PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol for a Systematic Review and Meta-Analysis of Long-Term Neurocognitive Outcomes in Paediatric Traumatic Brain Injury
AUTHORS	Looi, Dawn; Goh, Mark; Goh, Sharon; Goh, Jia Ling; Sultana, Rehena; Lee, Jan Hau; Chong, Shu-Ling

VERSION 1 - REVIEW

REVIEWER	Audrey McKinlay University of Canterbury
REVIEW RETURNED	24-Dec-2019

GENERAL COMMENTS	Thank you for the opportunity to review this manuscript which addresses an important topic that of long-term neurocognitive deficits associated with childhood traumatic brain injury. Overall the manuscript is clearly written and provides a reasonable introduction to the topic. There are some areas that require further justification and/or clarifications which are listed below: 1. The authors have used the age range of 0-18 years. Please justify this age range and clarify how outcomes will be evaluated for different age groups. 2. On page 7 line 22 the authors state that they will evaluate changes in neurcognitive outcomes over three defined time points. The first of these is 0-5 months does this mean that some of the studies will not be longitudinal? and how will this be managed? 3. The authors state that neurocognitive outcomes are chosen with reference to the DSM-V. However, studies are included from 1988 when the DSM-III was still being used. Some comment regarding the influence of this would be helpful for the readers. 4. It is not clear what the minimum criterion is for inclusion in the study nor how studies without a minimum inclusion will be managed. 5. It is not clear why studies with < 30 individuals can not be included in a meta-analysis? 6. The authors state on page 8 line 48 that the year of publication will span from 1988-2019. Understanding and definitions and methods of detecting brain damage for children has changed enormously over this time. Could the authors please clarify how these differences will be managed. 7. Could the authors please provide more information regarding the proposed narrative review. 8. Excluding authors who do not reply within one month appears somewhat arbitrary could the authors justify this. 9. On page 11 under Outcomes and Prioritisation there does not appear to be any consideration to the age of injury nor time since

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	injury. How will the authors manage this information? 10. The authors define controls as healthy typically developing children or orthopaedic patients could they clarify how they will manage studies that use different controls to those mentioned. The study limitations do not address some of the more difficult issues including age and mode of injury and time since injury. Thank you for the opportunity to review this protocol.

REVIEWER	Kelly Jones Auckland University of Technology, New Zealand
REVIEW RETURNED	20-Jan-2020

GENERAL COMMENTS	The authors present a carefully planned and detailed protocol for the systematic review and meta-analysis of long-term neurocognitive outcomes following paediatric traumatic brain injury (TBI). Use of latest DSM criteria is a strenght of the approach. The following recommendations are offered: Abstract: Clearly indicate that the review focuses on mild, moderate, and severe TBI. This is not currently stated. Introduction: It is suggested to keep the focus on paediatric TBI only. The third sentence should be replaced to report disability figures for children only (not children and adults combined). Too much emphasis is placed on an apparent certainty of functional difficulties and sequelae. The tone of the manuscript should reflect that the majority (90-95%) of all TBI are mild and that many children will fully recover without long-term consequences. As currently written, the manuscript gives the wrong and mis-leading impression that ALL children with TBI of any severity will experience numerous and significant long-term sequelae. Methods: This section is well-written with a good level of detail to enable replication of processes. More detail is required in some areas. Specifically, how will effect sizes be calculated (i.e. Cohen's d)? What will calibration exercises entail? Provide a clear justification for the time span included in the review. Be clear throughout that comparison groups will include well children or children with non-neurological single system injuries (only orthopaedic controls are mentioned earlier on page 7, for example). Discussion: Again, the authors are advised to use less inflammatory language about, for example, decreasing mortality. Again, most TBI are mild and many children will not live with "…long-term neurological sequelae" (page 13) and/or "…permanent and life-changing consequences of paediatric TBI…". (page 14) It is suggested that study findings may help neurorehabilitation professionals to select the best scales for assessment. Wouldn't it be preferable for professionals to be guided by available recommendations from dedicated working groups, such as common data elements recommended for paediatric TBI? Suggest to elaborate further or to revisit this point. Referring to neurodevelopmental delays should be avoided. It is not appropriate to assume that any declines in performance represent

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	developmental delays – has it been established that children's development is behind schedule? There are other possible explanations. For example, it may be that following TBI some children may be following a slightly different developmental pathway, for example. Related to previous comments about the tone of the manuscript, the first sentence of the conclusion is misleading ("Children who suffer from TBI develop irreversible neurocognitive deficits"). If this is the case, it would seem that the systematic review and meta-analysis are not required. This may be the case for some, but certainly not all children.

