Brain Oxygen Optimization in Severe TBI Phase 3 Protocol Training

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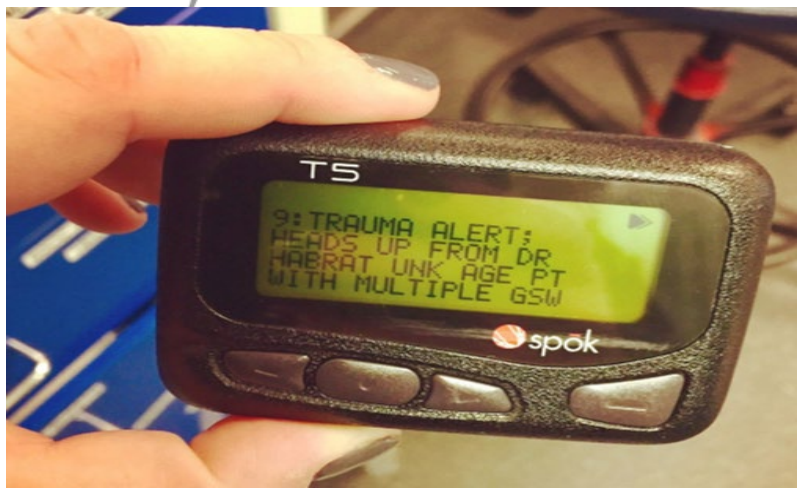
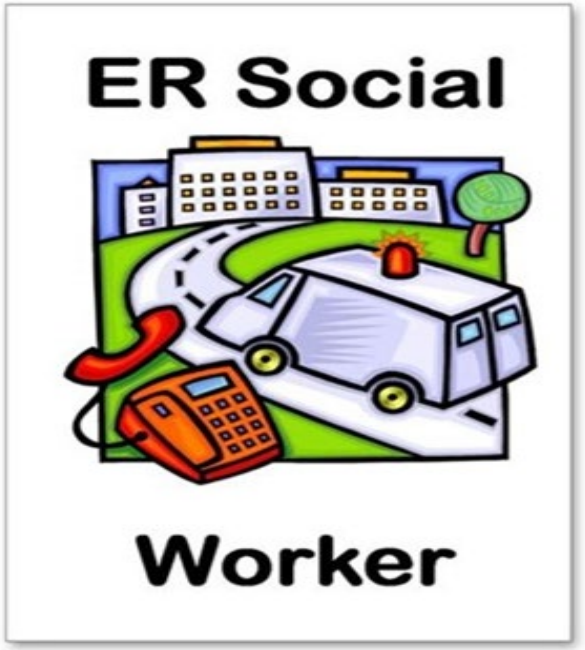
Subject Identification: Helpful Hints for Screening





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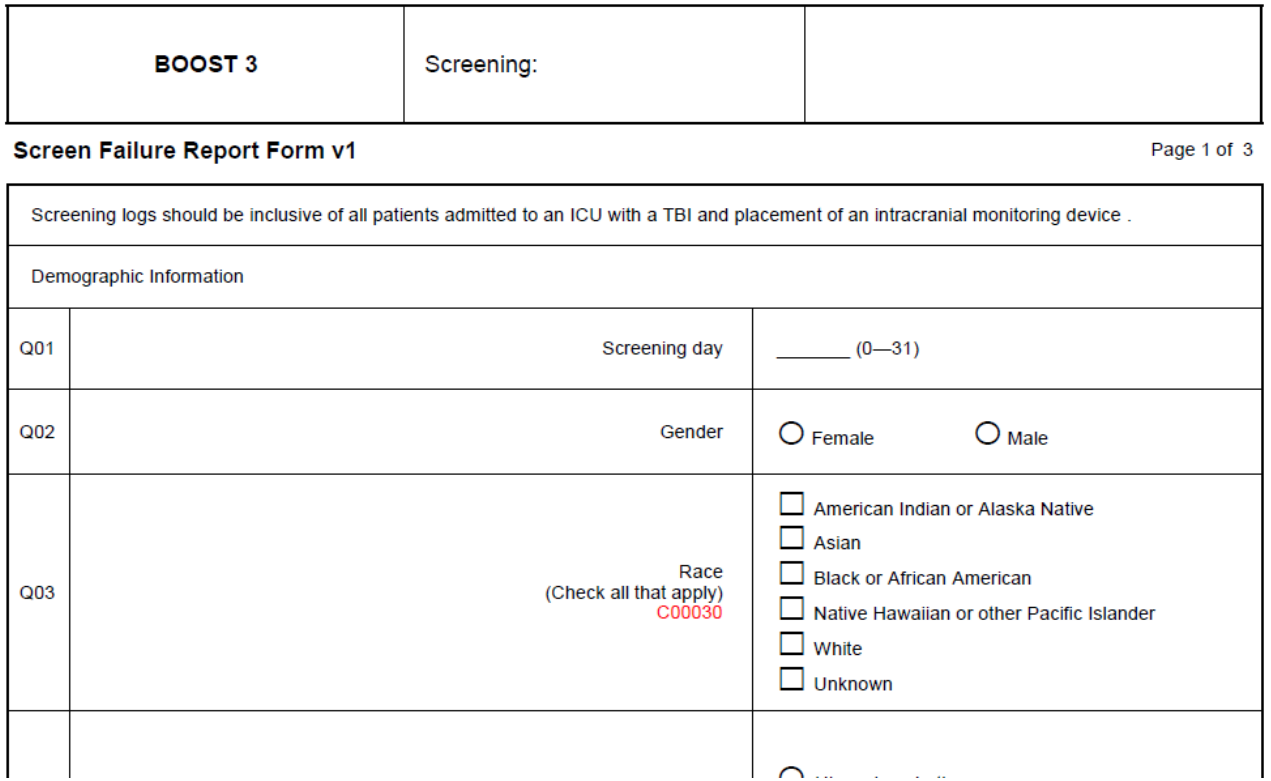
Screening for Enrollment

- A screening log should be maintained by each site
- All patients with the following should be included:
  - Admission to ICU
  - Positive TBI (CT scan)
  - Placement of intracranial monitoring



BOOST 3	Screening:	

Screen Failure Report Form v1 Page 1 of 3

Screening logs should be inclusive of all patients admitted to an ICU with a TBI and placement of an intracranial monitoring device .

Demographic Information

Q01	Screening day	_____ (0—31)
Q02	Gender	○ Female ○ Male
Q03	Race (Check all that apply) C00030	☐ American Indian or Alaska Native ☐ Asian ☐ Black or African American ☐ Native Hawaiian or other Pacific Islander ☐ White ☐ Unknown

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The Informed Consent Process

Establish line of sanguinity for next-of-kin:

1. **Spouse**
2. **Adult child** (age ≥18 years)
3. **Parent**
4. **Adult sibling** (age ≥18 years)
5. **Grandparent**
6. **Adult grandchild** (age ≥18 years)

- **Find an appropriate environment**
- **Ensure that LAR is updated on subjects condition and plan of care**
- **Explain purpose of trial**
- **Review consent form in detail**
- **Make sure all questions are addressed**

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EFIC Process:
Begins Upon Arrival of Potentially Eligible Subject

Determine availability of LAR

Document efforts on the informed consent log case report form

If an LAR is not available prior to the placement of intracranial monitors, eligible subjects will be enrolled with EFIC after intracranial monitors are placed.

When a subject is enrolled under EFIC, efforts to contact an LAR will continue.

LAR will be notified of an EFIC enrollment and consent to continue in the study will be sought at the earliest opportunity.

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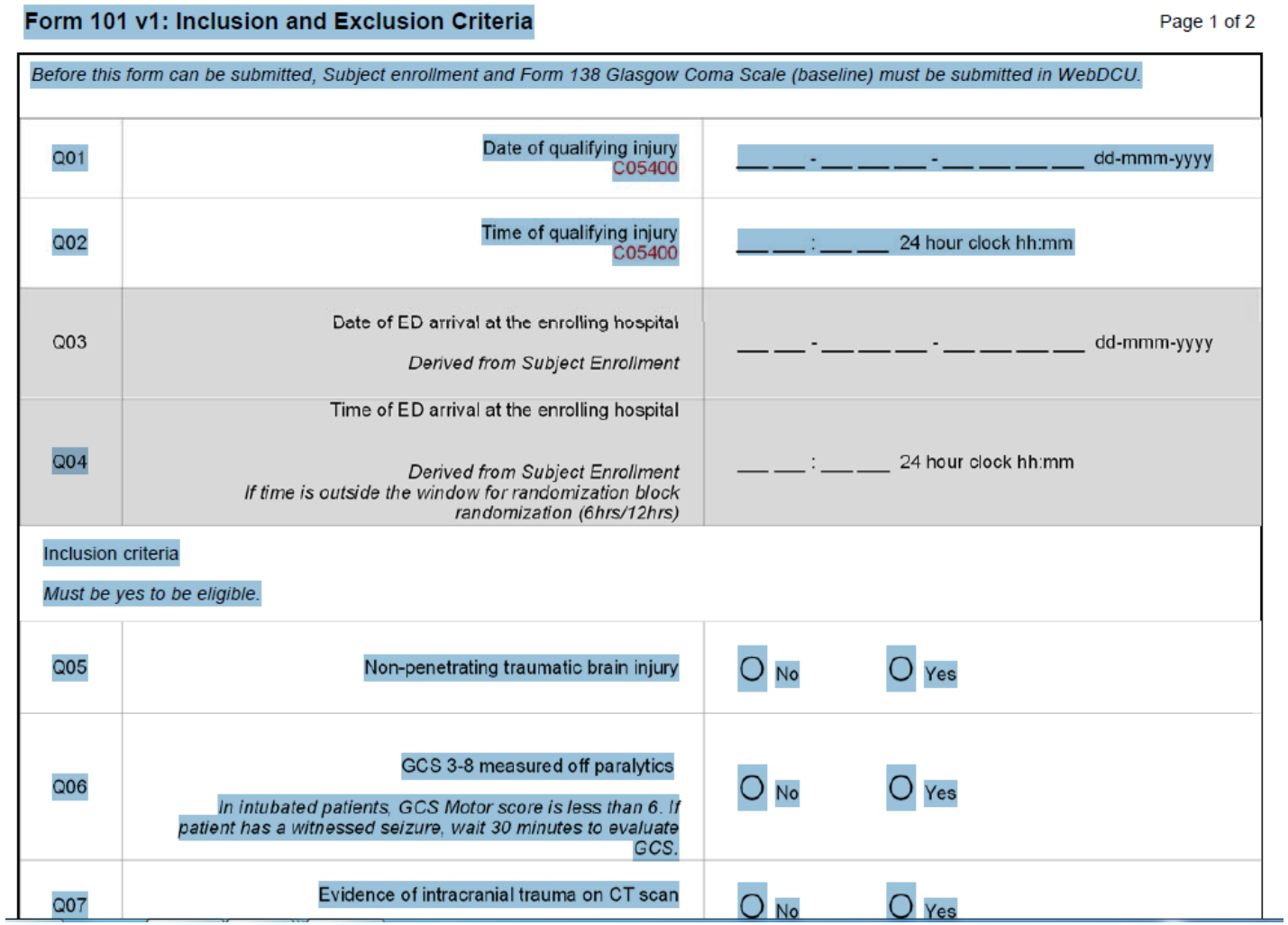
Randomization Procedure: CRFs to complete



Form 101 v1: Inclusion and Exclusion Criteria Page 1 of 2

Before this form can be submitted, Subject enrollment and Form 138 Glasgow Coma Scale (baseline) must be submitted in WebDCU.

