PROTOCOL NUMBER: HS-17-00617

TITLE:

The Impact of a Multifaceted Delirium Preventing Strategy in the ICU involving Psychiatry: Effects on Delirium Incidence and Outcomes

PRINCIPAL INVESTIGATOR(S):
CATHERINE KUZA, M.D.
Department of Anesthesiology, Division of Critical Care
KECK HOSPTIAL OF USC
1500 SAN PABLO STREET
LOS ANGELES, CA 90033

CO-PRINCIPAL INVESTIGATOR(S):
DAVID SHESKI, M.D.
Department of Psychiatry at KSOM of the USC

CO-INVESTIGATOR:
Kelly Jones, M.D.
Department of Psychiatry at KSOM of the USC

SPONSOR: none

PARTICIPANTS/LOCATONS: Keck Hospital of USC

AMENDMENTS/REVISIONS: Third Revision 11-02-2017

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1.0 BACKGROUND AND HYPOTHESIS

We are interested in evaluating a multifaceted prevention protocol for ICU delirium. Delirium affects 45-80% of elderly ICU patients, 60-80% of mechanically ventilated ICU patients, and 20-50% of non-mechanically ventilated ICU patients (1-4). About 30-40% of cases are preventable (1, 2). Without routine screening, delirium is often undiagnosed (5-7). Numerous studies have consistently shown that ICU delirium is associated with a worse prognosis (8). The annual cost of delirium and its ramifications in the U.S., is estimated to be $4-16 billion (1).

Delirium impacts emotional well-being, as delirious patients experienced delusional memories and had less factual recall than non-delirious patients (9-11). A meta-analysis performed by Zhang et al. found delirium to be associated with a higher mortality rate, longer ICU and hospital lengths of stay, longer duration of mechanical ventilation, and higher probability of discharge to a skilled placement facility. (9) ICU-acquired delirium is independently associated with increased cognitive and physical impairment and health care costs (6, 12). Delirium was also found to be associated with more complications (9,13). Patients who develop delirium have a 2-3 times increased risk of dying during ICU admission (8, 14), with ICU mortality ranging from 1-16% (15-17), and an in-hospital mortality rate of 25% to 33%. (12, 18). It is also associated with increased hospital length of stay (13, 19) and each additional day of delirium increases post-discharge mortality up to a year after discharge (14, 16, 19).

Patients with ICU delirium had a higher incidence of cognitive impairment at hospital discharge, and up to 18 months post-discharge (20, 21) A longer duration of delirium in the hospital was associated with worse global cognition and executive function scores at 3 and 12 months (22), and it is associated with the development of new-onset dementia, or worsening of existing dementia (2, 22). In addition to cognitive problems, delirium was found to be associated with more problems in activities of daily living and worse scores on sensorimotor function tests at follow-up (3). Anxiety, depression, and posttraumatic stress disorder are common in survivors of critical illness (20, 21).

Recent studies evaluating interventions to prevent delirium have focused on “care bundles”, which are comprised of several care procedures incorporated into routine clinical care, that improve patient outcomes. “Bundling” therapies used in the prevention of sepsis, ventilator-associated pneumonia, and central line infections have demonstrated improved clinical outcomes (12). The ABCDEF bundle (daily awakening and breathing coordination trials, delirium monitoring and treatment, early mobility, and family involvement), a multidisciplinary and multicomponent intervention strategy, is increasingly being used in ICUs to decrease length of stay, mechanical ventilation time, complications, and improve outcomes (23). The purpose is to minimize exposure to sedating medications and facilitate early extubation and mobilization (23). It has also been evaluated in the prevention and treatment of delirium and found to decrease delirium incidence and duration, mortality, mechanical ventilator days, hospital length of stay, and improve functional status and overall outcomes (12).

Psychiatric interventions have been evaluated in trauma patients (24), post-CABG patients who develop a psychiatric disorder postoperatively (25) post-intensive care syndrome (PICS) patients (26), and inpatients with delirium (27, 28) and were shown to have beneficial effects. The role of psychiatric interventions in the ICU has not been extensively studied. There are only 3 studies which evaluated the role of psychiatry in the ICU aimed at: 1. minimizing PTSD/anxiety/depression incidence in ICU patients (29), 2. providing a support system for ICU patients (30), and 3. improving the mental health

of ICU patients (31). Additionally, the presence of a psychiatry team rounding with a medical ICU team on nursing and resident education improvement was examined (32). No studies have evaluated the role of psychiatry rounding with the ICU team to prevent delirium and improve long-term outcomes.