REVIEWER	Wan-Jie Gu Department of Anesthesiology, Nanjing Drum Tower Hospital, Medical College of Nanjing University, Nanjing 210008, China
REVIEW RETURNED	07-Feb-2020

GENERAL COMMENTS	The authors state that this protocol was registered with PROSPERO on 27 September 2019, registration number 152680. I search the protocol in PROSPERO with number but not find any record. Then I search using “Traumatic Brain Injury”in PROSPERO. No record is found.Please provide the correct number or website link.

REVIEWER	Davide Paolo Bernasconi School of Medicine and Surgery, University of Milano Bicocca, Italy
REVIEW RETURNED	07-Feb-2020

GENERAL COMMENTS	The protocol is complete, accurate and clearly written. The PRISMA-P guidelines are fully accomplished. The only suggestion I have is to describe how you will handle outcomes reported as median (interquartile range or range) instead of mean (sd). Perhaps using methods explained in Hozo, S.P., Djulbegovic, B. & Hozo, I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 5, 13 (2005). https://doi.org/10.1186/1471-2288-5-13. Also, write Glasgow Coma Scale explicitly the first time you mention the acronym (page 7, line 43).

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Audrey McKinlay

Institution and Country: University of Canterbury

Please state any competing interests or state ‘None declared’: None

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Please leave your comments for the authors below

Thank you for the opportunity to review this manuscript which addresses an important topic that of long-term neurocognitive deficits associated with childhood traumatic brain injury. Overall the manuscript is clearly written and provides a reasonable introduction to the topic. There are some areas that require further justification and/or clarifications which are listed below:

1. The authors have used the age range of 0-18 years. Please justify this age range and clarify how outcomes will be evaluated for different age groups.

Reply: We chose 0–18 years old because of precedence in literature. Eighteen years old is the lower limit of age set by medical insurers for paediatric care in the United States (Hardin A. et al, 2017). Head-injured children will be divided by age group (0 – 5 and 6 – 18 years old) and will be analysed using meta-regression if we have an adequate number of studies in each of these groups.

We made the following changes to the manuscript under Eligibility Criteria (Page 3, Line 18): "This is consistent with the lower age limit for insurance coverage for children in the United States and has been used to define the paediatric age group in literature.[16]" And also under Eligibility Criteria (Page 3, Line 23): " Provided we have sufficient studies, age groups (0 – 5 and 6 – 18 years old) will be evaluated using meta-regression. We chose these 2 age categories because most children would have begun formal education by 6 years old and they have greater utilization of language and metacognitive skills, that separate them from the 0 – 5 age group.[4]"

2. On page 7 line 22 the authors state that they will evaluate changes in neurocognitive outcomes over three defined time points. The first of these is 0-5 months does this mean that some of the studies will not be longitudinal? and how will this be managed?

Reply: The reviewer is correct. Many studies may only study the specific outcomes in one time frame, and not across all 3 time frames. We intend to pool outcomes within the specific time frames. For example, all studies that measure neurocognitive outcomes at 0-5 months will be analysed and then presented together, studies that measure neurocognitive outcomes at 6-23 months will be analysed and then presented together (and again for studies that measure Time 3 at 24 months and after).

We have made the following change to Objectives (Page 3, Line 9):

"Patients will be stratified by TBI severity. Quantifiable outcome measures will be pooled within each time frame as defined."

We made the following changes to the manuscript under Data Synthesis (Page 8, Line 28): "Studies that report long-term respective outcomes longitudinally will be pooled by timepoint to account for within-subject correlation. Outcome estimates will be compared by TBI severity (mild versus moderate versus severe)."

3. The authors state that neurocognitive outcomes are chosen with reference to the DSM-V. However, studies are included from 1988 when the DSM-III was still being used. Some comment regarding the influence of this would be helpful for the readers.

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Reply: We recognise that while DSM-V, being the most updated criteria, is being used for this systematic review and meta-analysis, many older studies were performed when DSM-III and DSM-IV were in force. However, their specific neurocognitive outcome domains overlap and can still be mapped onto the current DSM-V criteria.

We made the following changes to the manuscript under Outcomes and Prioritisation (Page 8, Line 6): "Studies that used previous DSM (DSM-III and DSM-IV) criteria for neurocognitive domains will be mapped to the current DSM-V criteria."