Q01	Date of qualifying injury C05400	___ ___ - ___ ___ ___ - ___ ___ ___ ___ dd-mmm-yyyy
Q02	Time of qualifying injury C05400	___ ___ : ___ ___ 24 hour clock hh:mm
Q03	Date of ED arrival at the enrolling hospital *Derived from Subject Enrollment*	___ ___ - ___ ___ ___ - ___ ___ ___ ___ dd-mmm-yyyy
Q04	Time of ED arrival at the enrolling hospital *Derived from Subject Enrollment* *If time is outside the window for randomization block randomization (6hrs/12hrs)*	___ ___ : ___ ___ 24 hour clock hh:mm
Inclusion criteria *Must be yes to be eligible.*		
Q05	Non-penetrating traumatic brain injury	○ No ○ Yes
Q06	GCS 3-8 measured off paralytics *In intubated patients, GCS Motor score is less than 6. If patient has a witnessed seizure, wait 30 minutes to evaluate GCS.*	○ No ○ Yes
Q07	Evidence of intracranial trauma on CT scan	○ No ○ Yes

- CRFs to be completed prior to randomization:
  - Inclusion/Exclusion Criteria checklist
  - Randomization form
    - use GCS (in the absence of sedation/paralytics) that was performed closest to randomization
- Check Opt-out registry and document

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Randomization Procedure

- To receive a treatment assignment, site personnel will enter participant and covariate information into WebDCU™, the electronic Clinical Trial Management System run by the SIREN Data Coordinating Center (DCC) at the Medical University of South Carolina.

  https://webdcu.musc.edu/login.asp

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Case Study: **17** yo male s/p ATV accident on **6/27/19 at approximately 21:00**. GCS 3 at the scene, pupils 2mm and reactive. **Seizure activity** noted en route to OSH. Initial CT scan performed at OSH revealed a right EDH with midline shift; pupil exam changed from 2mm and reactive bilaterally to right pupil 7mm and nonreactive. Taken emergently to OR for **right decompressive craniectomy**. He **arrives at study hospital on 6/28/19 at 8:45am**, GCS 7T, pupils 4mm and reactive bilaterally. **ICP and $PbtO_2$ monitors were placed at 10:00.**

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Does this patient meet criteria for enrollment in BOOST-3?

A. Yes

B. No

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Why does this patient NOT meet eligibility criteria?

A. Age less than 18
B. Monitors were not placed within eligible time frame
C. Patient exhibited seizure activity at the scene
D. Patient underwent a right decompressive craniectomy, and the PbtO2 monitor must be placed in the right frontal lobe.

Case Study: 31 yo female s/p unhelmeted MCC on **5/31/19** at approximately **22:00**. Arrived to study hospital at 23:36 on 5/31.

Injuries: Diffuse SAH, IPH, left occipital bone fx, left post 9th rib fx, lung contusion, retroperitoneal hematoma.

Per chart review, the patient has no significant PMH, takes daily multivitamin, and has no known allergies. A loading dose of Phenytoin is started in the Trauma bay and an order for routine dosing for the next 7 days is placed.

Vitals: Stable en route. In Trauma Bay, **BP 130/96, HR 102, RR 14, SPO2 95%**

Neuro exam: Patient localizes RUE/withdraws LUE to painful stimuli, no eye opening, intubated—**GCS 7T**; **right pupil 3mm and sluggish, left pupil 5mm and reactive.**

The patient is transported to the ICU on 6/1/19, with the plan to place ICP and PbtO2 monitors. At this time, the patient's LAR (mother) has not been able to be notified of the patient's condition. No other emergency contacts have been identified.

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Based solely on the information provided, does this patient meet criteria for **enrollment and randomization** into BOOST3?

A. Yes
B. No
C. Need more information

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What further tests need to be performed before enrollment to confirm eligibility?

A. Repeat CT scan to confirm that intracranial monitors to confirm correct placement
B. Calculate PaO2/FiO2 ratio
C. Urine or serum pregnancy test
D. Check EFIC opt out registry
E. B, C, D
F. C, D
G. All of the above

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Withdrawal From Participation

- Reason for wishing to withdraw must be determined
- Study interventions and further data collection may be discontinued
- After withdrawal, the participant's care should revert to standard care at the enrolling site.
- Participant data collected prior to withdrawal from the study is maintained in the study database, but no additional participant data will be collected from the participant or medical record following study withdrawal.

Intracranial Monitors

- The type of monitors used at each site will be documented at time of site initiation.
  - Changes in equipment used will require notification to the monitoring team.
- An ICP and $PbtO_2$ monitor are required for every participant.
- Information from any neuro-monitoring device used must be collected as part of the study protocol.

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Considerations Related to Neuromonitoring

- **Neuromonitoring devices that are NOT acceptable include:**
  - NIRS
  - BIS (except in the OR)
  - Jugular bulb saturation monitors
  - Cerebral blood flow monitors
  - Routine transcranial doppler

- **Acceptable devices:**
  - EEG
  - Microdialysis
  - ECoG
  - Brain temperature
  - Cerebral autoregulation

These devices can provide indirect information regarding brain tissue oxygenation.

NOTE: The occasional use of TCDs to assess for vasospasm is allowed. If performed, this information should be collected

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Intracranial Monitors: Placement and Timing

- ICP and $PbtO_2$ monitors will be placed at the same time per local placement practices.
- The monitors should be placed as soon as possible after injury, *and need to be placed* ***within 12 hours after injury and within 6 hours of arrival at the enrolling hospital***.
- A non contrast head CT will be done on all patients as part of their initial evaluation. Another non contrast head CT should be obtained within 24 hours after placement of the ICP and $PbtO_2$ monitors to confirm location/assess for monitor placement.

Intracranial Monitors

- Continuous ICP monitoring is required. This can be done by either a parenchymal monitor or external ventricular drain (EVD).
  - If an EVD is placed, it is to be zeroed at the tragus.
  - An EVD may be used as the ICP monitor as long as continuous ICP measurements can be recorded. Whenever the EVD is open to drain, a method must be available to allow for continuous ICP measurements.
  - CSF drainage via the EVD can be either continuous or intermittent.

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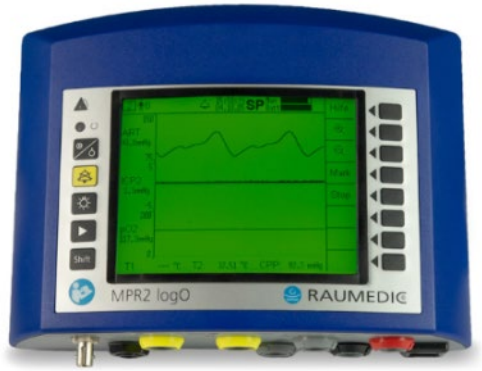
Intracranial Monitors: $PbtO_2$ placement

- The $PbtO_2$ probe will be introduced through either a burr hole in the skull via a bolt or via tunneling under the scalp using equipment per local institutional practices.
  - The goal is to place the $PbtO_2$ probe in a position **remote from any known or visible contusion.**
    - The $PbtO_2$ probe will generally be inserted into the **right frontal lobe**, unless there is a contraindication (ie craniotomy flap, compound depressed skull fracture, underlying contusion or intracerebral hematoma). In these cases, the probe will be inserted into the left frontal area.
- Function and reliability of the $PbtO_2$ probe will be assessed.



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Procedures To Check Reliability of $PbtO_2$ Measurements

Prior to Insertion

- Calibration of device will be checked according to manufacturer's instructions

FIO2 Challenge

- Each participant will have an FiO_2 challenge within 2 hours after catheter placement
  - Recorded measurements will be initiated 60 minutes after placement of monitor
  - Treatment staff will be blinded to results in control arm

Repeated Challenges

- FiO_2 Challenge will be repeated daily until probe is removed.
- Study staff may request a challenge at any time if they suspect the $PbtO_2$ probe is not working.

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Checking Reliability of $PbtO_2$ Data: FiO_2 Challenge

Only the research team will be able to see the results of the challenge in the blinded ICP-only group.

