PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effect of tranexamic acid on the prognosis of patients with traumatic brain injury undergoing craniotomy: study protocol for a randomized controlled trial
AUTHORS	Wu, Bei; Lu, Yu; Yu, Yun; Yue, Hongli; Wang, Jie; Chong, Yingzi; Cui, Weihua

VERSION 1 – REVIEW

REVIEWER	Kanmounye, US Association of Future African Neurosurgeons, Research
REVIEW RETURNED	26-Mar-2021

GENERAL COMMENTS	I read with a lot of interest the protocol by Bei et al. The study is very relevant in the post-CRASH-3 era, the authors have clearly defined the research question and methods. I congratulate the authors on a fantastic job and I recommend acceptance pending minor revisions. Please find our suggestions below: The authors mention that they will obtain informed consent from patients before surgery (Lines 27-28, Page 5 of 19). Considering that most patients undergoing craniotomy have a depressed Glasgow Coma Scale (moderate-to-severe TBI) as stated by the authors (Lines 11-14, Page 4 of 19), the authors should mention how informed consent ill be obtained in this situation. Please define how perioperative blood loss will be measured (Line 27, Page 6 of 19) Please clarify whether the CRS-R (Lines 40-42, Page 6 of 19) will be used for all TBI patients or just for those recovering after a coma. For reference please check this article https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5018674/ In the introduction, the authors mention: the disproportionate impact of severe TBI (Lines 11-14, Page 4 of 19) and penetrating TBI (Lines 33-37, Page 4 of 19) however it is not clear if and how this will be investigated in the study. Line 14, Page 4 of 19: Please replace "over 60% of them with severe TBI" with "over 60% of them have severe TBI" Line 36, Page 4 of 19: "Simplify acute Physiological Score" should read "Simplified Acute Physiology Score" Please make sure you capitalize the first letter of every word

	Lines 37-41, Page 4 of 19: The sentence could benefit from clarity. It appears the authors are making the argument that most TBI patients needing surgical interventions have severe TBI and the most common indication for surgery in TBI patients is the evacuation of hematomas. I recommend that the authors report the numbers supporting these statements as well as their references. After making this point, I recommend they begin a new sentence elaborating the following statement - "complicated by severe systemic inflammatory response and coagulation dysfunction" Lines 41-43, Page 4 of 19: Please rewrite the sentence "It is not clear, that for emergency TBI patients who need craniotomy, whether the use of TXA can improve the prognosis." as "It is not clear whether the use of TXA can improve the prognosis of TBI patients requiring emergency craniotomy." Lines 43-45, Page 4 of 19: Please rewrite the sentence "It still needs further research to determine..." as "Further research is needed to determine..." Line 45, Page 4 of 19: Please replace "who received" with "undergoing" Line 46, Page 4 of 19: Please replace "intravenously" with "intravenous" Line 50, Page 4 of 19: Please delete "of the patients" Line 7, Page 5 of 19: Please replace "scheduled to receive" with "schedule for a" Line 9, Page 5 of 19: Please delete the space between "hospital" and the comma Line 23 and line 30, Page 5 of 19: Please replace "person" with "staff" Please replace all mentions of "quality control person" with "quality control staff" Line 24, Page 5 of 19: Please replace "set up" with "hired" Line 24-25, Page 5 of 19: Please replace "with one drug" with "with each drug" Line 25, Page 5 of 19: Please replace "includes" with "will include" Line 31, Page 5 of 19: Please insert "the" between "with" and "corresponding" Lines 31-32, Page 5 of 19: Please insert "the" between "Ensure that" and "treatment"

