Supplementary Appendix

MIND-USA Study Exclusion Criteria

1. Rapidly resolving organ failure, indicated by planned discontinuation of mechanical ventilation, non-invasive positive pressure ventilation, or vasopressors at screening, such that inclusion criteria are no longer met.
2. Pregnancy or breastfeeding (negative pregnancy test required for female patients of childbearing potential prior to randomization).
3. Severe dementia or chronic neurologic disease/disorder rendering the patient incapable of independent living at baseline or resulting in an IQCODE ≥ 4.5.
4. Acute or subacute severe neurologic deficit expected to prevent independent living post-discharge due to cognitive deficits (e.g., stroke, intracranial hemorrhage, cranial trauma).
5. History of torsades de pointes, congenital long QT syndrome, or QTc ≥ 550 ms at screening due to uncorrectable causes.
6. Ongoing maintenance therapy with antipsychotics or lithium, with plans to continue during the ICU stay.
7. History of neuroleptic malignant syndrome, haloperidol allergy, or ziprasidone allergy.
8. Expected death within 24 hours of enrollment or lack of commitment to aggressive treatment (e.g., likely life support withdrawal within 24 hours of screening).
9. Inability to obtain informed consent due to:
    a. Attending physician refusal.
    b. Patient and/or surrogate refusal.
    c. Exceeded 72-hour period of eligibility before screening.
    d. Non-comatose patient unable to consent with no surrogate within 72 hours post-inclusion.
    e. Comatose patient unable to consent with no surrogate within 120 hours post-inclusion.
10. Blindness, deafness, or inability to speak/understand English (unless Spanish-speaking staff available at the site).
11. Incarceration, due to potential difficulties in long-term follow-up testing.
12. Current enrollment in a conflicting study or an interventional trial using delirium as a primary outcome.

ABCDE Protocol: Awakening and Breathing Coordination

The following describes the ABC protocol eligibility and progression:

Eligibility: Patients are candidates for Awakening and Breathing Coordination (ABC) if they are on mechanical ventilation.

Step 1: Spontaneous Awakening Trial (SAT) Safety Screen- pass/fail

SAT Safety Screen

- No active seizures—Currently receiving medications for active seizures?
- No alcohol withdrawal—Currently receiving medications for alcohol withdraw?
- No agitation—Currently agitated (RASS ≥ +2)?
- No paralytics—Currently on a paralytic infusion?
- No myocardial ischemia—Any documentation of myocardial ischemia in the last 24 hours?
- Normal ICP—Is there evidence of elevated intracranial pressure (ICP >20)?
- Patient off the unit (effort should be made to attempt screen when patient returns to unit)
- Other (explain)

If patient fails SAT safety screening → If a patient does not pass the safety screen then the protocol is stopped – it is not considered safe to turn off the sedatives. No further action is needed. Try again in 24 hours; bedside staff can reassess safety criteria before 24 hours if the patient's condition has changed and bedside staff or clinical team think the patient would pass the safety screen.

If patient passes SAT safety screening → Perform SAT (Step 2)

Step 2: Perform SAT. SAT is defined as discontinuation of all sedatives and analgesics being given for sedation; administration of medications being used for the purpose of analgesia should continue.
If patient fails SAT → restart sedatives, at ó dose and titrate as needed.

SAT failure criteria include:

- Sustained anxiety or agitation
- Respiratory rate >35 for 5 minutes
- SpO2 <88% for 5 minutes
- Respiratory distress
- Acute cardiac dysrhythmia

If patient passes SAT → when a patient exhibits either of the pass criteria below and no failure criteria he/she is advanced to Step 3 SBT Safety Screen.

SAT pass criteria include:

- Open eyes to voice (RASS ≥ -3) and tolerating sedative cessation
- Comatose and tolerating sedative cessation for >4 hours

Step 3: Spontaneous Breathing Trial (SBT) Safety Screen- pass/fail

SBT Safety Screen

- No agitation—Currently agitated (RASS ≥ +2)?
- Is the oxygen saturation > 88%?
- Is the FiO2 < 50%?
- Is the PEEP < 7.5 cm H2O?
- No myocardial ischemia— Any documentation of myocardial ischemia in the last 24 hours?
- Vasopressor use—Significant use of vasopressors? This includes:
    - dopamine or dobutamine infusion >5 mcg
    - norepinephrine or epinephrine infusion >2 mcg
    - vasopressin or milrinone at any dose
- Patient off the unit (effort should be made to attempt screen when patient returns to unit)
- Other (explain)

If patient fails SBT safety screen → Try again in 24 hours; bedside staff can reassess safety criteria before 24 hours if the patient remains off sedatives and his/her condition has changed and bedside staff or the clinical team think the patient would pass the safety screen.