4. It is not clear what the minimum criterion is for inclusion in the study nor how studies without a minimum inclusion will be managed.

Reply: We specified under the Eligibility criteria that we would include studies that met all aspects of our eligibility criteria. Our inclusion criteria includes: population of 0–18 years old, exposure of TBI, with a reported outcome in at least one neurocognitive domain, a reported timepoint, a control group, sample size of at least 30 in TBI and control groups, published between 1988 and 2019, and study designs of systematic review, meta-analysis, cohort study, cross-sectional study, randomised controlled trial, case-control study..

We made the following change under Eligibility criteria (Page 5, Line 7): "Exclusion criteria includes animal studies, non-traumatic acquired brain injuries, neurocognitive outcomes that do not fall into the domains chosen, or small studies with a study population < 30 children in each TBI severity group."

5. It is not clear why studies with < 30 individuals cannot be included in a meta-analysis?

Reply: Studies with small sample sizes may have selection bias and their results may not be generalizable nor representative. (Dechartes A. et al, 2013). Hence we chose an arbitrarily sufficient sample size of 30 for this cut-off.

We made the following changes to the manuscript under Eligibility Criteria (Page 4, Line 24): "to prevent selection bias that may be present in small studies.[21-22]".

6. The authors state on page 8 line 48 that the year of publication will span from 1988-2019. Understanding and definitions and methods of detecting brain damage for children has changed enormously over this time. Could the authors please clarify how these differences will be managed.

Reply: We thank the reviewer for this important comment on how TBI detection and diagnosis have changed over time, especially with the availability of new imaging and biomarker capability (Carroll L. et al, 2004). In our study, we choose to take a broad clinical approach to the definition of TBI: "an alteration in brain function, or other evidence of brain pathology, caused by an external force…. "(Menon D. et al, 2010). If the authors diagnosed the injury as that of TBI, the study will be included. The severity is then determined clinically by Glasgow Coma Scale (consistent regardless of when the study was performed). Therefore, this broad definition holds true despite the above changes in TBI detection and diagnosis over time.

7. Could the authors please provide more information regarding the proposed narrative

review.

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Reply: The narrative will be written about the different types of neurocognitive measures used for TBI and how often each outcome measure is used for each cognitive domain. This is important to inform and update future researchers of commonly used platforms so that future trials will choose common outcome measures for common-speak.

We made the following changes to the manuscript under Data Synthesis (Page 9, Line 14): "A narrative synthesis will then be written about the different types of outcome measures used and how often these measures are used to measure the various cognitive domains over time."

8. Excluding authors who do not reply within one month appears somewhat arbitrary could the authors justify this.

Reply: In an article on Cochrane “How do authors respond to written requests for additional information?” by Guevara 2005, authors took a mean of 36.3 (38.2) days to respond via email. We rounded this down to a month to facilitate our workflow process.

We made the following changes to the manuscript under Data Management (Page 7, Line 21): "We will contact study authors to resolve any uncertainties. A reminder will be sent to the author in 3 weeks. Should the author not reply within 1 month, we will consider the study excluded.[29]”

9. On page 11 under Outcomes and Prioritisation there does not appear to be any consideration to the age of injury nor time since injury. How will the authors manage this information?

Reply: We will record the age of the child at the point of injury. The primary purpose of the study is to understand neurocognitive outcomes with respect to severity and time post-injury. We recognise that the age of the child should be taken into account, given that some studies have suggested that a brain injury sustained in a younger child has a less favourable outcome (Sarnaik A et al, 2018). We plan to do a meta-regression based on age (0-5, 6-18 years old) if we have sufficient studies that span the stated age groups (Babikian T et al, 2009).

We have made the following changes under Outcomes and Prioritisation (Page 7, Line 26): “Our primary outcome is to determine the progression of each neurocognitive domain over time as a result of mild, moderate and severe TBI. This will be done quantitatively, taking into account the age of the children at the time of injury (0–5 and 6–18 years old).[4] We will then perform a meta-regression by age if we have sufficient studies in both categories.”

We have made the following changes under Limitations (Page 12, Line 17): “We will collect information on important prognostic factors (e.g. age at time of injury and the mechanism of injury) and present this as part of the systematic review. However, we recognise that not all variables will be used to stratify the neurocognitive outcomes at the meta-analysis and will give priority to the severity of TBI and the time since injury”.