How to perform the challenge

1. Increase FiO_2 to 100% for 20 minutes or until $PbtO_2$ increases by 5 mm Hg, whichever occurs first.
   - *If the $PbtO_2$ increases, you have confirmed accuracy of the $PbtO_2$ readings.*
   - *If the FiO_2 challenge fails, repeat the challenge in about 1 hour.*
   - *If the challenge fails again, further management will be determined by patient group.*
2. Document time and results of the challenge

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Checking Reliability of $PbtO_2$ Data: FiO_2 Challenge

If the FiO_2 challenge fails a second time, management is based on patient group:

- In the ICP + $PbtO_2$ treatment group, the PI is notified and a head CT should be obtained to assess position of $PbtO_2$ probe, contusion expansion, or other potential causes for inaccurate $PbtO_2$ measurements.
  - *In the event of a non-functioning or mal-positioned probe, or contusion expansion that results in the inability to obtain $PbtO_2$ values, a new $PbtO_2$ probe should be placed within 2 hours if at all possible.*
- In the ICP only group, the study team will document that the $PbtO_2$ probe is unreliable.
  - *The medical staff and PI will not be notified that the probe is not functioning.*
  - *The $PbtO_2$ probe will not be replaced but it should be checked daily by the study team in the event that it begins to record data again. It should remain in place until the removal criteria has been met.*

Checking Reliability of $PbtO_2$ Data: FiO_2 Challenge

Documentation

- Measurements to be obtained at both the start and completion of the required daily FiO_2 challenge include:
  - Time of the challenge, whether the $PbtO_2$ showed an appropriate response, the ICP, FiO_2, SaO_2, and an ABG for PaO_2 and pH.
  - This information will be recorded in the CRF.
- In the event of additional FiO_2 challenges performed by the clinical team, measurements to be recorded at both the start and completion of the challenge include:
  - Time of the challenge, whether the $PbtO_2$ showed an appropriate response, the ICP, FiO_2, and SaO_2. ABG data is optional for FiO_2 challenges performed by the treating physician.

Checking Reliability of $PbtO_2$ Data: FiO_2 Challenge

Notes:

- No other active changes in care should be done during the challenge, including but not limited to adjustments in sedation, analgesia, EVD drainage or other physiological parameters in order to avoid confounding the response to the FiO_2 challenge.
- At completion of any FiO_2 challenge the FiO_2 should be weaned back to the baseline level.
- Study staff may request FiO_2 challenge at any time if they suspect the $PbtO_2$ probe is not working.
- For participants in the ICP + $PbtO_2$ treatment group, the clinical team may perform a FiO_2 challenge at any time they feel it is indicated based on the clinical situation and local protocol.

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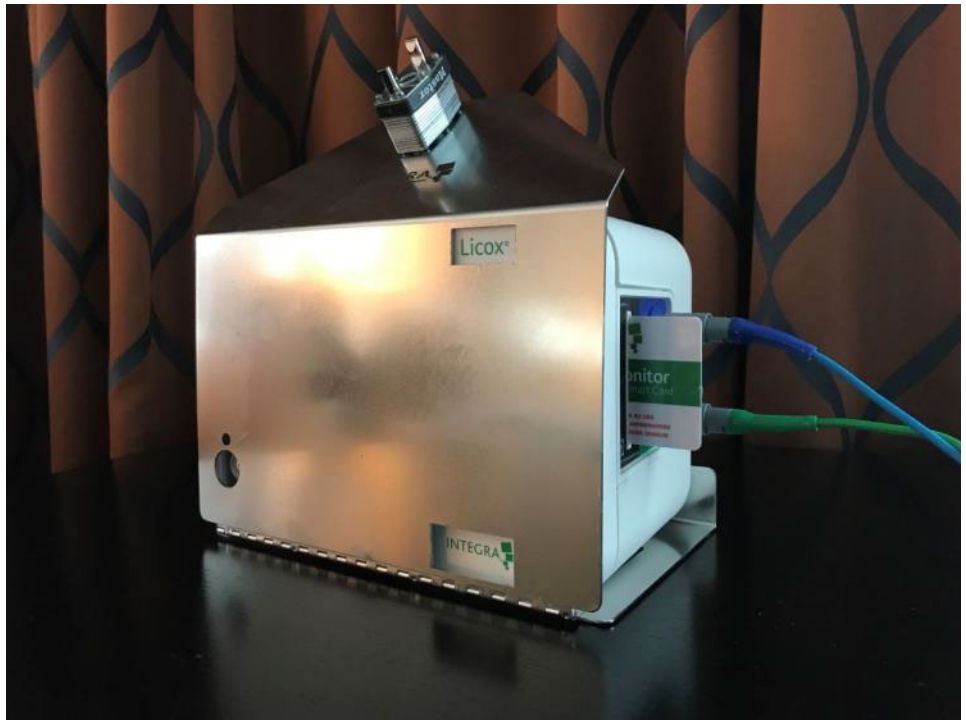
Handling of Study Interventions: Blinding

- $PbtO_2$ Monitors will be masked for subjects randomized into the Control Group

- **6 Month Outcomes Assessor must be blinded to randomization assignment**



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After confirming that the patient meets eligibility criteria, the study coordinator has been notified that the neurosurgeon has just completed placement of a ventriculostomy drain (EVD) and is currently placing a PbtO2 monitor. **What should the study coordinator remind the clinical team regarding placement of intracranial monitors or neuromonitoring?**

A. If the treating physician plans to leave the EVD open continuously, an intraparenchymal ICP monitor must be placed to allow for continuous ICP measurement.

B. Brain tissue oxygen values must not be treated prior to randomization.

C. Other neuromonitoring devices, such as a cerebral blood flow monitor, Jugular bulb saturation, NIRS, BIS or routine TCD cannot be used in a patient enrolled into BOOST3.

D. All of the above.

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The patient is randomized to the ICP + PbtO2 treatment group. An FiO2 challenge is performed to check functionality of the PbtO2 probe. The patient's inhaled oxygen is placed at 100% FiO2 via ventilator.

Initial PbtO2 value: 11mmHg
PbtO2 value after 20 minutes: 15mmHg

Does this suggest that the PbtO2 probe is properly functioning?

A. Yes
B. No

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The patient is randomized to the ICP + PbtO2 treatment group. An FiO2 challenge is performed to check functionality of the PbtO2 probe. The patient's inhaled oxygen is placed at 100% FiO2 via ventilator.

Initial PbtO2 value: 11mmHg
PbtO2 value after 20 minutes: 15mmHg

What is the next step in confirming functionality of the PbtO2 probe?

A. The PbtO2 probe should be replaced immediately in order to prevent delay of treatment of potentially low PbtO2 values

B. A head CT should be obtained to assess for the PbtO2 probe malpositioning, contusion expansion, or other potential causes for innacurate PbtO2 measurements.

C. The study or clinical team is required to immediately perform a MAP or CO2 challenge.

D. A repeat FiO2 challenge should be done within 1 hour of initial FiO2 challenge.

Recording of ICP and $PbtO_2$

- Continuous tracings of both ICP and $PbtO_2$ values will be recorded at the bedside using the Moberg CNS Monitor
  - This device will be calibrated and checked for proper functioning by both nursing and research staff.
  - These recordings have real time resolution.
  - The precise equipment and software used for the continuous recordings will be developed for each Clinical Site according to local needs and available equipment.
- These continuous records will become a source document for this study.
- The monitors and Moberg CNS system will both be outfitted with alarms that advise the ICU nursing staff whenever ICP rises above 22 mmHg or $PbtO_2$ falls below 20 mmHg.
  - The $PbtO_2$ alarms will be silenced for the ICP only group.

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Removal or Replacement of Probes

- In general, ICP and $PbtO_2$ probes will be removed by Day 5
  - Continued monitoring is allowed if clinically indicated.
  - Replacement of a $PbtO_2$ probe will only be considered in the ICP + $PbtO_2$ group.
- Probes may be removed before 5 days in the following situations:
  A. The participant awakens from coma (motor GCS score = 6).
  B. There is a medical indication for removal (ie, infection; associated bleeding).
  C. No abnormalities of ICP for 72 hours after injury in the ICP only arm
  D. No abnormalities of ICP or $PbtO_2$ are noted for 72 hours after injury in the ICP + $PbtO_2$ arm
  E. Withdrawal of care
- If a probe is removed, the reason will be documented in the CRF
  - An 'intent to treat analysis' will be used.

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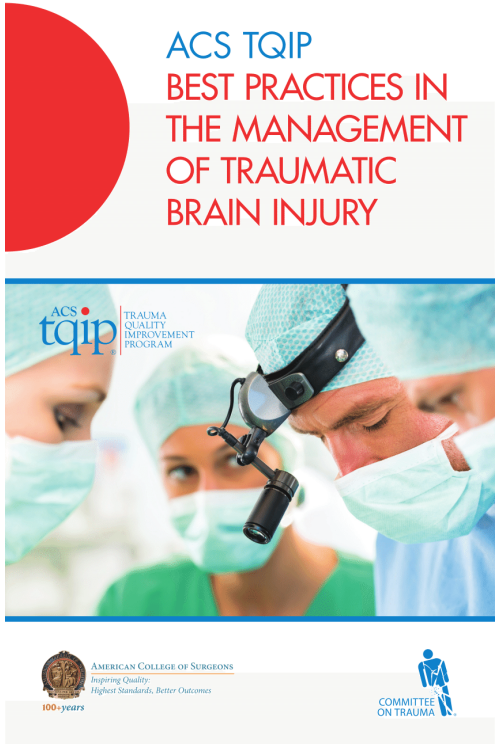
Clinical Standardization Guidelines

- Goal directed management of physiologic parameters will be in accordance with recommended treatment guidelines published by the Brain Trauma Foundation and the American College of Surgeons
- Clinical management of these parameters
  - Should be based on local protocols
  - Will be tracked on the daily CRFs

Brain Trauma FOUNDATION



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Clinical Standardization Guidelines

- We purposely have limited “rules” regarding clinical management. Topics for which we provide guidance are:
  - Hemodynamic Issues
  - Temperature management
  - Respiratory issues
  - Hematologic issues
  - Seizure prevention / Management
  - Withdrawal of care / Brain Death
- These will be presented tomorrow

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Withdrawal of Care / Brain Death

- The intent of the study is to **optimize therapy for 5 days after randomization**. Withdrawal of care during the first 5 days may be considered in dire circumstances or if requested by the patient's family.
  - **The site PI will call the study hotline to update the study leadership team about withdrawal of care for a subject.**
- Withdrawal of care will be documented on the End of Study form, and at the bedside on the Moberg monitoring device.
- Should the patient progress to brain death, determination is per local protocol. Participation in the clinical trial will not preclude a patient from consideration as an organ donor.

Assessing Patient Physiology: MAP Challenge

A MAP challenge is done at the discretion of the treating physician to assist in assessment of cerebral autoregulation. This can guide both MAP and CPP goals in individual patients.