If patient passes safety screen → Perform SBT

Step 4: Perform SBT; SBT is defined discontinuation of active ventilator support so that the patient is allowed to breathe through a T-tube circuit or the ventilator circuit with a respiratory rate set as 0 bpm, CPAP/PEEP ≤ 5 cmH2O, and pressure support of ≤ 5 cmH2O for a total of 2 hours.

If patient fails SBT → Return to ventilatory support at previous settings, failure criteria include:

SBT failure criteria include:

- Sustained respiratory rate >35
- Sustained respiratory rate <8
- Sustained SpO2 <88%
- Respiratory distress
- Mental status change
- Acute cardiac arrhythmia

If patient passes SBT→ when a patient exhibits no failure criteria for 2 hours. At this end of the 2 hours the clinical team should consider extubation.

ABCDE Protocol: Delirium Monitoring and Management

The following describes Delirium Nonpharmacologic Intervention eligibility and components:

Eligibility: Patients are candidates for Delirium Nonpharmacologic Interventions if they are RASS ≥ -3 (any movement or eye opening to voice)

Pain: Monitor and/or manage pain using an objective scale (e.g., FACES, BPS, VAS, etc.) Study staff will also inform clinical personnel (e.g. nurse or physician) if/when untreated pain is present according to study CPOT assessments which are part of the Daily Pain, Anxiety and Delirium (PAD) Assessments.

Orientation: Convey the day, date, place, and reason for hospitalization, update the whiteboards with caregiver names, request placement of a clock and calendar in room, discuss with patient current events.

Sensory: Determine need for hearing aids and/or eyeglasses. If needed, request that the surrogate provide these for the patient when appropriate

Sleep: Encourage ICU team to maintain sleep preservation techniques, including:

- noise reduction strategies (e.g. minimize noise outside the room, offer white noise or earplugs)
- normal day-night variation in illumination
- minimizing interruptions during normal sleeping hours via “time out” strategy
- maintaining ventilator synchrony
- promoting comfort and relaxation (e.g., back care, oral care, washing face/hands, and daytime bath, massage)

Mobility: early mobilization of patients in the ICU has been shown to reduce delirium duration by half. Thus, the trial’s ABCDE protocol incorporates the “E” of early mobility, which is integrally linked into the “D” of delirium management.

ABCDE Protocol: Early Exercise and Mobility

The following describes Early Exercise/Mobility eligibility and components:

Eligibility: All MIND-USA Study patients are eligible for Early Exercise and Mobility

Step 1: Exercise/Mobility Safety Screen (Patients must pass this safety screen in order to get therapy)

M – Myocardial stability
- No evidence of active myocardial ischemia (24 hrs)
- No arrhythmia requiring the administration of a new antiarrhythmic agent (24hrs)

O – Oxygenation adequate on
- FIO2 <0.6
- PEEP <10 cm H2O

V – Vasopressor(s) minimal
- No increase dose of any vasopressor infusion for at least 2 hours

E – Engages to voice
- Patient responds to verbal stimulation (i.e., RASS > -3); range of motion may be performed in comatose patients, but will not be considered Early Exercise/Mobility by study standards

If the patient fails the Exercise/Mobility safety screen $\rightarrow$ If a patient does not meet all of the criteria above then he/she fails the safety screen and should not have the Exercise/Mobility protocol performed. In essence the patient is to critically ill to tolerate exercise and/or movement.

If the patient passes the Exercise/Mobility safety screen $\rightarrow$ If a patient meets all of the safety criteria then he/she may move to Step 2: Exercise/Mobility Therapy

Step 2: Exercise/Mobility Therapy
Once patients pass the safety screen they may progress to have therapy performed. Therapy should be started at Level 1 (see listing below) and progress as the patient tolerates to Level 4; however, completion of any activity listed below is considered compliant with Exercise/Mobility Therapy. All events can be performed with assistance. The activities can be performed by bedside staff, including but not limited to the RN, PT, and OT as well as family members and patients themselves.

Levels of Therapy
- Level 1: Active ROM exercises in bed and/or sitting position in bed; this includes bed adjustment,
  passive transfer, or with lift assistance
- Level 2: Dangling
- Level 3: Transfer to chair (active), includes standing without marching in place
- Level 4: Ambulation (marching in place, walking in room/hall)

Bedside Checklist for ABCDE Protocol

DATE:_____/_____/_____

Awakening and Breathing Coordination

ABC

	Check if yes
SAT done?	
SBT done?	
SAT & SBT paired?	