The aim of our study is to determine the effect of delirium prevention care bundle protocols and a multi-disciplinary care model rounding with a psychiatry team (intervention group) on the incidence of delirium as compared to a group undergoing standard care without psychiatry participating in ICU rounds (control group). The psychiatric intervention entails a multidisciplinary approach to patient care during rounds, working with the ICU team to make recommendations on non-pharmacological and pharmacological prevention and treatment strategies for patients who are positive for delirium, and helping to differentiate delirium from other psychiatric conditions, that the ICU team may not have the training background to easily identify. Since the incidence of ICU delirium is so high and it has negative ramifications on patient survival, long-term outcomes, cognitive function, and places a heavy burden on the healthcare system and cost, preventative strategies are desperately needed. Using bundle care protocols and multidisciplinary rounding with psychiatry may be a feasible and cheap measure to help prevent delirium in ICU patients.

2.0 OBJECTIVES AND PURPOSE

The purpose of our study is to determine the effect of delirium prevention care bundle protocols, and a multi-disciplinary care model rounding with a psychiatry team (intervention group) on ICU delirium and patient outcomes as compared to a group undergoing standard care without routine psychiatry team participating in ICU rounds (control group). Since the incidence of ICU delirium is so high and it has negative ramifications on patient survival, long-term outcomes, cognitive function, and places a heavy burden on the healthcare system and cost, preventative strategies are desperately needed. Using bundle care protocols and multidisciplinary rounding with psychiatry may be a feasible and cheap measure to help prevent delirium in ICU patients.

The primary objective is the incidence of ICU delirium.

The secondary objectives are:
-duration of delirium
-ICU and hospital length of stay
-days of mechanical ventilation (if applicable)
-in-hospital mortality

Our primary hypothesis is that the intervention of psychiatry team participation in multidisciplinary ICU rounds with the surgical ICU team will result in a decreased incidence of delirium compared to standard care without routine psychiatry team involvement. Our secondary hypothesis is that psychiatric team participation in multidisciplinary ICU rounds will decrease delirium duration, decrease ICU and hospital length of stay, decrease mechanical ventilation duration, and decrease in-hospital mortality compared to the standard care group.

3.0 STUDY DESIGN

This is a prospective, single institution, controlled, pilot study of patients admitted to the 7W ICU which will compare the incidence and delirium rates among patients undergoing routine care before

intervention (no routine psychiatric involvement) (control group) and patients after the intervention (psychiatry team rounding with the ICU team daily) (intervention group) . Randomization is not possible for this study; although block randomization was considered, it will result in sub-optimal data subject to bias.

A sample size of 104 (52 per group) is targeted based on an *a priori* sample size calculation. Patients will be screened on a daily basis for study eligibility by study personnel and ICU team members, before delirium develops. Patients in both groups will be given and information sheet, verbal consent will be obtained, and the patient's agreement to participate will be documented in the medical record. For patients who are unable to make their own decisions, the information sheet will be given to their designated healthcare decision maker, verbal consent will be obtained, and the healthcare decision maker's agreement will be documented in the medical record.

The control group will receive standard care, including the use of the ABCDEF bundle (Appendix 1) daily, which involves delirium screening using the Confusion Assessment Method-Intensive Care Unit (CAM-ICU) score (Appendix 2), but will not have routine psychiatric involvement in care. The CAM-ICU is performed by the ICU nurses on a daily basis. It consists of several questions that assess patient's mental status, if the change in mental status fluctuates, the sedation score (using Richmond Agitation Sedation Score [RASS]), and the patient's attention span and if disorganized thinking is present by asking several questions. The CAM-ICU can be performed in intubated patients by asking the patient to follow commands with their hands, or squeeze the nurse's hand in response to a question. The CAM-ICU will be done every morning, but may also be repeated later on in the day if the patient's mental status changes from the morning-this will be the same for both the control and intervention group. Enrollment and data collection will continue for as long as it takes to reach the target sample size of 52 patients for this group. We will then provide standard care (including ABCDEF bundle implementation, which is standard practice in 7W ICU) and provide routine psychiatric care, which entails a member of the psychiatric team (attending, resident, and/or fellow) participating in daily (Monday-Friday) multidisciplinary rounds with the ICU team (intervention group); the psychiatry team will help provide nonpharmacological and pharmacological intervention strategies in patients diagnosed with delirium and help distinguish delirium from other psychiatric disorders which may be missed by the ICU team and provide earlier treatment of these conditions. This study phase will continue until the target sample size of 52 patients is reached.