	Line 36, Page 5 of 19: Please replace "According to" with "Depending on" Line 52, Page 5 of 19: Please replace "are pumped" with "will be pumped" Line 53, Page 5 of 19: Please replace "include" with "will include" Line 54, Page 5 of 19: Please replace "is followed by" with "will be followed by" Line 55, Page 5 of 19: Please replace "are adjusted" with "will be adjusted" Line 5, Page 6 of 19: Please insert a space between "removed" and the bracket Line 6, Page 6 of 19: Please insert "the" between "to" and "intensive care unit" Line 14, Page 6 of 19: Please insert a space between the reference and "at discharge" Line 24, Page 6 of 19: Please delete ":" and replace "include" with "including" Line 34, Page 6 of 19: Please delete ":" and replace "include" with "including" Line 40, Page 6 of 19: Please replace "Coma Recovery Scale score-Revised" with "Coma Recovery Scale - Revised" Line 40, Page 6 of 19: Please insert a space between the reference and "at discharge" Line 41, Page 6 of 19: Please replace "applied" with "used" Line 42, Page 6 of 19: Please insert "of" between "3mL" and "blood" Line 43, Page 6 of 19: Please replace "for" with "at" and add an "s" at the end of "rotation" Line 45, Page 6 of 19: Please replace "is collected" with "will be collected" Line 45, Page 6 of 19: Please delete ":" and replace "include" with "including" Line 55, Page 6 of 19: Please replace ", including" with ". These will include" Lines 7-9, Page 7 of 19: Please delete "retrospective" Also, please rewrite "the severe disability (Glasgow outcome score 1~3) rate undergoing craniotomy hematoma removal was 54%" as "54% of TBI patients undergoing craniotomy for

	hematoma evacuation had severe disability (Glasgow outcome score 1~3)." Line 11-12, Page 7 of 19: Please replace "on the basis of the anticipated the severe disability rate to reduce by 15% (54% to 46%)" with "on the basis that the rate of severe disability will be reduced by 15% from 54% to 46%." Line 18, Page 7 of 19: Please add information on the parent company that owns Stata the same way you did for PASS (Line 11, Page 7 of 19) Line 19, Page 7 of 19: Please replace "are" with "will be" Line 20, Page 7 of 19: Please replace "qualitative data use cases" with "qualitative data will be expressed as frequencies" Line 30, Page 7 of 19: Please replace "are defined" with "will be defined" Line 37, Page 7 of 19: Please define "CRF" in full - that is "Case Report Form" and put "CRF" in parentheses since this is the first time CRF is mentioned in the text Please correct the references in the following: - Line 59, Page 3-Line 5, Page 4 of 19 - Lines 5-8, Page 4of 19 - Lines 10-11, Page 4 of 19 - Lines 18-19, Page 4of 19 - Lines 23-26, Page 4 of 19: Please put the references at the end of the sentence - Lines 28-30, Page 4 of 19: The authors say "studies have shown" but they reference a single prospective observational cohort study by de Oliveira Manoel et al. We recommend that they either cite other studies that agree with de Oliveira Manoel et al. or they change "studies have shown" with "de Oliveira Manoel et al. have shown" - Lines 37-41, page 4 of 19: Please reference this - Lines 18-20, Page 6 of 19: Please reference this statement - Lines 7-9, Page 7 of 19: Please reference the previous studies

REVIEWER	Saffari, Seyed Ehsan Duke-NUS Medical School, Centre for Quantitative Medicine
REVIEW RETURNED	05-Apr-2021

GENERAL COMMENTS	1.The introduction, background, clinical significance and objectives of the study are clearly explained under Introduction section. 2.The objectives under Methods section are not detailed. They should specify the primary, secondary and exploratory aims separately. Under each, it should be clearly explained the key elements: ‘who’, ‘when’, ‘where’, ‘how’, ‘by what measure’.

	3.The study site (hospital) and duration of the study (2021-23) are not an inclusion criteria, and should move to the study settings. 4.More detailed information about randomization (method of randomization, any stratification factor, sofeware, etc) should be provided. It seems that the randomization will be on site and in real time? This is how the randomization is read, needs more clarifications if that is not the case. I am also wondering why the randomization is not going to perform by an independent statistician prior to the study, and needs to be on-site and in real time? At least, I do not see any benefit. 5.Randomization and blinding should be explained under two separate sections. In the current version, the blinding shortly described followed by randomization and again blinding is discussed. Easier to follow and read if they are discussed separately. 6.Under Intervention section, the intervention should be explained only. Afterwards, Placebo with another sub-heading should be discussed. 7.Under primary and secondary outcome sections, to be consistent with the study objectives mentioned earlier, the outcomes should be referred as efficacy/safety outcomes first. Then they should be defined in the current manner what such efficacy/safety would mean in this study. 8.Primary outcome needs justification and citations. More specifically, they should highlight whether this is a good and objective outcome and has been established and used in other studies. The mentioned reliability and validity without reference is not scientifically valid. What is the justification of the primary outcome at “discharge”, where such time point may vary among the patients? It is not clear how the primary outcome will be treated under this section (unfavorable vs favorable). 9.Some of the secondary outcomes do not look like an “outcome”. For example, how ‘pre-op blood loss’ could be an outcome? This makes some of the secondary outcomes clinically irrelevant. More clinical input is required. 10.Secondary outcomes should be defined clearly. For example, what is the start and end date of length of hospitalization and what is its planned unit of measure? Or for hospitalization cost, it should be mentioned what kind of cost are planned to be included. 11.I would also suggest to collect pre-op GOSE data. 12.Are the study team planning to collect some data on the surgery (ex. Duration of surgery) itself?

