**Dear Editorial Board for JoVE:**

**Thank you for the opportunity to address your comments and peer review. Please find each comment addressed below:**

**Editorial comments:**

Changes to be made by the Author(s) regarding the written manuscript:  
1. Please take this opportunity to thoroughly proofread the manuscript to ensure that there are no spelling or grammar issues.

Response: This is completed.

2. Affiliations: Please provide the full postal address of each affiliation.

Response: This has now been added to lines 6-11 on the title page.

3. Please provide an email address for each author.

Response: This is now included in the title page

4. Please include an ethics statement before the numbered protocol steps, indicating that the protocol follows the guidelines of your institution’s human research ethics committee.

Response: The following was added to the paper on page 2:

*This protocol was developed as a standard of care within our institution. The retrospective use of data gathered during the course of care was approved through a waiver of informed consent by the University of Cincinnati’s Institutional Review Board.*

5. Please revise the protocol text to avoid the use of any personal pronouns (e.g., "we", "you", "our" etc.).

Response: Text has been revised.

6. Please revise the protocol to contain only action items that direct the reader to do something (e.g., “Do this,” “Ensure that,” etc.). The actions should be described in the imperative tense in complete sentences wherever possible. Avoid usage of phrases such as “could be,” “should be,” and “would be” throughout the Protocol. Any text that cannot be written in the imperative tense may be added as a “Note.” Please include all safety procedures and use of hoods, etc. However, notes should be used sparingly and actions should be described in the imperative tense wherever possible.

Response: Edits were made to focus on the imperative tense.

7. 1.1.1, lines 100-107: Please write the text in the imperative tense.

Response: This has been edited and included as part of 1.2:

*Patients are excluded if they exhibit command following or if they cannot follow commands due to aphasia and have eye opening spontaneously or to voice.*

8. Line 127: Please note that the items listed in 3.1.2.1-3.1.2.5 do not correspond exactly to those listed in Table 1. Please revise.

Response: Both the text and the table have been revised accordingly.

9. 7.2 and sub-steps (lines 187-216): Please write the text in the imperative tense.

Response: This has been revised, how lines 185-216.

10. Lines 190-191: Please describe in detail how to Raumedic intracranial pressure data.

Response: As detailed in step 7.2, equipment will vary. The Raumedic ICP data can be plugged into a bedside monitor or another monitoring device and data capture steps are outside of the scope of this manuscript.

11. Lines 192-201: The Protocol should be made up almost entirely of discrete steps without large paragraphs of text between sections. Please simplify the Protocol so that individual steps contain only 2-3 actions per step and a maximum of 4 sentences per step. Use sub-steps as necessary.

Response: This has been broken up into sections with a “Note” for text that is meant to be explanatory.

12. Lines 202-211: The Protocol should be made up almost entirely of discrete steps without large paragraphs of text between sections. Please mention how to measure cerebral blood flow. Please move the discussion about the protocol to the Discussion.

Response: This has been broken up into sections with “Notes” for the larger text sections that are required for troubleshooting, but outside of the scope of the Discussion (which is more about the operative surgical technique). At the Editors discretion, data verification may be omitted if it detracts from the discrete operative steps described in prior sections.

13. At the end of the procedure, please mention how the patients are treated for any pain or recovery.

Response: The following section was added to address pain and recovery:

*8. Patient Care*

*8.1 Following the procedure, no further pain control is necessary and no prophylactic antibiotics are required.*

*8.2 At the end of the clinical monitoring period, remove the bolt by first removing each of the probes individually. Then, twist the bolt counterclockwise until it comes loose from the skull and can be removed.*

*8.3. Use sterile technique to suture the skin opening and monitor for any cerebrospinal fluid leakage, bleeding, or swelling at the site.*

14. Please include single-line spaces between all paragraphs, headings, steps, etc.

Response: Completed; paragraphs are denoted by indentation now.

15. After you have made all the recommended changes to your protocol (listed above), please highlight 2.75 pages or less of the Protocol (including headings and spacing) that identifies the essential steps of the protocol for the video, i.e., the steps that should be visualized to tell the most cohesive story of the Protocol.