How to perform the challenge

1. Initiate or titrate a vasopressor to increase MAP by 10 mm Hg for approximately 20 mins or until the PbtO2 has increased by 5 mm Hg, whichever occurs first.
2. Measurements to be obtained at both the start and completion of any MAP challenge include:
   - Time of the challenge, whether the PbtO2 showed an appropriate response, the ICP, MAP and CPP.
   - This information will be recorded in WebDCU

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Assessing Patient Physiology: MAP Challenge

Notes:

- No other active changes in care should be done during the MAP challenge, including but not limited to adjustments in sedation, analgesia, EVD drainage or other physiological parameters in order to avoid confounding the response to the MAP challenge.
- At completion of the MAP challenge the vasopressor should be either returned to the baseline infusion rate or discontinued if it had been initiated specifically for the challenge.

Assessing Patient Physiology: CO_2 Challenge

A CO2 challenge may be done by the treating physician to assist in assessment of cerebral CO2 vasoreactivity to guide ventilator adjustments and may indirectly provide input regarding potential hyperemia. This challenge can use either hyperventilation or hypoventilation based on the patient's individual clinical situation.

How to perform the challenge

1. Adjust the respiratory rate by 25% and then in increments of 2 breaths/min with the goal of changing PaCO2 by up to 10 mm Hg (either increase or decrease).
2. The duration of this challenge is approximately 20 mins or until the PbtO2 has increased or decreased by 5 mm Hg, whichever occurs first.
3. End-tidal CO2 and PbtO2 are monitored continuously to follow the response to ventilatory changes and the effect on PbtO2, and the challenge should be terminated if PbtO2 approaches 15 mm Hg or decreases by greater than 50% of the value attained during a FiO2 challenge.

Assessing Patient Physiology: CO_2 Challenge

Documentation

- Measurements to be obtained at both the start and completion of any CO2 challenge include:
  - Time of the challenge, whether the PbtO2 showed an appropriate response, the ICP, end tidal CO2, and an ABG for PaCO2, and pH.
  - This information will be recorded in the WebDCU.

Notes:

- No other active changes in care should be done during the challenge, including but not limited to adjustments in sedation, analgesia, EVD drainage or other physiological parameters in order to avoid confounding the response to the CO2 change.
- At completion of the CO2 challenge the respiratory rate should be returned to the baseline rate.

Management of elevated ICP and/or low PbtO2

Types of events		ICP < 22 mm Hg	ICP ≥ 22 mm Hg
$PbtO_2 \geq 20$		**Type A** **No interventions directed at $PbtO_2$ or ICP needed**	**Type B** **Interventions directed at lowering ICP**
$PbtO_2 < 20$		**Type C** **Interventions directed at increasing $PbtO_2$**	**Type D** **Interventions directed at lowering ICP and increasing $PbtO_2$**

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Managing ICP and $PbtO_2$

- Tiered algorithm based approach similar to BOOST II
  - Tiers are hierarchical, with increased aggressiveness of interventions

- Guided provider determined management
  - Aimed at minimizing treatment variability across study centers while respecting local protocols and expertise
  - Decisions regarding which intervention to use within any tier should be based on and aimed at addressing the presumed underlying pathophysiology contributing to that individual episode

Scenario Based Patient Management

- Elevations in ICP > 22 mm Hg, or a decline in $PbtO_2$ < 20 mm Hg, which are sustained for more than 5 minutes will trigger an intervention.
- **Treatments must be initiated within 15 minutes of the start of the episode, as detected by the continuous ICP and $PbtO_2$ recordings.**
  - The Moberg monitor will signal the treating team in real time, when an intervention is recommended. It is expected that a treatment intervention will be initiated as soon as possible after the start of the episode**.**
- Participants may start in one type of episode and move to another.
  - Therapy will depend on which type of episode they are in at any given time.
  - For ICP only group, only Type A and Type B episodes are relevant.
  - For ICP + $PbtO_2$ group, any of the 4 scenarios (Type A, B, C, or D).

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Scenario Based Patient Management

- Therapeutic strategies are divided into tiers that are organized in a hierarchical fashion
  - Less aggressive interventions are in the lower tiers and more aggressive maneuvers in the higher tiers.
- Treatment interventions within any one tier can be attempted in any order or combination.
  - At least one treatment in Tier 1 must be tried before moving on to Tier 2.
  - It is not necessary to use all treatments in the tier, but it is expected that at least one intervention from each tier will be used before proceeding to the next tier.
  - Tier 3 treatments are optional.

Scenario Based Patient Management

- The initial choice of a treatment option from any tier should be determined based on what may be the most effective for the current clinical situation, participant characteristics and local protocols.
  - Any intervention chosen should be aimed at addressing the underlying pathophysiology that is contributing to each individual episode.

- For any treatment chosen, a rapid response to that treatment is expected.
  - Should a treatment not be effective in a timely fashion, additional interventions within the same tier may be attempted, or a decision may be made to quickly move to the next tier.

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Scenario Based Patient Management

- While there is no maximum number of treatment options that can be attempted from any one tier, **no more than 60 minutes should be spent trying interventions within any single tier prior to moving on to the next tier**.
- The bedside treatment team has the option to **progress to higher tiers as rapidly as they feel is clinically indicated**.

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Documentation of Interventions

- Treatment interventions triggered by elevations in ICP and/or decreases in $PbtO_2$ will be recorded by the ICU nurses on the Moberg or in bedside flow sheets
  - The time the abnormality was noted by nursing staff and the time the intervention started should also be recorded in the medical record, with the goal of an intervention initiation within 15 minutes of onset of the event.
- Study coordinators will transfer information about those interventions into WebDCU™.
  - Data to be collected includes information regarding the efficacy of the intervention in reversing the abnormal physiologic parameter.
  - Pertinent information from the ICU flow chart, nurses' notes, as well as the continuous record of ICP and $PbtO_2$, will be collected daily by the study coordinators.

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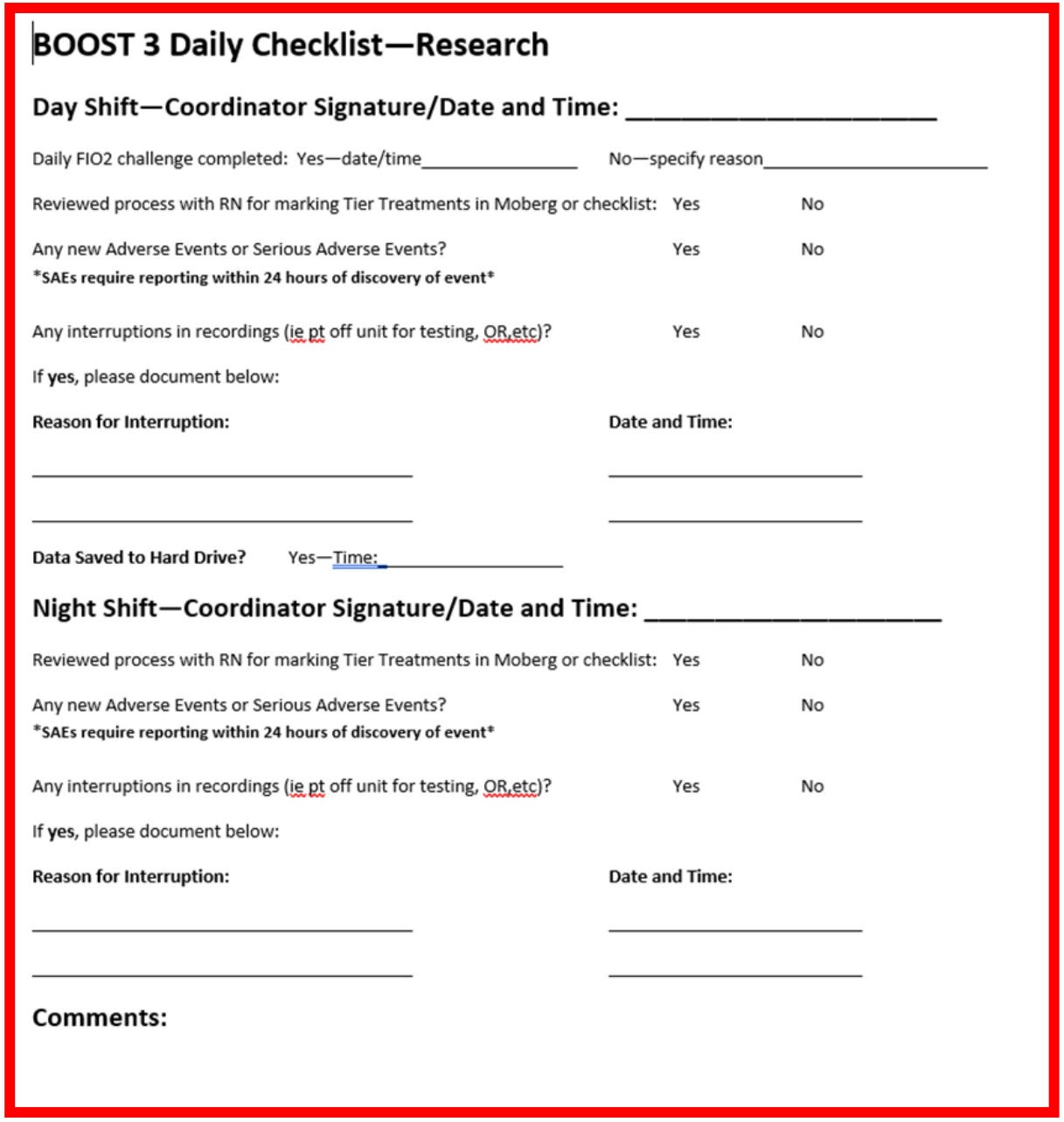
Data Capture is Essential to Study Success!

