff will work closely with the staff of the Cardiac Care, Medical, Neuro, Surgical, and Specialty ICUs, nurse managers, and medical directors to ensure that all eligible patients have an equal opportunity for inclusion.

In our experience in conducting clinical research in the critical care areas, we have found that potential subjects who are mechanically ventilated are generally sedated to some degree. In addition, since use of mechanical ventilation primarily occurs during periods of patient instability, the use of sedation at these times is extensive and compromises patient's ability to communicate effectively which is compounded by the presence of the endotracheal tube. As a result, we have always found it appropriate to contact the legally authorized representative for consent. However, there may be rare occurrences when potential subjects are adequately oriented and lucid to be able to provide informed consent. Therefore, we will use the 2-step procedure described by Fan et al.[76] to determine the patient's ability to provide informed

consent. Step 1 is objective evaluation with the Richmond Agitation-Sedation Scale (RASS) and the Confusion Assessment Method for Intensive Care Unit (CAM-ICU). Patients who score -1, 0,
+1 on the RASS indicating drowsy, alert, or restless respectively and are not delirious (CAM-ICU = No) will move to Step 2. Step 2 is assessment for competency using the MacArthur Competence Assessment Tool for Clinical Research: MacCAT-CR that evaluates all four capacity domains for consent (understanding, appreciation, reasoning, expression of a choice). Evaluation of Step 1 requires approximately 2-3 minutes, Step 2 requires approximately 15 minutes. Fan et al.[76] found in consent evaluations of 150 ICU patients that 89% were sedated/delirious, and unable to provide consent; our experience in previous research is similar. Therefore, we expect that few potential subjects will move to Step 2 while critically ill and mechanically ventilated. The LAR will be contacted for those who fail Step 1 or Step 2.
We will evaluate the potential subject's level of orientation and response to our discussions of the study on a daily basis during the hospital phase, and if the potential subject is able to respond in a manner that is clearly understandable, we will use the potential subject's own consent to continue participation. However, in any instance where the potential subject's ability to comprehend and communicate his/her desires is in question, we will seek consent for continued participation from the LAR and will invite the research subject to provide his/her assent. Verbal consent to continue participation and for post-hospital follow up will be obtained from the subject as soon as their medical condition permits. We will follow UM IRB, JMH, and UMH Policies and Procedures.

Non-English-Speaking Subjects
The consenting process for Spanish patients, family members, and/or LAR's will be the same process only with the addition of an individual UMH or JMH Spanish translator or by use of the UMH translation language line phone service, which is available 24 hours a day, 7 days a week.

Cognitively Impaired Adults
In our experience in conducting clinical research in the critical care areas, we have found that potential subjects who are mechanically ventilated are generally sedated to some degree. In addition, since use of mechanical ventilation primarily occurs during periods of patient instability, the use of sedation at these times is extensive and compromises patient's ability to communicate effectively which is compounded by the presence of the endotracheal tube. As a result, we have always found it appropriate to contact the legally authorized representative for consent. However, there may be rare occurrences when potential subjects are adequately oriented and lucid to be able to provide informed consent. Therefore, we will use the 2-step procedure described by Fan et al.[76] to determine the patient's ability to provide informed consent. Step 1 is objective evaluation with the Richmond Agitation-Sedation Scale (RASS) and the Confusion Assessment Method for Intensive Care Unit (CAM-ICU). Patients who score -1, 0,
+1 on the RASS indicating drowsy, alert, or restless respectively and are not delirious (CAM-ICU = No) will move to Step 2. Step 2 is assessment for competency using the MacArthur Competence Assessment Tool for Clinical Research: MacCAT-CR that evaluates all four capacity domains for consent (understanding, appreciation, reasoning, expression of a choice). Evaluation of Step 1 requires approximately 2-3 minutes, Step 2 requires approximately 15 minutes. Fan et al.[76] found in consent evaluations of 150 ICU patients that 89% were sedated/delirious, and unable to provide consent; our experience in previous research is similar. Therefore, we expect that few potential subjects will move to Step 2 while critically ill and mechanically ventilated. The LAR will be contacted for those who fail Step 1 or Step 2. We will

evaluate the potential subject's level of orientation and response to our discussions of the study on a daily basis during the hospital phase, and if the potential subject is able to respond in a manner that is clearly understandable, we will use the potential subject's own consent to continue participation. However, in any instance where the potential subject's ability to comprehend and communicate his/her desires is in question, we will seek consent for continued participation from the LAR and will invite the research subject to provide his/her assent.