In both the control and intervention groups, delirium will be diagnosed by a positive CAM-ICU score. Both groups will have the CAM-ICU test administered by the patient's nurse on a daily basis (which is standard practice in 7W ICU) in the morning and may be repeated later on in the day if the patient's mental status changes. Data on the incidence of ICU delirium, duration of delirium/mechanical ventilation, in-house mortality, hospital and ICU length of stay will be collected.

Additionally, we will collect the following data: age, gender, body mass index, history or alcohol or substance abuse, admitting diagnosis, dementia, comorbid conditions, admitting Sequential Organ Failure Assessment (SOFA) score, deliriogenic medications used during study enrollment, the interventions/medications used to treat delirium as designated by psychiatry and the ICU team (in intervention group) and the ICU team (control group), and the number of days from ICU admission to study enrollment. We will input data into a secure, password protected, encrypted, electronic database, RedCap.

The data points will be compared between the control and intervention groups (see section 13.0).

Our primary outcome is: incidence of ICU delirium.

The secondary outcomes are: duration of delirium/mechanical ventilation, in-house mortality, and hospital and ICU length of stay.

4.0 DRUG/DEVICE INFORMATION

Not applicable

5.0 SELECTION AND WITHDRAWAL OF SUBJECTS

Inclusion criteria are:

1. Patients who are ≥18 years of age
2. Patients admitted to the surgical ICU for >48 hours OR
3. Patients admitted to the ICU <24 hours who have been in the hospital >48 hours OR
4. Patients who return to the ICU after being discharged from the ICU to the floor due a complication or need for higher acuity care.
5. Patients admitted to any surgical service who are receiving care in the 7 West surgical ICU, who are either medically or conservatively managed (non-surgical) or surgically managed as part of their care

Exclusion criteria are:

1. Patients in whom CAM-ICU cannot be performed (severe dementia, stroke or other neurological condition, encephalopathy, mental retardation, severe psychiatric disorder, vegetative state, severe traumatic brain injury, deaf/blind, etc.)
2. Patients who don't speak or understand English
3. Current alcohol or substance abuse
4. Patients who already have delirium within 24-48 hours of their ICU admission [Defined as a positive CAM-ICU test, or based on the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (* DSM-V) diagnostic criteria:

- Disturbance in attention (ie, reduced ability to direct, focus, sustain, and shift attention) and awareness.

- Change in cognition (eg, memory deficit, disorientation, language disturbance, perceptual disturbance) that is not better accounted for by a preexisting, established, or evolving dementia.

- The disturbance develops over a short period (usually hours to days) and tends to fluctuate during the course of the day.

- There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by a direct physiologic consequence of a general medical condition, an intoxicating substance, medication use, or more than one cause.]

Patients will be screened for eligibility on rounds daily. Patients may withdraw from the study at any point without impacting their healthcare.

6.0 STRATIFICATION/DESCRIPTIVE FACTORS/RANDOMIZATION SCHEME

This is a prospective, single institution, controlled, pilot study of patients admitted to the 7W ICU. A sample size of 104 (52 per group) is targeted. Patients will be screened for study eligibility on a daily basis The control group will undergo standard ICU care, which includes the use of the ABCDEF bundle (Appendix 1) daily, which involves delirium screening using the CAM-ICU tool (Appendix 2), but will not have routine psychiatric involvement in care. Enrollment and data collection will continue for as long as it takes to reach the target sample size of 52 patients for this group. We will then proceed to enroll patients into the intervention group, who undergo standard care (including ABCDEF bundle implementation, which is standard practice in 7W ICU) in addition to a psychiatric team intervention, which entails having a member of the psychiatric team (attending, resident, and/or fellow) participate in daily (Monday-Friday) multidisciplinary rounds with the ICU team; they will help provide nonpharmacological and pharmacological intervention strategies in patients diagnosed with delirium and help distinguish delirium from other psychiatric disorders which may be missed by the ICU team and provide earlier treatment of these conditions. This study phase will continue until the target sample size of 52 patients is reached.

Data will be collected for both the control and intervention groups (see Section 12) and compared.

Randomization is not possible for this study; although block randomization was considered, it will result in sub-optimal data subject to bias.