- Use of a daily checklist completed by the study coordinator at the bedside may contribute to fewer protocol deviations from delayed/missed tier interventions or missing data



BOOST 3 Daily Checklist—Research

Day Shift—Coordinator Signature/Date and Time: _____

Daily FIO2 challenge completed: Yes—date/time_____ No—specify reason_____

Reviewed process with RN for marking Tier Treatments in Moberg or checklist: Yes No

Any new Adverse Events or Serious Adverse Events? Yes No

SAEs require reporting within 24 hours of discovery of event

Any interruptions in recordings (ie pt off unit for testing, OR,etc)? Yes No

If **yes**, please document below:

Reason for Interruption: **Date and Time:**

_____ _____

_____ _____

Data Saved to Hard Drive? Yes—Time:_____

Night Shift—Coordinator Signature/Date and Time: _____

Reviewed process with RN for marking Tier Treatments in Moberg or checklist: Yes No

Any new Adverse Events or Serious Adverse Events? Yes No

SAEs require reporting within 24 hours of discovery of event

Any interruptions in recordings (ie pt off unit for testing, OR,etc)? Yes No

If **yes**, please document below:

Reason for Interruption: **Date and Time:**

_____ _____

_____ _____

Comments:

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General Caveats

- Targets of osmolality therapy with mannitol or saline:
  - Most centers use osmolality targets for mannitol treatment and Na^+ target for saline, with values checked every 6- 12 hours.
  - Target serum osmolality (Sosm) is < 320 mOsm, osmolar gap (Ogap) < 20, and serum sodium (sNa) < 160 mEq/L.

- Active weaning of any changes made to address an acute episode should be initiated once the patient is back at scenario A levels (ie, ICP and $PbtO_2$ within goal range) and the bedside provider feels the patient has stabilized.

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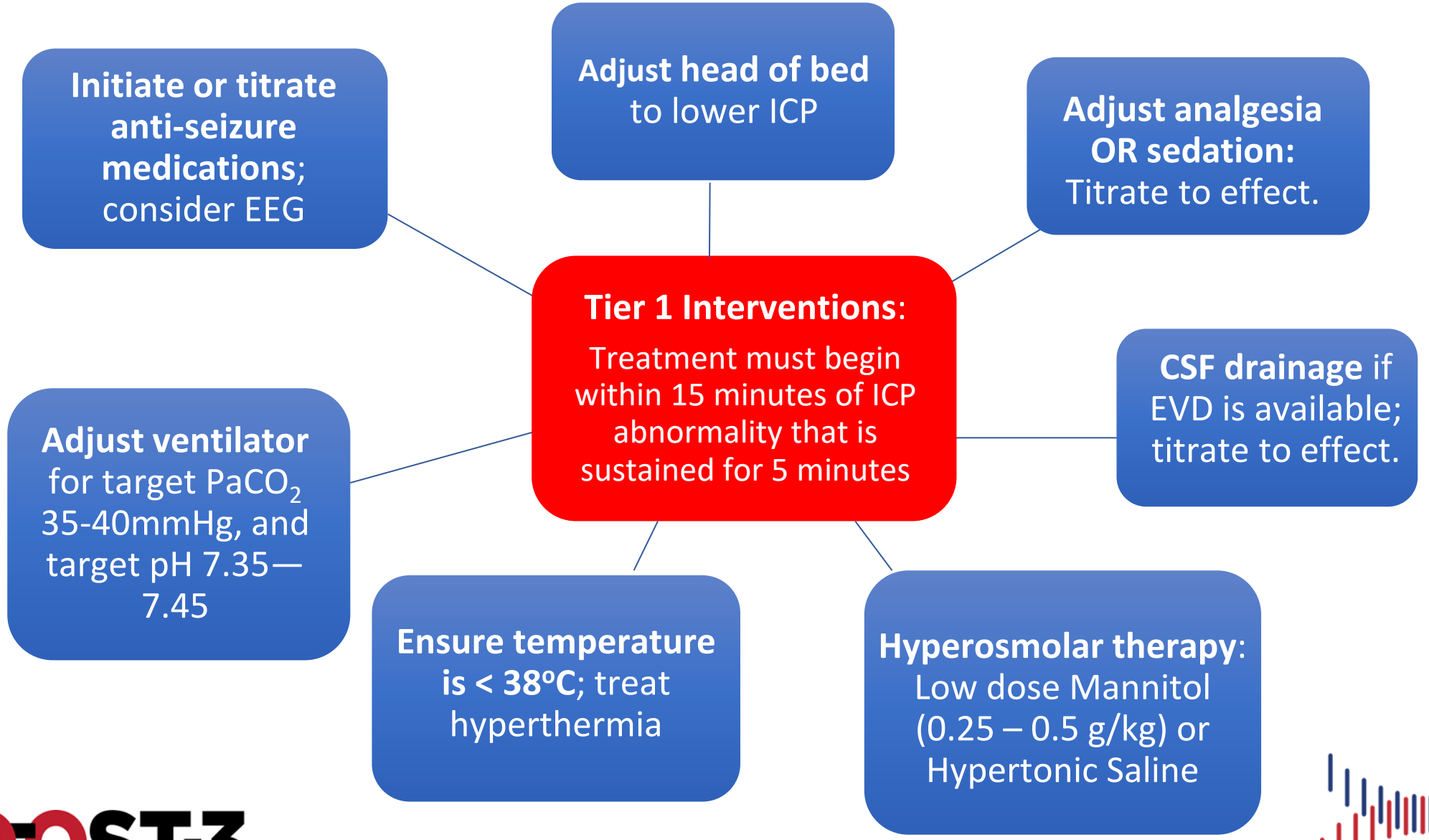
Scenario Based Patient Management

- **Type A** (ICP < 22 mm Hg; $PbtO_2$ > 20 mm Hg)
  - This is the target range and no additional therapy is needed.

Isolated ICP increase	Isolated $PbtO_2$ drop	ICP increase + $PbtO_2$ drop
TIER 1 • Adjust head of the bed to lower ICP • Ensure Temperature < 38°C. • Titrate pharmacologic analgesia or sedation • Titrate pharmacologic sedation • CSF drainage (if EVD available) • Low dose Mannitol (0.25 – 0.5 g/kg), to be administered as bolus infusion. • Hypertonic saline. Titrate to ICP control and avoid serum Na+ above 160. • Initiate or titrate anti-seizure medications (AEDs) • Adjust ventilator for a target PaCO2 of 35 - 40 mm Hg and target pH of 7.35 - 7.45	**TIER 1** • Adjust head of the bed to improve Pbt)2 • Ensure Temperature < 38°C. • Optimize CPP to a max of 70 mm Hg with fluid bolus or pressors. • Optimize hemodynamics by: 1) Treating hypovolemia; 2) Avoid hypervolemia • Adjust PaO2 by: 1) increasing FiO2 up to 60%; 2) adjusting PEEP; 3) Pulmonary toileting (suctioning) • Adjust ventilator for a target PaCO2 of 38-42 mm Hg and target pH of 7.35 - 7.45 • Initiate or titrate anti-seizure medications (AEDs)	**TIER 1** • Adjust head of the bed to lower ICP • Ensure Temperature < 38°C. • Pharmacologic analgesia and sedation • CSF drainage (if EVD available). • Increase CPP to a maximum >70 mm Hg with fluid bolus. • Low dose Mannitol, (0.25 – 0.5 mg/kg) or Hypertonic saline • Optimize hemodynamics by: 1) Treating hypovolemia; 2) Avoid hypervolemia; • Increase PaO2 by: 1) increasing FiO2 up to 60%; 2) adjusting PEEP; 3) Pulmonary toileting (suctioning) • Adjust ventilator for a target PaCO2 of 38-42 mm Hg and target pH of 7.35 - 7.45 • Initiate or titrate anti-seizure medications (AEDs).
TIER 2 • Adjust ventilatory rate for target PaCO2 of 33 – 38 mm Hg and target pH of 7.30-7.45 • High dose Mannitol 1-1.5 g/kg or higher frequency of standard dose mannitol • Hypertonic saline bolus (i.e., 30 ml of 23.4%). • Treat surgically remediable lesions according to guidelines • Adjust temperature to 35 – 36°C, using active cooling measures. • Neuromuscular blockade with short acting agents, use a bolus dose to determine effect	**TIER 2** • Adjust ventilatory rate to increase PaCO2 to 40 – 45 mm Hg and target pH of 7.35-7.45 • Increase PaO2 by: 1) increasing FiO2 up to 100%; 2) adjusting PEEP; 3) bronchoscopy • Increase CPP above 70 mmHg with fluids or vasopressors. • Neuromuscular blockade with short acting agents, use a bolus dose to determine effect • Transfuse pRBCs. • Decrease ICP to < 15 mm Hg. • CSF drainage. • Increased sedation	**TIER 2.** • High dose Mannitol 1-1.5 g/kg, or frequent boluses standard dose Mannitol • Hypertonic saline bolus (i.e., 30 ml of 23.4%) • Increase CPP above 70 mm Hg with vasopressors. • Increase PaO2 by: 1) increasing FiO2 to 100%; 2) adjusting PEEP; 3) bronchoscopy • Transfuse pRBCs • Treat surgically remediable lesions according to guidelines • Adjust temperature to 35 - 36°C, using active cooling measures. • Neuromuscular paralysis blockade with short acting agents, use a bolus dose to determine effect
TIER 3 (Tier 3 therapies are optional). • Pentobarbital coma, according to local protocol. • Decompressive craniectomy. • Adjust temperature to 32-35°C, using active cooling measures. • Adjust ventilatory rate for target PaCO2 of 30 – 35 mm Hg and target pH of less than 7.50 • Other salvage therapy per local protocol and practice patterns	**TIER 3** (Tier 3 therapies are optional). • Adjust ventilatory rate to increase PaCO2 to > 45 mm Hg if ICP is < 22 mm Hg and maintain a target ph of 7.30 – 7.45 • Increase cardiac output with inotropes (milrinone, dobutamine) • Assess for vasospasm, if present augment CPP • Consider hyperventilation for reverse Robin-Hood syndrome • Other salvage therapy per local protocol and practice patterns • Consider other causes: PE, CSDs, CST	**TIER 3.** (Tier 3 therapies are optional). • Pentobarbital coma: • Decompressive craniectomy. • Induced hypothermia. hypothermia to 32-35° C. • Increase cardiac output with inotropes (milrinone, dobutamine) • Assess for vasospasm, if present augment CPP • Consider hyperventilation for reverse Robin-Hood syndrome • Other salvage therapy per local protocol and practice patterns • Consider other causes: PE, CSDs, CST

Scenario B: ICP>22; $PbtO_2 \geq 20$



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Scenario B: ICP>22; $PbtO_2 \geq 20$

Hyperosmolar Therapy
- High dose mannitol (1.0—1.5 g/kg)
- Hypertonic Saline bolus (30 ml of 23.4%).