Response: This is now highlighted in yellow.

16. Please highlight complete sentences (not parts of sentences). Please ensure that the highlighted part of the step includes at least one action that is written in imperative tense. Please do not highlight any steps describing anesthetization and euthanasia.

17. Please include all relevant details that are required to perform the step in the highlighting. For example: If step 2.5 is highlighted for filming and the details of how to perform the step are given in steps 2.5.1 and 2.5.2, then the sub-steps where the details are provided must be highlighted.

Response: Areas have been highlighted in the Revised text.

18. Figure 1 and Table 1: Please remove commercial language including trademark symbols (™), registered symbols (®), and manufacturer/product names (Neurovent®, Qflow 500TM, Spencer®).

Response: This is done in both Figure 1 Revised and Table 1 Revised.

19. Discussion: Please describe critical steps within the protocol.

Response: If the Editor would provide additional guidance, I would be happy to include critical steps within the discussion. All steps are described within the protocol and non-imperative information is primarily discussed with regard to feasibility and safety in the Discussion.

20. Please revise the table of the essential supplies, reagents, and equipment to include the name, company, and catalog number of all relevant materials in separate columns in an xls/xlsx file. Please remove trademark (™) and registered (®) symbols.

Response: This is done per comment 18. Catalog numbers are not available for some devices and are not necessarily relevant to this list but the name of supplies, company, and even information about the sampling frequency of the devices is included.  
  
  
**Reviewer #1:**  
  
Manuscript Summary:  
Foreman and colleagues have succinctly and nicely described the role of invasive intracranial multimodality monitoring following acute bran injury, such as TBI and stroke, and provided a thorough, yet easily followed, protocol for the bedside placement of multiple intraparenchymal monitors, such as ICP, PbtO2, CBF, EEG depth electrodes, and (optionally) microdialysis. The protocol is similar to that used at several institutions well-known for their multimodality monitoring programs, however, as yet I am unaware of a published protocol that summarizes the benefits, patient selection, and steps in monitor placement as evidenced by this manuscript.  
  
Major Concerns:  
None.  
  
Minor Concerns:  
Some minor edits and/or additions could be considered to the protocol:  
  
1. Technically, I would describe the technique as a twist drill craniostomy, rather than a burr hole, as traditionally a burr hole is somewhat larger in diameter (~1-1.4 cm). These are relative semantics, however, and seems the terms are frequently used interchangeably nowadays.

Response: The reviewer raises a good point, and the following was added to the introduction to make it clear that the terms are being used interchangeably, as per modern parlance.

*…introduced through a twist drill craniostomy (often referred to interchangeably as a burr hole)* (lines 52-53)

2. Lines 154-155: While some practitioners prefer a scalpel blade to incise the dura, others (particularly those using other cranial access kits), may find that the scalpel blade is too large or not particularly conducive to this when a small twist drill craniostomy is used. Another technique commonly employed is to perforate the intact dura several times with an 18-guage needle using tactile feedback until the dura is sufficiently opened.

Response: In order to allow flexibility for individual technique, the following note was added to 4.5:

*Note: Some practitioners may use alternative approaches, such as using an 18-guage needle to perforate the dura using tactile feedback until the dura is sufficiently opened. Adequate durotomy is critical regardless of the technique, and incomplete durotomy may lead to difficulty passing thin, flexible catheters or malpositioning of the catheters.*

3. Line 173: The word "tape" is misspelled as "table".

Response: This has been corrected.

4. Lines 176-177: Another option is to wrap a thin strip of xeroform gauze around the base of the bolt housing where in comes in contact with the skin. This provides a barrier to infection and is also bacteriostatic.

Response: This was added to Section 6.4:

*Optional: Use a large 6”x2” tegaderm or a thin strip of xeroform gauze to wrap the base of the bolt, reducing the exposure of the skin-to-burr-hole interface. Xeroform gauze also provides bacteriostatic function.*

5. Lines 202 and 212: The section number 7.1.2 is inadvertently repeated. The sections on Cerebral Blood Flow and Depth EEG should be renumbered to 7.1.3 and 7.1.4, respectively.