7.0 STUDY AGENT ADMINISTRATION OR INTERVENTION AND TOXICITY MANAGEMENT PLAN

In addition to standard care (ABCDEF bundle, which includes daily CAM-ICU screening for Delirium by ICU nurses), the intervention will be daily multidisciplinary ICU rounds with a psychiatry team member, who will collaborate with the ICU team in implementing preventative strategies, assist in the pharmacological and nonpharmacological treatment of patients with delirium, and assist in differentiating delirium from other psychiatric disorders which may not be detected by ICU providers, thus, identifying, addressing, and treating these illnesses at an earlier time.

8.0 ASSESSMENT OF EFFICACY AND SAFETY

Not applicable

9.0 CLINICAL AND LABORATORY EVALUATIONS AND STUDY CALENDAR

We will collect basic demographic data and screen for delirium using the CAM-ICU (which is standard practice in the ICU). The ABCDEF bundle and CAM-ICU screening tool are performed by the ICU nurses on a daily basis in the morning. The CAM-ICU may be performed later on in the day if the patient's mental status changes. The findings in the ABCDEF bundle and CAM-ICU screening tool are communicated to the ICU team on morning rounds. In patients who develop delirium, we will

collect data on their total ICU/hospital LOS (length of stay), days on mechanical ventilation (if applicable), duration of delirium, and in-hospital mortality.

No additional laboratory studies or investigative studies will be performed for the study.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

Primary outcome: incidence of delirium, defined by a positive CAM-ICU.

Secondary outcomes: delirium duration, ICU/hospital length of stay, in-hospital mortality, and mechanical ventilation duration**.**

11.0 SPECIAL INSTRUCTIONS:

Not applicable

12. DATA COLLECTION AND MONITORING

Data which will be collected includes: age, gender, body mass index, history or alcohol or substance abuse, admitting diagnosis, dementia, comorbid conditions, admitting Sequential Organ Failure Assessment (SOFA) score, deliriogenic medications used during study enrollment, the interventions/medications used to treat delirium as designated by psychiatry in conjunction with the ICU team (in intervention group) and the ICU team (control group), and the number of days from ICU admission to study enrollment. Data on the incidence of ICU delirium, duration of delirium/mechanical ventilation, in-house mortality, and length of stay will also be collected.

Data will be collected using RedCap, a password protected website. No patient identifiers will be used. A copy of the information sheet will be provided to the patient and be placed in the patient's chart. We will retain a copy of the information sheet in a double locked storage office.

13.0 STATISTICAL CONSIDERATIONS

In this pilot study, sample size considerations were based on obtaining sufficient patient numbers to assess feasibility of the intervention and data collection on the surgical unit, as well as to obtain estimates of incidence of delirium in the current care model (the base incidence) and the magnitude of effect of introduction of psychiatric involvement on the unit. All of these data are required for determination of feasibility of and sample size estimation for a larger definitive trial that would likely be a multi-centered cluster randomized trial. Based on our clinical experience in the 7W ICU, the incidence of delirium over the past year was roughly 40%; from the literature, a large intervention effect would be on the order of 25% reduction in incident delirium. We used these initial approximations to determine the precision (i.e., width of a 95% confidence interval) with which we can estimate these two parameters for use in future trial planning. Given a sample size of 94 patients (47 in each group), we will be able to estimate the actual difference in the incidence of delirium in our proposed intervention group (compared to SOC) with a precision (95% confidence interval) of 8%-42%. In the 47 in the SOC group, we will be able to estimate the base rate of delirium incidence with a 95% confidence interval of 26%-55%. The effect size and base rate estimated from this pilot trial will help us design future multi-center, larger population studies.
A sample size of 104 will be targeted to account for a 10% drop-out rate.

Descriptive statistics, including Student's t-test or Mann–Whitney U-test, for continuous variables and χ^2 or Fisher's exact test, for categorical variables, will be used to summarize the data and compare

characteristics between the 2 groups. The incidence of delirium will be compared using χ^2 test and multivariable logistic regression. Differences in the duration of delirium and MV between the intervention and control groups will be analyzed by analysis of variance (ANOVA). The length of stay will be compared by truncated negative binomial regression, while mortality rates will be compared via logistic regression. A sensitivity analysis will be performed in order to assess the possible confounding effect of the non-randomized nature of our study design. A propensity score model for receipt of standard care vs. psychiatric involvement will be performed in order to approximate a balanced covariate distribution between the 2 groups as that would be expected by randomization. We will then use the propensity score for each subject to perform an inverse probability weighted comparison of the groups on our trial outcomes.