	13.Sample size calculation is based on the primary outcome which is binary (unfavorable vs favorable). How come sample size was calculated using mean differences instead of proportion differences? Does “previous retrospective studies” refer to some publications? If so, this needs citations. If not and that refers to some pilot data, this should be clarified. There also should be some justification as whether such sample size is achievable based on clinical experience and the current number of monthly patients. No adjustment for potential/expected dropout rate? 14.Statistical analysis plan should be revised substantially. More scientific statistical terms should be used (what is classified data or unordered outcome?). What variables are planned to be included in the multivariable analysis? What about clinical confounders? What about potential interactions? Strategy for handling missing data? How to analyze the several secondary outcomes? What is the strategy to avoid inflation in type-I error due to multiple comparisons? 15.Potential issues over operation and over hospitalization should be mentioned and addressed. 16.Citations are necessary where needed. For example, they should cite literature when talking about “standardized procedure” without further details. Of course this is just one example. 17.It is not mentioned whether any interim analysis is planned. If that’s the case, it should be still justified why not. Same point about termination rules and futility analysis.

VERSION 1 – AUTHOR RESPONSE

Responses to reviewer 1

The authors mention that they will obtain informed consent from patients before surgery (Lines 27-28, Page 5 of 19). Considering that most patients undergoing craniotomy have a depressed Glasgow Coma Scale (moderate-to-severe TBI) as stated by the authors (Lines 11-14, Page 4 of 19), the authors should mention how informed consent will be obtained in this situation.
Response: We appreciate your suggestions. TBI patients undergoing neurosurgery are always unconsciousness. Therefore, the legal representative of the participants has the right to obtain all relevant information and sign the consent. We have revised this part in the manuscript (Page 6, line 9-10).

Please define how perioperative blood loss will be measured (Line 27, Page 6 of 19)
Response: We appreciate your suggestions. In the manuscript, we have cited the standard blood loss calculation method. he intraoperative blood loss will be calculated based on the previous study. The blood loss via the suction will be determined by subtracting the added fluids (heparin and saline solutions) from the total volume contained in the surgical canister. The cotton slivers and pieces used during operation

will also be calculated at the end of the surgery. A soaked sliver equals 5 mL blood. A soaked pieces equals 1 mL blood (Page 9, line 10-15).

Please clarify whether the CRS-R (Lines 40-42, Page 6 of 19) will be used for all TBI patients or just for those recovering after a coma. For reference please check this article https://www.ncbi.nlm.nih.gov/pmc/articlesR/PMC5018674/
Response: Thank you for your suggestions. We used CRS-R as a secondary outcome to evaluate the differences of consciousness recovering state between the two groups. In this study, we will do this evaluation for every participant. We have read the reference you have mentioned here. We really appreciate your suggestion here. And in our statistical analysis, we will choose a cut-off score of 8 in our assessment because of the best odds avoiding false positive and negative errors and we cited this reference (Page 9, line 25-28).

In the introduction, the authors mention: the disproportionate impact of severe TBI (Lines 11-14, Page 4 of 19) and penetrating TBI (Lines 33-37, Page 4 of 19) however it is not clear if and how this will be investigated in the study.
Response: We appreciate your suggestions. We agree that it was confusing that we mentioned severe TBI and penetrating TBI in the previous manuscript. Because this is a RCT research, after strict randomization, the baseline situation of the two groups should be similar. We have revised this section and deleted this statement in the manuscript.