Neuromuscular Blockade with short acting agents

Adjust temperature to 35—36°C using active cooling measures

Tier 2 Interventions: Treatment must begin *within* 60 minutes if ICP is still >22

Treat surgically remediable lesions according to guidelines

Hyperventilation to PCO_2 goal 33—38 mmHg and target 7.35—7.45

Hyperosmolar Therapy Notes
- Mannitol: may also use more frequent lower dose mannitol (0.25—0.5 g/kg); keep serum osm < 320 mOsm
- HTS: may repeat, keep serum Na levels <160 mEq/L.

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Scenario B: ICP>22; $PbtO_2 \geq 20$

Tier 3 Interventions (optional)				
Pentobarbital coma, per local protocol. Notes: • Use an initial bolus of 5 mg/kg to determine if effective. If the bolus is effect, a continuous infusion may be used. • Pentobarbital should be rapidly weaned upon clinical stabilization	**Decompressive craniectomy**	**Adjust temperature to 32-35° C**, using active cooling measures.	**Adjust ventilatory rate:** target $PaCO_2$ of 30 - 35 mm Hg while maintaining a pH less than 7.5	**Other salvage therapy** per local protocol & practice patterns.

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Scenario C: ICP≤22 $PbtO_2$<20

Initiate or titrate **anti-seizure medications**

Adjust head of the bed to improve brain oxygen level

Ensure Temperature < 38°C; Treat fever

Adjust ventilator rate to a **PaCO2 38-42 mmHg** while maintaining target pH 7.35—7.45

Tier 1 Interventions: Treatment must begin within 15 minutes of $PbtO_2$ abnormality that is sustained for 5 minutes

Optimize CPP up to 70 mm Hg with fluid bolus or vasopressors

PaO_2 adjustments: (***obtain ABG*** **before treating with PaO2 adjustments)**

Optimize hemodynamics

Increase FiO_2 up to *60%*.

Pulmonary toilet including suctioning of secretions

Adjust PEEP by a max of 5 cm H20 over baseline; monitor ICP response

Resuscitation - address hypovolemia to achieve euvolemia with volume per local protocol

Diuresis - avoid hypervolemia, consider furosemide or diuretic

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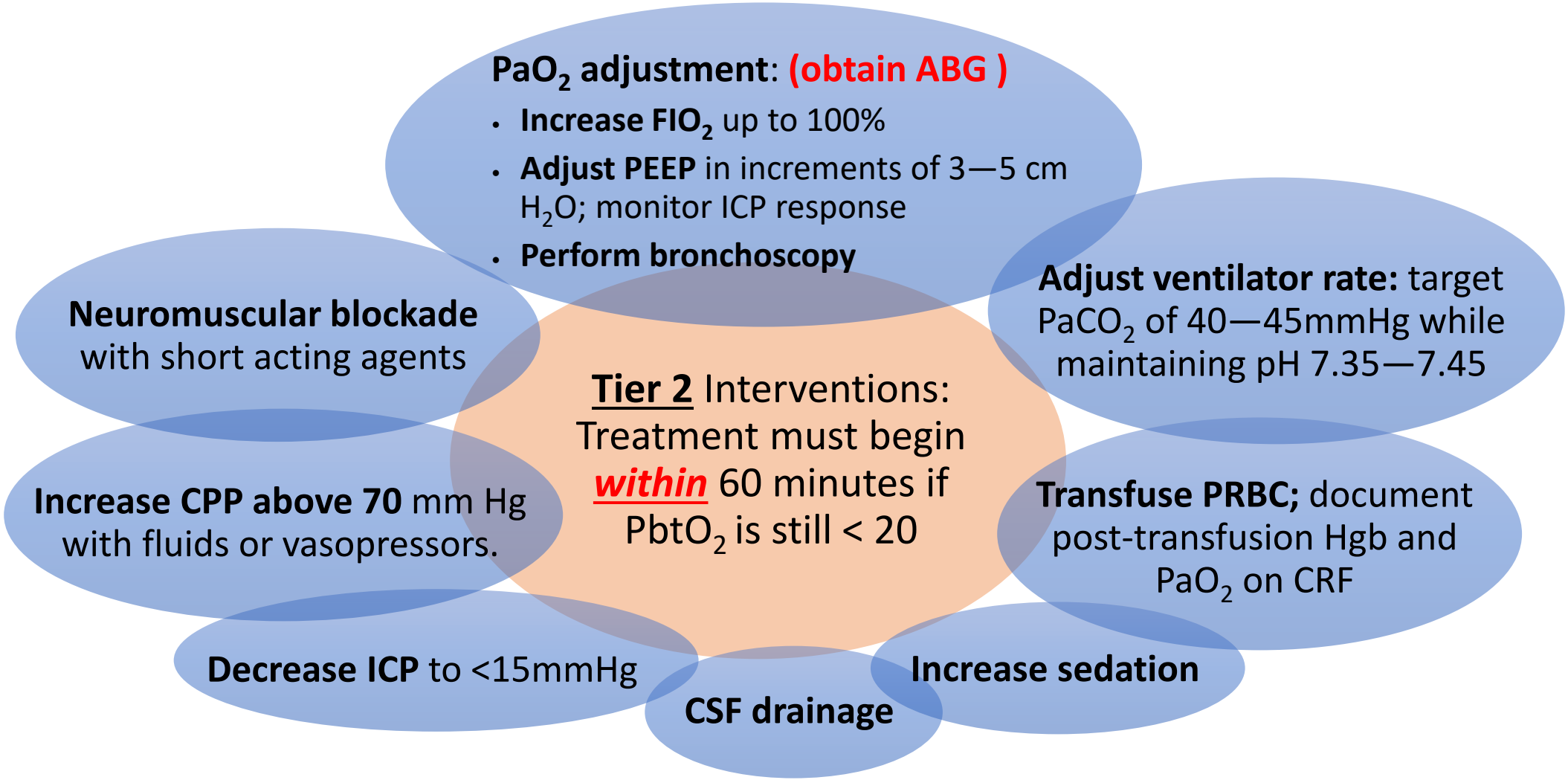
Scenario C: ICP≤22 $PbtO_2$<20



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Scenario C: ICP≤22; $PbtO_2$<20

Tier 3 Interventions (optional)				
Increase cardiac output with inotropes (milrinone, dobutamine) Notes: Consider use of CO/CI monitoring per local protocol if starting inotropes.	**Assess for vasospasm** with TCDs, CTA, or DSA. Notes: If present, treat with augmentation of CPP.	**Hyperventilation** (per CO_2 challenge) to address possible 'reverse Robin-Hood syndrome'	**Adjust ventilatory rate:** target $PaCO_2$ to > 45 mm Hg, maintain a target pH of 7.30 – 7.45 Notes: only if ICP under control	**Other salvage therapy** per local protocol & practice patterns. Notes: Consider other causes of low $PbtO_2$, ie CSDs, PE, CST

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Scenario D: ICP>22, $PbtO_2$<20

Treatment for this group is primarily aimed at lowering ICP with a secondary focus on raising PbtO2

Tier 1 Interventions: Treatment must begin within 15 minutes of abnormality that is sustained for 5 minutes

- **Hyperosmolar therapy:** Low dose Mannitol (0.25 – 0.5 g/kg) or Hypertonic Saline
- **Adjust head of the bed** to lower ICP
- **Ensure Temperature < 38°C** Treat fever
- **Adjust analgesia OR sedation**; titrate to effect
- **CSF drainage** if EVD available
- Initiate or titrate **anti-seizure medications**
- **Optimize CPP** up to ***70 mm Hg*** with fluid bolus or pressors
- **Adjust ventilator rate** to a **$PaCO_2$ 38-42 mmHg** while maintaining target pH 7.35—7.45
- **PaO2 adjustments**: (*obtain ABG* before treating with PaO2 adjustments)
  - **Pulmonary toilet**
  - **Increase FiO_2** up to *60%*.
  - **Adjust PEEP**
- Optimize hemodynamics using either:
  - **Diuresis**
  - **Resuscitation**

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Scenario D: ICP>22; $PbtO_2$<20

Hyperosmolar Therapy
- High dose mannitol (1.0—1.5 g/kg)
- Hypertonic Saline bolus (30 ml of 23.4%).

Neuromuscular blockade with short acting agents

Transfuse PRBC; document post-transfusion Hgb and PaO_2 on CRF

Adjust temperature to 35—36°C using active cooling measures

Tier 2 treatment must begin *within* 60 minutes if $PbtO_2$ and ICP remain abnormal

PaO_2 adjustment: **(obtain ABG)**
- **Increase FIO_2** up to 100%
- **Adjust PEEP** in increments of 3—5 cm H_2O; monitor ICP response
- **Perform bronchoscopy**

Increase CPP above 70 mmHg with fluid boluses or vasopressors.

Treat surgically remediable lesions according to guidelines

Hyperosmolar Therapy Notes
- Mannitol: may also use more frequent lower dose mannitol (0.25—0.5 g/kg); keep serum osm < 320 mOsm
- HTS: may repeat, keep serum Na levels <160 mEq/L.

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Scenario D: ICP>22; $PbtO_2$<20

Tier 3 Interventions (optional)						
Pentobarbital coma, per local protocol. Notes: • Determine effectiveness • Rapidly wean upon stabilization	**Decompressive craniectomy**	**Adjust temperature to 32-35° C**, using active cooling measures.	**Increase cardiac output with inotropes** (milrinone, dobutamine) Notes: Consider use of CO/CI monitoring per local protocol if starting inotropes.	**Assess for vasospasm** with TCDs, CTA, or DSA. Notes: If present, treat with augmentation of CPP.	**Hyper-ventilation** (per CO_2 challenge) to address possible 'reverse Robin-Hood syndrome'	**Other salvage therapy** per local protocol & practice patterns. Notes: Consider other causes of low $PbtO_2$, ie CSDs, PE, CST

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Reminder: Contact Information

- **For immediate emergency assistance (enrollment, clinical, protocol, adverse events, etc.), please use the 24/7 BOOST-3 Principal Investigator Hotline:**
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- Clinical questions for BOOST3 trial PIs: boost-PIs@umich.edu
- For non-urgent data entry/WebDCU questions call: 1-866-450-2016
- For all other non-urgent questions: boost-contact@umich.edu
- **For all email communications, please include BOOST-3 at the beginning of the subject line.**

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The patient is randomized to the ICP + $PbtO_2$ treatment group. A second FiO_2 challenge is performed which confirms that the probe is functional—Initial $PbtO_2$ values increase from 14mmHg to 25mmHg after repeating the FiO_2 challenge.