We have made the following changes under Data Synthesis (Page 9, Line 18): “If we have adequate studies, we will do an age-stratified subgroup analysis for each domain and timepoint.”

10. The authors define controls as healthy typically developing children or orthopaedic patients could they clarify how they will manage studies that use different controls to those mentioned.

Reply: Healthy controls were preferred over Orthopaedic Injury controls and were preferentially chosen if both control groups were present. We are able to combine healthy and Orthopaedic Injury control studies as research on the adult population found that both groups were comparable on all levels that were relevant to our study (Mathias J.L et al, 2013). If sufficient studies are available we

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will do a sensitivity analysis by stratifying healthy and orthopaedic injury patients to address this concern. Controls that are classified otherwise will be excluded (e.g., ADHD)

We made the following changes to the manuscript under Data Management (Page 7, Line 9): "The same information will also be extracted for the control group for the analysis. These controls include healthy children or children with non-neurological single-system injuries (e.g., children with only orthopaedic injuries). If healthy and orthopaedic injury controls are present, we will preferentially select the healthy control. Subsequently, studies with healthy and orthopaedic injury controls are combined.[28] Controls that are classified otherwise will be excluded (e.g., Attention Deficit Hyperactivity Disorder)."

The study limitations do not address some of the more difficult issues including age and mode of injury and time since injury.

Reply: We will account for the time since injury since the analysis specifically stratifies by time since injury. We will also include age at injury and mode of injury at the systematic review (descriptive) phase. We plan to do a meta-regression based on age (0-5, 6-18 years old) if we have sufficient studies spanning the stated age groups (Babikian T et al, 2009).

Under Limitations (Page 12, Line 17) we have clarified: “We will collect information on important prognostic factors (e.g., age at time of injury and the mechanism of injury) and present this as part of the systematic review. However, we recognise that not all variables will be used to stratify the neurocognitive outcomes at the meta-analysis and will give priority to the severity of TBI and the time since injury”

Under Outcomes and Prioritisation (Page 7, Line 26) we have clarified: “Our primary outcome is to determine the progression of each neurocognitive domain over time as a result of mild, moderate and severe TBI. This will be done quantitatively, taking into account the age of the children at the time of injury (0–5 and 6–18 years old).[4] We will then perform a meta-regression by age if there are sufficient studies in both categories.”

Thank you for the opportunity to review this protocol.

Reviewer: 2

Reviewer Name: Kelly Jones

Institution and Country: Auckland University of Technology, New Zealand

Please state any competing interests or state ‘None declared’: None declared.

Please leave your comments for the authors below

The authors present a carefully planned and detailed protocol for the systematic review and meta-analysis of long-term neurocognitive outcomes following paediatric traumatic brain injury (TBI). Use of latest DSM criteria is a strength of the approach. The following recommendations are offered:

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Abstract: Clearly indicate that the review focuses on mild, moderate, and severe TBI. This is not currently stated.

Reply: We thank the reviewer for this important addition to the Abstract.

We made the following change to the manuscript under Abstract Methods (Page 1, Line 14): "mild, moderate and severe TBI as determined by the Glasgow Coma Scale (GCS)".

Introduction: It is suggested to keep the focus on paediatric TBI only. The third sentence should be replaced to report disability figures for children only (not children and adults combined).

Too much emphasis is placed on an apparent certainty of functional difficulties and sequelae. The tone of the manuscript should reflect that the majority (90-95%) of all TBI are mild and that many children will fully recover without long-term consequences. As currently written, the manuscript gives the wrong and mis-leading impression that ALL children with TBI of any severity will experience numerous and significant long-term sequelae.

Reply: We thank the reviewer for helping us adjust our focus.

We made the following changes to the manuscript under Rationale (Page 2): removed “children and adults included”.

In order to better represent the potential for neurocognitive delays, we have made the following changes to the manuscript under Rationale (Page 2, Line 9): we have added “Children affected by TBI may experience a combination of cognitive, behavioural, and emotional sequelae.[3] While more than 80% of TBI cases are mild[1] and among these few sustain long-term neurocognitive impairments,[4] children with moderate and severe TBI show deficits that persist past a child’s developmental years into adulthood, affecting educational outcomes, employment outcomes, psychosocial functioning and quality of life.[4-6]”

Methods: This section is well-written with a good level of detail to enable replication of processes.

More detail is required in some areas. Specifically, how will effect sizes be calculated (i.e. Cohen's d)?