Line 14, Page 4 of 19: Please replace "over 60% of them with severe TBI" with "over 60% of them have severe TBI"
Response: It has been revised as suggested (Page 2, line 22).

Line 36, Page 4 of 19: "Simplify acute Physiological Score" should read "Simplified Acute Physiology Score" Please make sure you capitalize the first letter of every word
Response: Thank you. It has been revised as suggested (Page 3, line 9-10).

Lines 37-41, Page 4 of 19: The sentence could benefit from clarity. It appears the authors are making the argument that most TBI patients needing surgical interventions have severe TBI and the most common indication for surgery in TBI patients is the evacuation of hematomas. I recommend that the authors report the numbers supporting these statements as well as their references. After making this point, I recommend they begin a new sentence elaborating the following statement - "complicated by severe systemic inflammatory response and coagulation dysfunction"
Response: We appreciate your suggestions. We have cited the references supporting the statement that “Urgent decompressive craniotomy is recommended for severe TBI patients with severe craniocerebral trauma, severe cerebral edema, epidural hematomas and subdural hematomas to reduce ICP and mortality and improve neurological clinical outcomes” in the original place of the manuscript. And in a new sentence, we elaborated the statement that “For severe TBI patients complicated by acute traumatic coagulopathy and severe systemic inflammatory response, promptly correction of coagulopathies and anti-inflammatory treatment should take into consideration.” (Page 3, line 11-16).

Lines 41-43, Page 4 of 19: Please rewrite the sentence "It is not clear, that for emergency TBI patients who need craniotomy, whether the use of TXA can improve the prognosis." as "It is not clear whether the use of TXA can improve the prognosis of TBI patients requiring emergency craniotomy."
Response: Thank you. It has been revised as suggested (Page 3, line 16-17).

Lines 43-45, Page 4 of 19: Please rewrite the sentence "It still needs further research to determine..." as "Further research is needed to determine..."
Response: Thank you. It has been revised as suggested (Page 3, line 18).

Line 45, Page 4 of 19: Please replace "who received" with "undergoing"
Response: Thank you. It has been revised as suggested (Page 3, line 19).

Line 46, Page 4 of 19: Please replace "intravenously" with "intravenous"
Response: Thank you. It has been revised as suggested (Page 3, line 21,29; Page 6, line 6,10,11,13; Page 13, line 10; Page 15, line 17).

Line 50, Page 4 of 19: Please delete "of the patients"
Response: Thank you. It has been revised as suggested (Page 3, line 23).

Line 7, Page 5 of 19: Please replace "scheduled to receive" with "schedule for a"
Response: Thank you. It has been revised as suggested (Page 5, line 4).

Line 9, Page 5 of 19: Please delete the space between "hospital" and the comma
Response: Thank you. It has been revised as suggested (Page 7, line 11).

Line 23 and line 30, Page 5 of 19: Please replace "person" with "staff"
Please replace all mentions of "quality control person" with "quality control staff"
Response: Thank you. It has been revised as suggested (Page 6, line 2,28; Page 9, line 2, 25).

Line 24, Page 5 of 19: Please replace "set up" with "hired"
Response: Thank you. We have revised this part and deleted this sentence.

Line 24-25, Page 5 of 19: Please replace "with one drug" with "with each drug"
Response: Thank you. We have revised this part and deleted this sentence.

Line 25, Page 5 of 19: Please replace "includes" with "will include"
Response: Thank you. It has been revised as suggested (Page 7, line 21).

Line 31, Page 5 of 19: Please insert "the" between "with" and "corresponding"
Response: Thank you. we have deleted this sentence.

Lines 31-32, Page 5 of 19: Please insert "the" between "Ensure that" and "treatment"
Response: Thank you. we have revised this sentence.

Line 36, Page 5 of 19: Please replace "According to" with "Depending on"
Response: Thank you. It has been revised as suggested (Page 6, line 29).

Line 52, Page 5 of 19: Please replace "are pumped" with "will be pumped"
Response: Thank you. It has been revised as suggested (Page 5, line 21).

Line 53, Page 5 of 19: Please replace "include" with "will include"
Response: Thank you. It has been revised as suggested (Page 8, line 16).