Subjects will be withdrawn if they appear to be unduly distressed. For example, if a 20% or larger fluctuation in vital signs (heart rate and blood pressure) during the delivery of the recorded message occur, research staff will turn off the recorded message. The clinical nurse assigned to the subject will be immediately notified, and the clinical medical provider will be notified as well. The message will be restarted when the critical care nurse or physician indicates the patient is stable. If the 20% or larger fluctuation in vital signs re-occurs, the intervention will be discontinued and the in-hospital data only up to that point will be included in the study.

Verbal consent to continue participation and for post-hospital follow up will be obtained from the subject as soon as their medical condition permits. We will follow UM IRB, JMH, and UMH policies and procedures. The consenting process for Spanish patients, family members, and/or LAR's will be the same process only with the addition of an individual UMH or JMH Spanish translator or by use of the UMH translation language line phone service, which is available 24 hours a day, 7 days a week.

Adults Unable to Consent

In our experience, potential subjects who are critically ill, especially during the first 48 hours of intubation, are always sedated to some degree, and their ability to communicate effectively is compromised by endotracheal intubation; for these reasons, permission for the subject's participation has generally been obtained from the LAR. Upon the initial screening of the medical record for eligibility, we will review the medical record for any named health care surrogate or a court appointed guardian. If neither of these are named, the following order of potential LARs will be assessed: spouse, adult child, parent, adult sibling, adult relative, a close friend, or a clinical social worker.

We will evaluate the potential subject's level of orientation and response to our discussions of the study on a daily basis during the hospital phase, and if the potential subject is able to respond in a manner that is clearly understandable, we will use the potential subject's own consent to continue participation. However, in any instance where the potential subject's ability to comprehend and communicate his/her desires is in question, we will seek consent for continued participation from the LAR and will invite the research subject to provide his/her assent.

Subjects will be withdrawn if they appear to be unduly distressed. For example, if a 20% or larger fluctuation in vital signs (heart rate and blood pressure) during the delivery of the recorded message occur, research staff will turn off the recorded message. The clinical nurse assigned to the subject will be immediately notified, and the clinical medical provider will be notified as well. The message will be restarted when the critical care nurse or physician indicates the patient is stable. If the 20% or larger fluctuation in vital signs re-occurs, the intervention will be discontinued and the in-hospital data only up to that point will be included in the study.

Verbal consent to continue participation and for post-hospital follow up will be obtained from the subject as soon as their medical condition permits. We will follow UM IRB, JMH, and UMH policies and procedures. The consenting process for Spanish patients, family members, and/or LAR's will be the same process only with the addition of an individual UMH or JMH Spanish translator or by use of the UMH translation language line phone service, which is available 24 hours a day, 7 days a week.

27. Process to Document Consent in Writing

The RAs and Project Director will follow the steps in the consent checklist to obtain written consent and HIPAA authorization. In our experience, potential subjects who are critically ill, especially during the first 48 hours of intubation, are always sedated to some degree, and their ability to communicate effectively is compromised by endotracheal intubation; for these reasons, permission for the subject's participation has generally been obtained from the LAR. Upon the initial screening of the medical record for eligibility, we will review the medical record for any named health care surrogate or a court appointed guardian. If neither of these are named, the following order of potential LARs will be assessed: spouse, adult child, parent, adult sibling, adult relative, a close friend, or a clinical social worker. We will verify the subject or LAR understands English or Spanish and utilize the language version of their preference.

The entire informed consent form and HIPAA authorization will be thoroughly verbally explained to the subject or LAR with questions of understanding throughout each section. Reinforcement that the level of care they receive is not impacted whether they participate in the study or not will be provided. The subject or LAR will be asked if they would like more time to think about their decision to participate or not to participate in the study. If more time is requested, the study staff will leave copies of the consent and HIPAA authorization forms, provide contact information of the study staff, and the amount of remaining time they are eligible to participate due to the requirement of enrollment within 48 hours of ICU admission & initial intubation. We will have the subject or LAR (and the person obtaining consent) personally print, sign, and date the consent and HIPAA authorization documents. If the LAR is contacted by phone or HIPAA compliant Zoom, and not available in person, verbal consent will be obtained over the phone or by Zoom. Waiver of wet signature will be documented by the person obtaining consent.

Copies of the signed consent and HIPAA authorization forms will be provided to the subject or LAR. Copies of the signed consent form, HIPAA authorization, and/or consent checklist will be provided to UMH and JMH according to their current practice. The Project Director will place original signed consent forms, HIPAA authorizations, and consent checklists in a study binder to be secured in a double-locked room at UM SONHS, supervised by the Principal Investigator, for at least 5 years following study completion.

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