Reply: Standardised mean differences between TBI and comparator groups will be calculated using a random effects model. Random effects is subsequently mentioned in the paragraph.

We made the following changes to the manuscript under Data Synthesis (Page 8, Line 22): "All assigned cognitive outcome measures will be analysed separately. Each cognitive domain will be pooled and stratified by TBI severity and different timepoints. Studies will be pooled using the DerSimonian and Laird method[31-32] of inverse variance random effects standardised mean differences (SMD) between control and TBI severity groups. The pooled SMD with 95% Confidence Interval (CI) will be presented in forest plots. Studies that report long-term respective outcomes longitudinally will be pooled by timepoint to account for within-subject correlation. Outcome estimates will be compared by TBI severity (mild versus moderate versus severe). For studies that report cognitive outcomes for pre- and post- injury TBI groups, a separate analysis will be done, using paired standardised mean differences to pool the studies.”

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We made the following changes to the manuscript under Outcomes and Prioritisation (Page 8, Line 3): “Studies will be presented and compared to controls where healthy, typically developing children will be preferentially picked over single-system orthopaedic patients. When pre-injury data is present, we will perform a longitudinal design analysis.”

What will calibration exercises entail?

Reply: These exercises involved independent data extraction for separate reviewers on the same data sources followed by resolution of differences and development of a common understanding.

We made the following changes to the manuscript under Data Management (Page 7, Line 17): “The reviewers will extract data independently and in duplicate from each eligible study. To ensure consistency across reviewers, we will conduct training for all reviewers prior to the start of data extraction. We will do this by independent data extraction of separate reviewers on the same data sources followed by resolution of differences and development of a common understanding.”

Provide a clear justification for the time span included in the review.

Reply: We intend to update the meta-analysis performed by Babikian et al, in 2009 (Babikian T et al, 2009)

We made the following changes to the manuscript under Eligibility Criteria (Page 5, Line 2): ”We chose the year of publication based on our objective to update the meta-analysis performed by Babikian.[4] We also limited the earliest year of publication to 1988 (3 decades) to limit heterogeneity given the changes in identification and management of TBI.[4]”

Be clear throughout that comparison groups will include well children or children with non-neurological single system injuries (only orthopaedic controls are mentioned earlier on page 7, for example).

Reply: Comparison groups (healthy and orthopaedic injury) are now mentioned on page 4. We subsequently combined healthy and orthopaedic injury control studies as research on the adult population found that both groups were comparable on all levels that were relevant to our study (Mathias J.L et al, 2013).

We made the following changes to the manuscript under Data Management (Page 7, Line 10): "These controls include healthy children or children with non-neurological single-system injuries (e.g., children with only orthopaedic injuries). If healthy and orthopaedic injury controls are present, we will preferentially select the healthy control. Subsequently, studies with healthy and orthopaedic injury controls will be combined.[28]”

Discussion: Again, the authors are advised to use less inflammatory language about, for example, decreasing mortality. Again, most TBI are mild and many children will not live with “…long-term

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neurological sequelae" (page 13) and/or "…permanent and life-changing consequences of paediatric TBI…". (page 14)

Reply: We thank the Reviewer for this important point.

We made the following changes to the manuscript under Discussion (Page 10, Line 12): "The burden of paediatric TBI is increasing, as shown by rising hospital admission rates,[40] and increasing costs.[41] With improved trauma resuscitation and TBI management, mortality for severe TBI has decreased, but patients with both moderate and severe TBI often live with long-term neurological sequelae.[42] There is an urgent need to accurately define the devastating effects of paediatric TBI, especially those with moderate and severe TBI on short- and long-term neurocognition. Children with mild TBI often have good recovery, nevertheless, their neurocognitive outcomes over time deserve study and proper documentation." And (Page 11, Line 15) "This study has the potential to define the permanent and life-changing consequences that are more often found in moderate and severe paediatric TBI, to inform decisions made by policy-makers and government agencies." Under Conclusion (Page 12, Line 23): "Children who suffer from TBI, in particular moderate to severe TBI, suffer from neurocognitive deficits."

It is suggested that study findings may help neurorehabilitation professionals to select the best scales for assessment. Wouldn't it be preferable for professionals to be guided by available recommendations from dedicated working groups, such as common data elements recommended for paediatric TBI? Suggest to elaborate further or to revisit this point.