Line 54, Page 5 of 19: Please replace "is followed by" with "will be followed by"

Response: Thank you. It has been revised as suggested (Page 10, line 20).

Line 55, Page 5 of 19: Please replace "are adjusted" with "will be adjusted"
Response: Thank you. It has been revised as suggested (Page 7, line 24,26).

Line 5, Page 6 of 19: Please insert a space between "removed" and the bracket
Response: Thank you. It has been revised as suggested (Page 7, line 28).

Line 6, Page 6 of 19: Please insert "the" between "to" and "intensive care unit"
Response: Thank you. It has been revised as suggested (Page 7, line 29).

Line 14, Page 6 of 19: Please insert a space between the reference and "at discharge"
Response: Thank you. It has been revised as suggested (Page 8, line 21).

Line 24, Page 6 of 19: Please delete ":" and replace "include" with "including"
Response: Thank you. We have revised this part and deleted the sentence.

Line 34, Page 6 of 19: Please delete ":" and replace "include" with "including"
Response: Thank you. We have revised this part and deleted this sentence.

Line 40, Page 6 of 19: Please replace "Coma Recovery Scale score-Revised" with "Coma Recovery Scale - Revised"
Response: Thank you. It has been revised as suggested (Page 9, line 26).

Line 40, Page 6 of 19: Please insert a space between the reference and "at discharge"
Response: Thank you. We have revised this part and deleted this sentence.

Line 41, Page 6 of 19: Please replace "applied" with "used"
Response: Thank you. We have revised this part and deleted this sentence.

Line 42, Page 6 of 19: Please insert "of" between "3mL" and "blood"
Response: Thank you. It has been revised as suggested (Page 8, line 4).

Line 43, Page 6 of 19: Please replace "for" with "at" and add an "s" at the end of "rotation"
Response: Thank you. It has been revised as suggested (Page 8, line 5).

---Line 45, Page 6 of 19: Please replace "is collected" with "will be collected"
Response: Thank you. It has been revised as suggested (Page 8, line 6).

---Line 45, Page 6 of 19: Please delete ":" and replace "include" with "including"
Response: Thank you. We have revised this part and deleted this sentence.

Line 55, Page 6 of 19: Please replace ", including" with ". These will include"
Response: Thank you. It has been revised as suggested (Page 8, line 16).

Lines 7-9, Page 7 of 19: Please delete "retrospective"
Also, please rewrite "the severe disability (Glasgow outcome score 1~3) rate undergoing craniotomy hematoma removal was 54%" as "54% of TBI patients undergoing craniotomy for hematoma evacuation had severe disability (Glasgow outcome score 1~3)."

Response: Thank you. It has been revised as suggested (Page 11, line 13-14).

Line 11-12, Page 7 of 19: Please replace "on the basis of the anticipated the severe disability rate to reduce by 15% (54% to 46%)" with "on the basis that the rate of severe disability will be reduced by 15% from 54% to 46%."
Response: Thank you for your suggestions. It has been revised to “So we suppose the unfavorable clinical outcome rate in the placebo group is 54%, and the anticipated unfavorable clinical outcome rate in the TXA group to reduce by 15% (54% to 46%).” (Page 11, line 13-15).

Line 18, Page 7 of 19: Please add information on the parent company that owns Stata the same way you did for PASS (Line 11, Page 7 of 19)
Response: Thank you. It has been revised as suggested (Page 12, line 13-14).

Line 19, Page 7 of 19: Please replace "are" with "will be"
Response: Thank you. We have revised this part and deleted this sentence.

Line 20, Page 7 of 19: Please replace "qualitative data use cases" with "qualitative data will be expressed as frequencies"
Response: Thank you. We revised the statistical analysis and deleted this sentence.

Line 30, Page 7 of 19: Please replace "are defined" with "will be defined"
Response: Thank you. It has been revised as suggested (Page 12, line 16-17).

Line 37, Page 7 of 19: Please define "CRF" in full - that is "Case Report Form" and put "CRF" in parentheses since this is the first time CRF is mentioned in the text
Response: Thank you. We revised this part and deleted this sentence.

Please correct the references in the following:
- Line 59, Page 3-Line 5, Page 4 of 19
- Lines 5-8, Page 4of 19
- Lines 10-11, Page 4 of 19
- Lines 18-19, Page 4of 19
- Lines 23-26, Page 4 of 19: Please put the references at the end of the sentence
Response: Thank you for your suggestions. We have revised the reference part as you suggested.