14.0 REGISTRATION GUIDELINE

Not applicable

15.0 BIOHAZARD COMTAINMENT

Not applicable

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

All institutional and Federal regulations concerning the Informed Consent form will be fulfilled. The study will be conducted in adherence to ICH Good Clinical Practice.

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APPENDICES

APPENDIX 1. ABCDEF BUNDLE USED IN 7 West ICU.

Symptoms **Pain, Agitation, Delirium Guidelines**	**Monitoring** **Tools**	**Care** **ABCDEF Bundle**
Pain	Critical-care Pain Observation Tool (CPOT) Numeric Rating Scale (NRS) Behavioral Pain Scale (BPS)	**A**: Assess, prevent and manage pain **B**: Both spontaneous awakening trials (SAT) and spontaneous breathing trials (SBT) **C**: Choice of analgesia/sedation **D**: Delirium-Assess, prevent and manage **E**: Early mobility/exercise **F**: Family engagement and empowerment
Agitation	Richmond Agitation Sedation Scale (RASS)	
Delirium	Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)	

APPENDIX 2. CAM-ICU.

CAM-ICU Worksheet

Feature 1: Acute Onset or Fluctuating Course	Score	Check here if Present
Is the patient different than his/her baseline mental status? OR Has the patient had any fluctuation in mental status in the past 24 hours as evidenced by fluctuation on a sedation/level of consciousness scale (i.e., RASS/SAS), GCS, or previous delirium assessment?	Either question Yes →	☐
Feature 2: Inattention		
Letters Attention Test (See training manual for alternate **Pictures**) Directions: Say to the patient, *"I am going to read you a series of 10 letters. Whenever you hear the letter 'A,' indicate by squeezing my hand."* Read letters from the following letter list in a normal tone 3 seconds apart. **S A V E A H A A R T** or **C A S A B L A N C A** or **A B A D B A D A A Y** **Errors are counted when patient fails to squeeze on the letter "A" and when the patient squeezes on any letter other than "A."**	Number of Errors >2 →	☐
Feature 3: Altered Level of Consciousness		
Present if the Actual RASS score is anything other than alert and calm (zero)	RASS anything other than zero →	☐
Feature 4:Disorganized Thinking		
Yes/No Questions (See training manual for alternate set of questions) 1. Will a stone float on water? 2. Are there fish in the sea? 3. Does one pound weigh more than two pounds? 4. Can you use a hammer to pound a nail? **Errors are counted when the patient incorrectly answers a question.** **Command** Say to patient: "Hold up this many fingers" (Hold 2 fingers in front of patient) "Now do the same thing with the other hand" (Do not repeat number of fingers) *If the patient is unable to move both arms, for 2nd part of command ask patient to "Add one more finger" **An error is counted if patient is unable to complete the entire command.**	Combined number of errors >1→	☐

Overall CAM-ICU		
Feature 1 plus 2 and either 3 or 4 present = CAM-ICU positive	**Criteria Met →**	☐ **CAM-ICU Positive** (Delirium Present)
	Criteria Not Met →	☐ **CAM-ICU Negative** (No Delirium)

APPENDIX 3. Critical-Care Pain Observational Tool (CPOT).

Critical-Care Pain Observation Tool (CPOT)

Indicator	Description	Score
Facial expression	No muscular tension observed	Relaxed, neutral 0
	Presence of frowning, brow lowering, orbit tightening, and levator contraction	Tense **1**
	All of the above facial movements plus eyelid tightly closed	Grimacing **2**
Body movements	Does not move at all (does not necessarily mean absence of pain)	Absence of movements 0
	Slow, cautious movements, touching or rubbing the pain site, seeking attention through movements	Protection 1
	Pulling tube, attempting to sit up, moving limbs/ thrashing, not following commands, striking at staff, trying to climb out of bed	Restlessness 2
Muscle tension Evaluation by passive flexion and extension of upper extremities	No resistance to passive movements	Relaxed **0**
	Resistance to passive movements	Tense, rigid **1**
	Strong resistance to passive movements, inability to complete them	Very tense or rigid **2**
Compliance with the ventilator (intubated patients)	Alarms not activated, easy ventilation	Tolerating ventilator or movement **0**
	Alarms stop spontaneously	Coughing but tolerating **1**
	Asynchrony: blocking ventilation, alarms frequently activated	Fighting ventilator **2**
or		
Vocalization (extubated patients)	Talking in normal tone or no sound	Talking in normal tone or no sound **0**
	Sighing, moaning	Sighing, moaning **1**
	Crying out, sobbing	Crying out, sobbing **2**
Total, range	**Sum each category**	**0-8**