The patient remains sedated on **15mcg/kg/min propofol and fentanyl at 100mcg**. EVD is open continuously to allow for **CSF drainage**. She is afebrile at **37°C**.
At 8:05am, the patient alarm notifies the bedside nurse of he following values
ICP: 26 mmHg
$PbtO_2$: 22 mmHg

Based on this information, the appropriate intervention should be selected from which type scenario:

A. Type A
B. Type B
C. Type C
D. Type D

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The patient remains sedated on **15mcg/kg/min propofol and 100mcg fentanyl.** EVD is open continuously to allow for **CSF drainage.** She is afebrile at **37°C.**
Vent settings: AC 12/500/40%/5 PEEP

At 8:05am, the patient alarm notifies the bedside nurse of he following values:

ICP: 26 mmHg
$PbtO_2$: 22 mmHg

Based on this information, the appropriate intervention should first be:

A. Ensure Temperature is < 38°C: place the patient on a cooling blanket
B. High dose Mannitol: give the patient 1g/kg Mannitol IV
C. Adjust sedation: increase Propofol to 20mcg/kg/min
D. Optimize CPP: increase CPP (max 70mmHg) using a fluid bolus

Following the increase in sedation performed at 8:06am, the patient remains sedated on **20mcg/kg/min propofol and 100mcg fentanyl.** EVD is open continuously to allow for **CSF drainage.** She is afebrile at **37°C.**

An 8:10am **ABG has the following results**: **pH 7.38/$PaCO_2$ 39/PaO_2 197/HCO3 22**
Vent settings: AC 12/500/40%/5 PEEP

Based on this information, which interventions should be documented on the CRF for this episode?

A. CSF Drainage
B. Adjust sedation
C. Adjust ventilator for target $PaCO_2$ 35—40mmHg/target pH 7.35—7.45
D. All of the above

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Following the increase in sedation performed at 8:06am, the patient remains sedated on **20mcg/kg/min propofol and 100mcg fentanyl**. EVD is open continuously to allow for **CSF drainage**. She is afebrile at **37°C**.
An 8:10am **ABG has the following results**: **pH 7.38/PaCO2 39/PaO2 197/HCO3 22**
Vent settings: AC 12/500/40%/5 PEEP

ICP at 8:15 am: 28mmHg
$PbtO_2$ at 8:15am: 20 mmHg

Based on this information, which interventions may be performed **at this time (8:15am)**?

A. Adjust temperature to 32—35°C: start intravascular cooling
B. Assess for surgical remediable lesion
C. Adjust ventilator for target $PaCO_2$ 33—38mmHg; pH 7.35-7.45
D. A, B, C
E. B, C
F. None—ICP must remain elevated for ≥ 60 minutes in order to perform another intervention.

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Following the change in AC rate, the patient is taken to CT scan at 8:45am which shows an enlarged left frontal contusion with left to right midline shift. Patient remains sedated on **20mcg/kg/min propofol and fentanyl at 100mcg.** EVD is open continuously to allow for **CSF drainage.** She is afebrile at **36.5°C**.

An 8:55 am **ABG has the following results**: **pH 7.44/$PaCO_2$ 33/PaO_2 195/HCO3 23**

Vent settings: AC 14/500/40%/5 PEEP

ICP at 8:55 am: 30mmHg

$PbtO_2$ at 8:55am: 18 mmHg, sustained for >5minutes

Based on this information, which interventions are ideally **required** to be performed **at this time**?

A. Mannitol (low dose)
B. Optimize CPP: Increase CPP up to a maximum of 70mmHg with fluid bolus or vasopressors
C. PaO_2 adjustment: Increase FiO_2 to 60%
D. A, B
E. A, B, and C

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The patient ultimately is started on norepinephrine to achieve a target CPP of 70mmHg and emergently brought to the OR for a left DHC. Following surgery, the patient returns to the ICU and is sedated on **propofol at 20mcg/kg/min and fentanyl at 150mcg/hr**. EVD remains open for **CSF drainage**. Temperature is maintained at **36.5°C** with intravascular cooling. It is now PTD 3 (6/3/19), with $PbtO_2$ and ICP values within normal range since surgery.

Vent settings: AC 16/500/60%/5PEEP
ABG from 12pm, 6/3/19: 7.43, PCO_2 33, PaO_2 105, HCO_3 22

The bedside nurse responds to an alarm from the patient monitor:
ICP at 12:15 pm: 12 mmHg
$PbtO_2$ at 12:15pm: 14 mmHg

Based on this information, which interventions are ideally **required** to be performed **at this time**?

A. Type A
B. Type B
C. Type C
D. Type D

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The patient ultimately is started on norepinephrine to achieve a target CPP of 70mmHg and emergently brought to the OR for a left DHC. Following surgery, the patient returns to the ICU and is sedated on **propofol at 20mcg/kg/min and fentanyl at 150mcg/hr**. EVD remains open for **CSF drainage**. Temperature is maintained at **36.5°C** with intravascular cooling. It is now PTD 3 (6/3/19), with PbtO2 and ICP values within normal range since surgery.

Vent settings: AC 16/500/60%/5PEEP
ABG from 12:10pm, 6/3/19: 7.43, PCO_2 33, PaO_2 105, HCO_3 22

ICP at 12:15 pm: 12 mmHg
$PbtO_2$ at 12:15pm: 14 mmHg

Based on this information, the appropriate intervention that should be done within 15 minutes is:

A. PaO_2 adjustment: Increase FiO_2 to 100%
B. PaO_2 adjustment: Increase PEEP to 10
C. Lower head of bed to improve brain oxygenation
D. B and C

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The patient ultimately is started on norepinephrine to achieve a target CPP of 70mmHg and emergently brought to the OR for a left DHC. Following surgery, the patient returns to the ICU and is sedated on **propofol at 20mcg/kg/min and fentanyl at 150mcg/hr**. EVD remains open for **CSF drainage**. Temperature is maintained at **36.5°C** with intravascular cooling. It is now PTD 3 (6/3/19), with PbtO2 and ICP values within normal range since surgery.

Vent settings: AC 16/500/60%/10PEEP
ABG from 1:15 pm, 6/3/19: 7.39, PCO_2 35, PaO_2 241, HCO_3 21

ICP at 1:15 pm: 17 mmHg
$PbtO_2$ at 1:15pm: 20 mmHg

Based on this information, the appropriate intervention at this time is:

A. PaO_2 adjustment: Increase FiO_2 to 100%
B. Decrease ICP to < 15mmHg
C. A and B
D. None of the above

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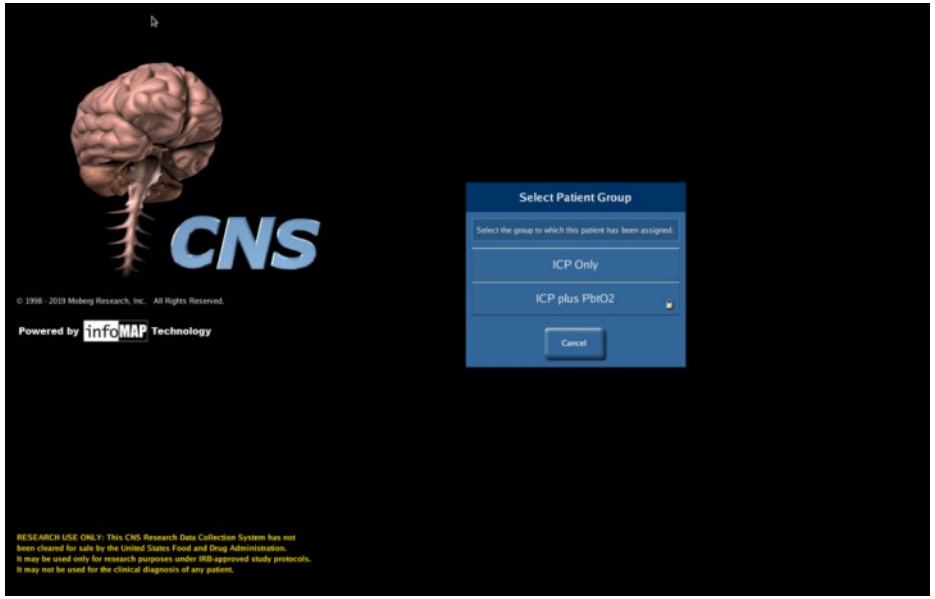
It is now PTD 4. Both ICP and $PbtO_2$ values have been well controlled and have remained within the desired range for at least 24 hours. The patient is now opening her eyes and localizes both upper extremities to painful stimuli (GCS 9T). A neurosurgery resident places an order for a routine Brain MRI and informs the bedside nurse that the $PbtO_2$/ICP monitor that was placed through a bolt will be removed later in the day, prior to MRI.