Lines 28-30, Page 4 of 19: The authors say "studies have shown" but they reference a single prospective observational cohort study by de Oliveira Manoel et al. We recommend that they either cite other studies that agree with de Oliveira Manoel et al. or they change "studies have shown" with "de Oliveira Manoel et al. have shown"
Response: Thank you. We have revised this sentence to “de Oliveira Manoel et al. have shown”.

Lines 37-41, page 4 of 19: Please reference this
Response: Thank you for your suggestion. We have revised this part (Page 2, line 19).

Lines 18-20, Page 6 of 19: Please reference this statement
Response: Thank you. We have referenced this statement (Page 2, line 25).

Lines 7-9, Page 7 of 19: Please reference the previous studies

Response: Thank you for your suggestions. we have revised the sample size calculations part of the manuscript and deleted the “previous studies” (Page 11, line 11).

Responses to reviewer 2

1. The introduction, background, clinical significance and objectives of the study are clearly explained under Introduction section.
Response: We appreciate your comment.

2. The objectives under Methods section are not detailed. They should specify the primary, secondary and exploratory aims separately. Under each, it should be clearly explained the key elements: ‘who’, ‘when’, ‘where’, ‘how’, ‘by what measure’.
Response: We appreciate your suggestions. We have added a part of ‘’specific objectives” in the manuscript. We stated the primary and secondary objectives separately according to the primary and secondary outcomes of the study (Page 4, line 4-22).

3. The study site (hospital) and duration of the study (2021-23) are not an inclusion criteria, and should move to the study settings.
Response: Thank you for your suggestion. We have added a section of “study design and setting” in the manuscript. We move the study site and duration of study to this part and deleted them from the inclusion criteria (Page 4, line 26-29; Page 5, line 1-2).

4. More detailed information about randomization (method of randomization, any stratification factor, sofeware, etc) should be provided. It seems that the randomization will be on site and in real time? This is how the randomization is read, needs more clarifications if that is not the case. I am also wondering why the randomization is not going to perform by an independent statistician prior to the study, and needs to be on-site and in real time? At least, I do not see any benefit.
Response: We appreciate your suggestions. We have revised the randomization section. Randomization will not be on site and in real time. It was done and kept by an independent statistician prior to the study (Page 6, line 22-24).

5. Randomization and blinding should be explained under two separate sections. In the current version, the blinding shortly described followed by randomization and again blinding is discussed. Easier to follow and read if they are discussed separately.
Response: Thank you for your comment. We have separately explained the randomization and blinding in two separate sections (Page 6, line 17-29).

6. Under Intervention section, the intervention should be explained only. Afterwards, Placebo with another sub-heading should be discussed.
Response: Thank you for your suggestions. We have separately explained the intervention and placebo in two separate sections (Page 5, line 19-26).

7. Under primary and secondary outcome sections, to be consistent with the study objectives mentioned earlier, the outcomes should be referred as efficacy/safety outcomes first. Then they should be defined in the current manner what such efficacy/safety would mean in this study.
Response: We appreciate your comment. In the outcome section, the primary outcome and secondary outcome are consistent with the study objectives mentioned earlier. We moved some outcomes to the “explored outcomes” following the “secondary outcomes”, including hospitalization length and costs, laboratory indicators (Page 8, line 19-29; Page 9, line 1-29; Page 10, line 1-15).

8. Primary outcome needs justification and citations. More specifically, they should highlight whether this is a good and objective outcome and has been established and used in other studies. The mentioned reliability and validity without reference is not scientifically valid. What is the justification of the primary outcome at “discharge”, where such time point may vary among the patients? It is not clear how the primary outcome will be treated under this section (unfavorable vs favorable).
Response: Thank you for your suggestions. Glasgow Outcome Scale – Extended (GOSE) is logistically simple, reliable, valid, stable and free to administer, and is widely recommended as the main outcome measure in studies of TBI. We cited the reference supporting these statements in the primary outcome section.
We also explained the discharge time point in this section. In our hospital, The discharge time will be determined by the neurosurgeon. A TBI patient will be allowed to discharge when meeting the following conditions: ① intracranial hematoma is in stable absorption phase; ② intracranial pressure (ICP) is stable, no more dehydration treatment is needed; ③ no more surgical treatment is needed; ④ severe complications (such as pneumonia) are controlled well; ⑤ incision is dry without infection and effusion (Page 8, line 20-29; Page 9, line 1-8).