Delirium Nonpharmacologic Interventions

D

Intervention	Check if done
Pain assessment/management	
Orientation	
Sensory (eyes/ears)	
Sleep (nonpharm)	
Check any intervention that was performed during your shift (including night shift).	

Early Exercise and Mobility

E

Intervention	Check if done
Active ROM & Sitting Position	
Dangle	
Transfer to chair (active), Standing	
Marching in place, Walking	
Check any level of activity the patient performed during your shift (including night shift).	

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Outcome Measure Descriptions

The TICS[1] is an 11-item measures assessing orientation, attention, language, and memory domains. Scores range from 0-41, with scores <31 indicating cognitive impairment. The TICS correlates strongly with the Mini-Mental State Examination and is validated for telephone administration in post-ICU populations. The Katz ADL[2] is a 6-item assessment of the ability to independently perform basic ADLs (e.g., bathing, dressing, toileting). Items are scored from 0 (independent) to 2 (dependent) with summary scores ranging from 0-12 where higher scores indicate greater disability. The FAQ[3] is a 10-item assessment that measures the ability to perform instrumental ADLs (e.g., meal preparation, finance management). Items are scored as 0 (independent) to 3 (dependent) with summary scores ranging from 0-30 where higher scores indicate greater disability. The PCL-C[4] is a 17-item measure of symptoms of post-traumatic stress disorder (i.e., intrusive, avoidance, hyperarousal) in the past month, with the ICU hospitalization and any medical/surgical events occurring at that time as the referent traumatic event. Items are scored from 1 (not at all) to 5 (extremely) with summary scores ranging from 17-85 where higher scores indicate more severe symptoms. The EQ-5D[5] measures health status across 5 domains with items scored on 3 levels of severity ranging from no problems, some problems, to extreme problems. Scores range from 0 to 1.0, with higher scores indicating better health-related quality of life.

Supplement Table 1. Aggregated long-term outcome scores at 3 and 12 months

	3-month (n=304)	**12-month** (n=251)
Cognitive Endpoint		
Telephone Interview for Cognitive Status (TICS) T-score*	39 [30-51] (n=259)	42 [30-51] (n=222)
Functional, Psychological, and Quality of Life Endpoints		
Katz Activities of Daily Living (ADL)	1 [0-4] (n=298)	0 [0-2] (n=249)
Functional Activities Questionnaire (FAQ)	5 [1-13] (n=297)	3.5 [0-9.3] (n=248)
Post-Traumatic Stress Disorder Checklist (PCL-C)	26 [22-37] (n=243)	27 [21-37] (n=211)
EuroQol-5D (EQ-5D) Quality of Life Index	0.7 [0.4-0.8] (n=258)	0.8 [0.5-0.8] (n=221)

*Scores are age-adjusted. Data are median [interquartile range]. Sample sizes differ by measure and timepoint and are thus not reported here.

Scoring Interpretation:

- Telephone Interview for Cognitive Status (TICS) T-Score: Normalized mean of 50 with standard deviation of 10 points. Lower scores indicate worse cognition. Scores of 35 or lower are consistent with impaired cognitive function.
- Katz Activities of Daily Living (ADL): Scores ranges from 0 to 12 with higher scores indicating worse disability in basic activities of daily living.
- Functional Activities Questionnaire (FAQ): Scores range from 0 to 30 with higher scores indicating worse disability in instrumental activities of daily living.
- Post-Traumatic Stress Disorder Checklist (PCL-C) -Civilian Score: Scores range from 17 to 85 with higher scores indicating worse PTSD symptoms.
- EuroQol-5D (EQ-5D) Quality of Life Index: Scores range from 0.0 to 1.0 with higher scores indicating better quality of life.

Supplement References

1. Brandt J, Spencer M, Folstein M. The telephone interview for cognitive status. *Neuropsychiatry Neuropsychol Behav Neurol*. 1988;1(2):111-117.

2. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of Illness in the Aged. The Index of Adl: A Standardized Measure of Biological and Psychosocial Function. *JAMA*. Sep 21 1963;185:914-9.

3. Pfeffer RI, Kurosaki TT, Harrah CH, Jr., Chance JM, Filos S. Measurement of functional activities in older adults in the community. *J Gerontol*. May 1982;37(3):323-9. doi:10.1093/geronj/37.3.323

4. Andrykowski MA, Cordova MJ, Studts JL, Miller TW. Posttraumatic stress disorder after treatment for breast cancer: Prevalence of diagnosis and use of the PTSD Checklist—Civilian Version (PCL—C) as a screening instrument. *Journal of consulting and clinical psychology*. 1998;66(3):586.

5. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med*. Jul 2001;33(5):337-43. doi:10.3109/07853890109002087