Based on this information, per protocol, can the ICP and $PbtO_2$ probes be removed on PTD 4? :

A. Yes, values have been normal for at least 24 hours
B. Yes, in order to do the MRI, the bolt must be removed
C. Yes, GCS is now > 8T
D. No

Data Capture



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Breaks

- Moberg monitor training
  - Sign up sheet at the Moberg desk for training
- Integra monitoring
- Raumedic monitoring

PLEASE USE THE BREAK TIME TO STOP BY THE DIFFERENT STATIONS

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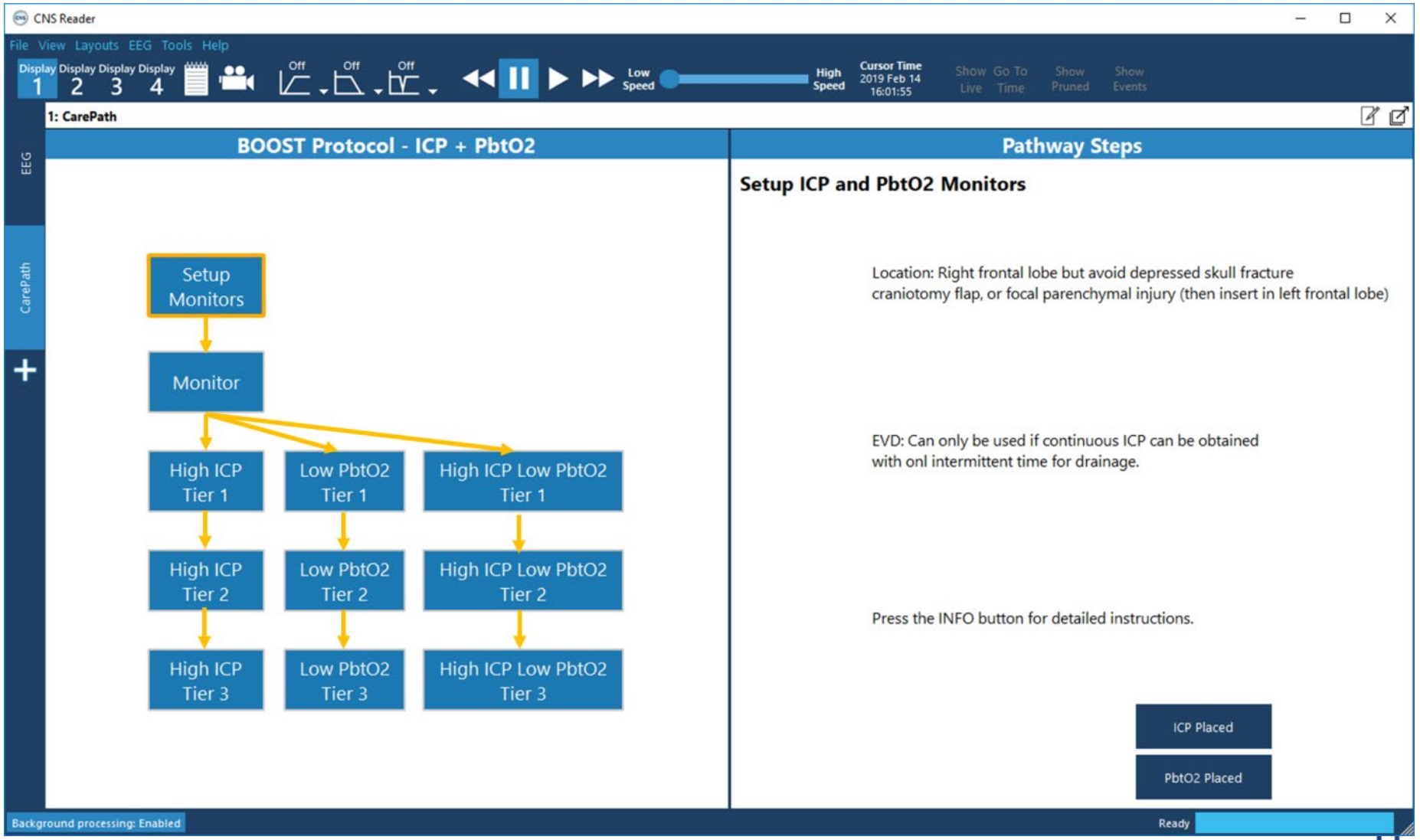
Data Capture



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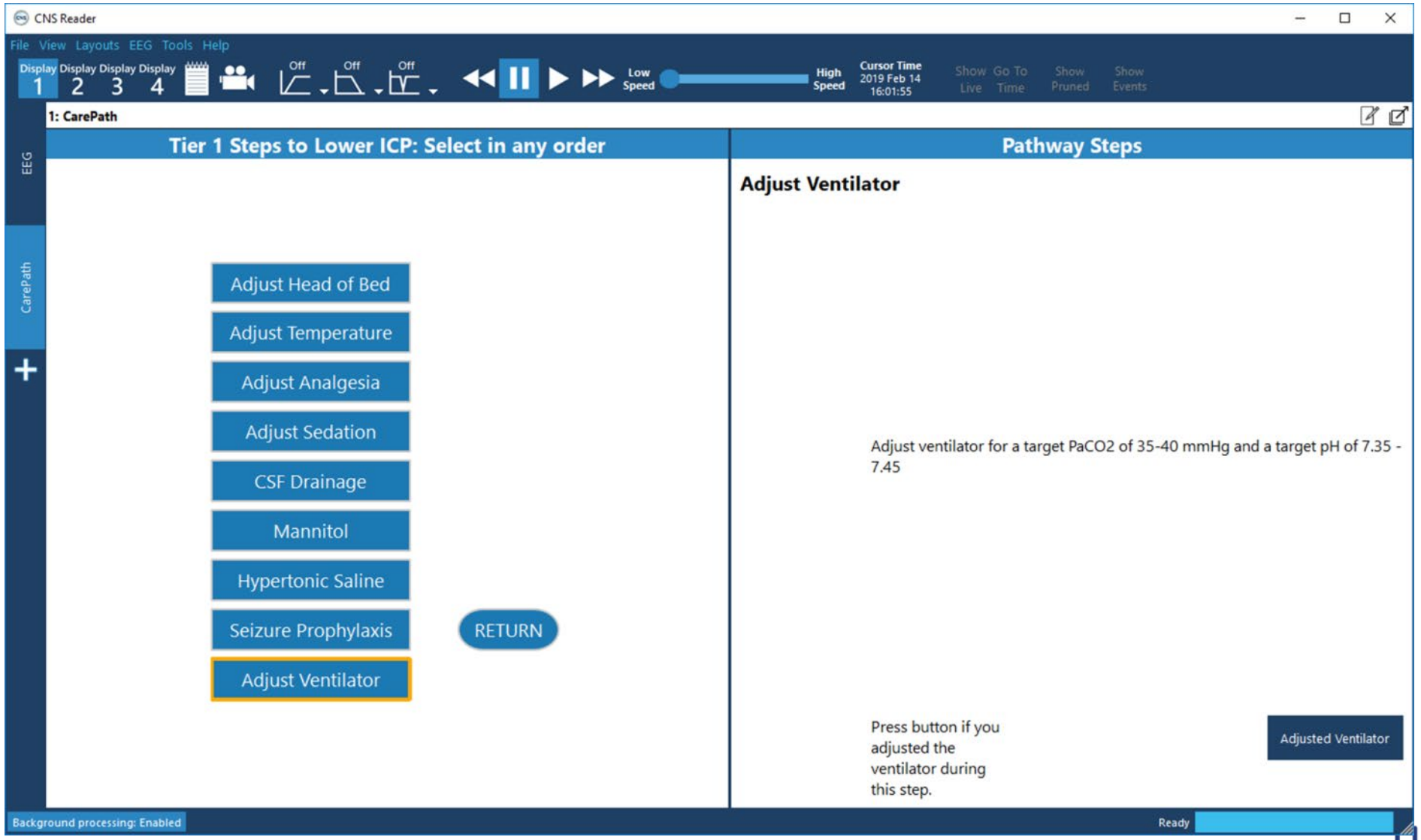
Data Capture



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Documentation of Tier Treatments

	Tier 1 Interventions: Begin within 15 minutes of episode							Tier 2 Interventions: begin within 60 min of episode if Tier 1 Therapies are not					Tier 3 Interventions: Optional–utilize if Tier 2 Therapies are not effective			
Scenario B: **ICP > 22, PbtO2 > 20 or Pbt O2 is blinded** Interventions aimed at decreasing ICP	Raise HOB	Treat fever (T>38C)	Adjust analgesia, sedation	Open EVD to drain CSF	Anti-Seizure med	Mannitol bolus (0.25-1g/kg)	Hypertonic saline	Increase Ventilator Rate	Mannitol high dose bolus (>1g/kg)	Repeat head CT	Surgery	Lower core temp to 35-37°C	Neuro-muscular paralysis	Pentobarbital coma	Decompressive craniectomy	Lower Core Temp to 32-34.5C
Date/Time	RN	RN	RN	RN	RN	RN	RN	RN	RN	RN	RN	RN	RN	RN	RN	RN

Scenario B: abnormal ICP only	ICP > 22
Interventions directed at lowering ICP	Note date/time of initiation of treatment and initials

Elevations in ICP above 22mmHg <u>for more than 5 minutes</u> are episodes that will trigger an intervention. *An episode is defined to start at the time the abnormality is noted on the continuous electronic recordings of ICP and PbtO2. Not all therapies must be used. In the events that interventions are ineffective, it is recommended that no more than 60 minutes be spent using treatment options in one tier prior to moving on to the next tier.*

Clinical Site Responsibilities for Data Review & Annotations

- Analysis of continuous ICP and $PbtO_2$ data will be an important secondary analysis of BOOST-3.
- Investigators at the clinical sites (or their designees as needed to maintain blinding) should review the continuous ICP and $PbtO_2$ data at least daily to ensure that it is clean and free of artifacts.
  - In order to maintain blinding for those in the ICP-only group, these daily reviews should take place in such a manner that others do not see the $PbtO_2$ data.
  - Periods when such data is artifactual should be annotated using software tools in the Moberg CNS monitor by the research team.
  - Research coordinators should review the clinical chart and query bedside nurses to confirm times when the patient was disconnected and identify explanations for periods of artifactual data.
- At the end of the monitoring period, after the continuous physiologic data is fully cleaned and annotated, it should be uploaded to the secure web server.

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EEG Monitoring

- EEG monitoring is not required for research purposes.
- Sites may use continuous video EEG (cvEEG) monitoring to manage severe TBI patients, or may use EEG monitoring on an as needed basis (i.e monitoring 30 - 60+ minutes at a time, when clinically indicated).
  - In both settings, treatment of seizures will be according to clinical protocols at each site, and information about anti-epileptic treatments will be recorded in CRFs.

Who to Contact?

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QUESTIONS?

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