Response: The numbering in this section required editing and now should be accurate.

6. Line 294: Change the word "adequate" to "adequately".

Response: This has been edited.

**Reviewer #2:**  
In this observational, single center study, the authors described the method of recording multimodality monitoring signals in patients with severe traumatic brain injury via single Burr hole placement. The study describes a technique that allow the simultaneous placement of multiple modality probes that measure ICP, PbtO2, rCBF and iEEG in hopes of targeted monitoring of multiple physiological parameter in hopes of mitigating secondary brain injuries. The authors described a patient cohort of forty three patients who underwent invasive multimodality monitoring using a pre-determined standardized protocol. This well designed study showed merit but had limitation and weakness.  
  
Specific Comments:  
1. The major weakness of the study in my opinion is that despite the invasive nature of the procedure, Multimodality monitoring still does not provide a global assessment of brain tissue as the probes only provide localize assessment of brain tissue. A PET scan or MRI might provide such assessment but having a ICP bolt might preclude patients from having this neuroimaging modality as most of the ICP Bolts monitors are not compatible. This might cause a delay in patient care who might have benefited from neuroimaging sooner.

Response: Our intent with this manuscript is to describe a technique that allows for continuous measures of brain physiology. We acknowledge that imaging exhibits better spatial resolution and provides important complementary information, but a full discussion of the differences in modalities is beyond the scope of this manuscript. However, we have added some text to our discussion to address the important limitation that multimodality monitoring does not provide an assessment of global brain tissue. Our technique is performed during the acute period (a median of 12.5 hours following injury) when patients are often unstable to travel to PET or MRI scans. However, there were several patients in this cohort who underwent urgent MRI to gauge the extent of diffuse axonal injury prior to bolt placement, so this procedure does not preclude imaging assessments in appropriate patients. Finally, our median monitoring duration was only 4 days, allowing for PET or MRI testing as needed within a week of injury, and in time for prognostic decision-making.

I have added the following to the Discussion (pg 6):

*Importantly, the use of multimodality monitoring is designed to provide time-resolute data during the acute period in which many patients are unstable to travel to MRI. Patients described here underwent monitoring within a median of 12.5 hours and were monitored for a median of 4 days after trauma, which allowed for advanced imaging within a reasonable time frame.*

I have also added the following to the Discussion (pg 8):

*Although this approach does not provide a global assessment of brain tissue, the ability to continuously monitor a vulnerable brain region provides the advantage of real-time patient care decision making.*

2. The other concern is that the authors failed to describe the patient selection process that they used in their decision making. I commend them for doing a great job in detailing their methods but a useful guide should include patient selection process and potential complications.

Response: Patient selection is likely to be site specific, but we agree this is an important aspect to deploying this or similar protocols. We included a sample protocol in our recent publication (Foreman, B., Ngwenya, L.B., Stoddard, E., Hinzman, J.M., Andaluz, N., Hartings, J.A. Safety and Reliability of Bedside, Single Burr Hole Technique for Intracranial Multimodality Monitoring in Severe Traumatic Brain Injury. *Neurocritical Care*. doi: 10.1007/s12028-018-0551-7 (2018)) which is referenced within the text, and included the following in 1.2:

*Patients are excluded if they exhibit command following or if they cannot follow commands due to aphasia and have eye opening spontaneously or to voice.*

Complications are mentioned in 1.3 and discussed in detail within the Discussion. I would be happy to address specific complications further with guidance from the Reviewer.

3. Despite the above limitations, I feel that this is a well-designed study. I commend the authors for taking the initiative in trying to solve the mystery of brain monitoring which still remains a "black box." I would recommend that the authors expand this to a multi-center study in hopes of creating a comprehensive protocol.

Response: We share the Reviewer’s optimism that this can be performed across multiple centers and have been working with others who have employed a similar procedure successfully. By standardizing this procedure, we hope that patient safety, data quality, and clinical management are positively impacted.

Sincerely,

Brandon Foreman, on behalf of the authors