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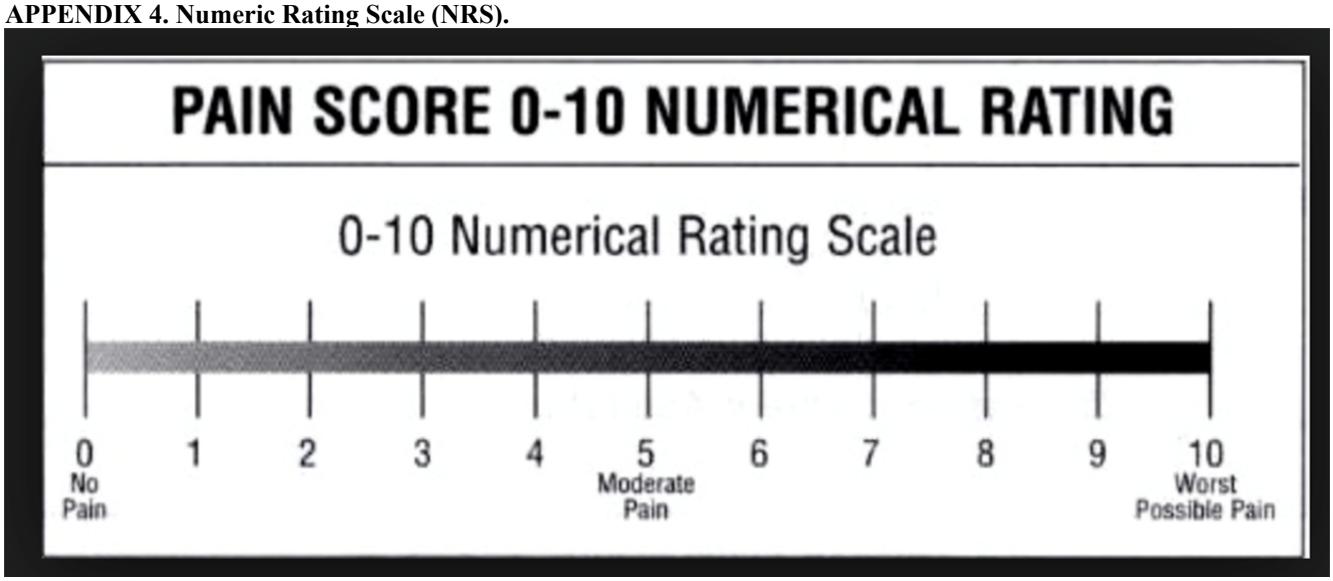
APPENDIX 4. Numeric Rating Scale (NRS).



APPENDIX 5. Behavioral Pain Scale (BPS).

Behavioral Pain Scale (BPS)

Item	Description	Score
Facial expression	Relaxed	1
	Partially tightened (e.g., brow lowering)	2
	Fully tightened (e.g., eyelid closing)	3
	Grimacing	4
Upper limb movements	No movement	1
	Partially bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
Compliance with mechanical ventilation	Tolerating movement	1
	Coughing but tolerating ventilation for the most of time	2
	Fighting ventilator	3
	Unable to control ventilation	4

BPS score ranges from 3 (no pain) to 12 (maximum pain).

APPENDIX 6. Richmond Agitation-Sedation Score (RASS).

Richmond Agitation Sedation Scale (RASS)

Target RASS	RASS Description
+ 4	Combative, violent, danger to staff
+ 3	Pulls or removes tube(s) or catheters; aggressive
+ 2	Frequent nonpurposeful movement, fights ventilator
+ 1	Anxious, apprehensive , but not aggressive
0	Alert and calm
- 1	awakens to voice (eye opening/contact) >10 sec
- 2	light sedation, briefly awakens to voice (eye opening/contact) <10 sec
- 3	moderate sedation, movement or eye opening. No eye contact
- 4	deep sedation, no response to voice, but movement or eye opening to physical stimulation
- 5	Unarousable, no response to voice or physical stimulation