9. Some of the secondary outcomes do not look like an “outcome”. For example, how ‘pre-op blood loss’ could be an outcome? This makes some of the secondary outcomes clinically irrelevant. More clinical input is required.
Response: We appreciate your comment. We revised the “peri-operative blood loss” into intraoperative blood loss. And explained the calculation method of blood loss (Page 9, line 10-15).

10. Secondary outcomes should be defined clearly. For example, what is the start and end date of length of hospitalization and what is its planned unit of measure? Or for hospitalization cost, it should be mentioned what kind of cost are planned to be included.
Response: We thank you for your comment. We defined the start and end date of the length of hospitalization. The planned unit of measure is day. The hospitalization costs include the total cost, drug costs, examination and laboratory costs and nursing costs. These will be analyzed separately (Page 10, line 3-5).

11. I would also suggest to collect pre-op GOSE data.
Response: We appreciate your comment. GOSE is always used to evaluate the clinical outcome for TBI patients. So we would not to collect the pre-op GOSE data. But we will collect Glasgow Coma Scale (GCS) data for every patients.

12. Are the study team planning to collect some data on the surgery (ex. Duration of surgery) itself?
Response: Thank you for your suggestions. The anesthesiologist in charge will record the patients’ intraoperative data, including blood pressure, heart rate, oxygen saturation, blood loss, urine volume, medicine, infusion volume, transfusion volume and operation time, et al. We explained this in the “Data collection and management” section (Page 11, line 26-28).

13. Sample size calculation is based on the primary outcome which is binary (unfavorable vs favorable). How come sample size was calculated using mean differences instead of proportion differences? Does “previous retrospective studies” refer to some publications? If so, this needs citations. If not and that refers to some pilot data, this should be clarified.There also should be some justification as whether such sample size is achievable based on clinical experience and the current number of monthly patients. No adjustment for potential/expected dropout rate?

Response: We appreciate the reviewer's comment. We have cited the unfavorable clinical outcome (GOS1~3) rate (42%-59%) of severe TBI patients reported by other studies. In our study, we used 54% based on our previous study. The research results of this previous study is not published yet (under review). We have added "Considering a 5% rate of loss to follow-up" and expanded the sample size of our study. We have added "There are approximately 40 TBI patients undergoing craniotomy in Beijing Tian Tan hospital every month. So such a sample size could be achieved in our study." in the sample size calculation section (Page11, line 10-21).

14. Statistical analysis plan should be revised substantially. More scientific statistical terms should be used (what is classified data or unordered outcome?). What variables are planned to be included in the multivariable analysis? What about clinical confounders? What about potential interactions? Strategy for handling missing data? How to analyze the several secondary outcomes? What is the strategy to avoid inflation in type-I error due to multiple comparisons?
Response: Thank you very much for your comments. We have consulted the statistician and revised the statistical analysis plan substantially. We deleted the nonstandard terms and used the scientific terms. We explained the detailed statistical method used to analyze every outcomes in this section (Page 12, line 12-29).

15. Potential issues over operation and over hospitalization should be mentioned and addressed.
Response: We thank you for your comment. We explained the adverse events and the solutions in the "Safety considerations, safety monitoring and adverse events (AEs) reporting" section. And in the discussion, we explained the potential safety issues might be involved in our study (Page 10, line 17-27; Page 15, line 2-13).

16. Citations are necessary where needed. For example, they should cite literature when talking about "standardized procedure" without further details. Of course this is just one example.
Response: Thank you for your suggestions. We have cited the literature in the "Anesthesia management" section (Page 7, line 17).

17. It is not mentioned whether any interim analysis is planned. If that's the case, it should be still justified why not. Same point about termination rules and futility analysis.
Response: We appreciate your comment. We do not have a plan to perform interim analyses. Therefore, we do not have stopping guidelines based on the results of interim analyses (Page 11, line 6-8).