Reply: We thank the Reviewer for this important point. Indeed, we hope that this detailed and comprehensive assessment of neurocognitive outcomes will provide information for dedicated TBI work groups to make future decisions as to which common data elements are relevant and important for TBI research. While dedicated working groups may make recommendations based on various factors such as ease of assessment or accessibility to such tests, our paper provides a historical perspective on the more commonly used measures that allow for inter-study comparisons.

We made the following changes under Discussion (Page 11, Line 23): "This study will also enable us to understand how different neurocognitive scales are being used in various parts of the world. It can provide valuable data to dedicated TBI work groups when making future decisions on which common data elements are relevant and important for TBI research."

Referring to neurodevelopmental delays should be avoided. It is not appropriate to assume that any declines in performance represent developmental delays – has it been established that children's development is behind schedule? There are other possible explanations. For example, it may be that following TBI some children may be following a slightly different developmental pathway, for example.

Reply: We understand the Reviewer's concerns.

We made the following changes under Abstract Introduction (Page 1, Line 5): "Children who suffer from traumatic brain injury (TBI) are at risk of permanent brain damage and developmental deficits."

We made the following changes under Discussion (Page 10, Line 21): "A systematic appraisal is needed to understand these long-term neurocognitive deficits. Current limitations to individual studies include a great variability in the TBI severity, definition of neurocognitive deficits and outcome measures used."

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Related to previous comments about the tone of the manuscript, the first sentence of the conclusion is misleading ("Children who suffer from TBI develop irreversible neurocognitive deficits"). If this is the case, it would seem that the systematic review and meta-analysis are not required. This may be the case for some, but certainly not all children.

Reply: We thank the Reviewer for this important point.

We made the following changes under Conclusion (Page 12, Line 23): “Children who suffer from TBI, in particular moderate to severe TBI, suffer from neurocognitive deficits.”

Reviewer: 3

Reviewer Name: Wan-Jie Gu

Institution and Country: Department of Anesthesiology, Nanjing Drum Tower Hospital, Medical College of Nanjing University, Nanjing 210008, China

Please state any competing interests or state ‘None declared’: None declared.

Please leave your comments for the authors below

The authors state that this protocol was registered with PROSPERO on 27 September 2019, registration number 152680. I search the protocol in PROSPERO with number but not find any record. Then I search using “Traumatic Brain Injury”in PROSPERO. No record is found. Please provide the correct number or website link.

Reply: It was registered on 28/9/19 and has since been processed. The registration number is: CRD42020152680.

Reviewer: 4

Reviewer Name: Davide Paolo Bernasconi

Institution and Country: School of Medicine and Surgery, University of Milano Bicocca, Italy

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

The protocol is complete, accurate and clearly written. The PRISMA-P guidelines are fully accomplished.

The only suggestion I have is to describe how you will handle outcomes reported as median (interquartile range or range) instead of mean (sd). Perhaps using methods explained in Hozo, S.P., Djulbegovic, B. & Hozo, I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 5, 13 (2005). https://imsva91-ctp.trendmicro.com:443/wis/clicktime/v1/query?url=https%3a%2f%2fdoi.org%2f10.1186%2f1471%2d2288%2d5%2d13&umid=F6EEEFAA-9E4B-E105-ADFF-

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0E422F717D97&auth=6e3fe59570831a389716849e93b5d483c90c3fe4-553a247e88b7082b2836485c31a201977a42c041.

Reply: We thank the Reviewer for this important point. Cochrane states that the median is similar to the mean when the data distribution is symmetrical. We estimated the sample mean and standard deviation from sample size, median, range or interquartile range (Wan X. et al, 2014)(Luo D. et al, 2016)(Hozo S.P et al, 2005).

We made the following changes to the manuscript under Data Synthesis (Page 9, Line 6): "For outcomes reported as median (interquartile range or range) instead of mean (standard deviation), the median will be used to estimate the mean if the sample size is larger than 30 and there is no mention of the data being skewed.[33-36]

Also, write Glasgow Coma Scale explicitly the first time you mention the acronym (page 7, line 43).

Reply: We thank the Reviewer for this comment.

We made the following changes to the manuscript under Eligibility Criteria (Page 3, Line 27): “Glasgow Coma Scale (GCS) scores…”

VERSION 2 – REVIEW

REVIEWER	Kelly Jones Auckland University of Technology New Zealand
REVIEW RETURNED	16-Apr-2020

GENERAL COMMENTS	Thank you for your considered and detailed responses.

REVIEWER	Davide Paolo Bernasconi School of Medicine and Surgery, University of Milano Bicocca, Italy
REVIEW RETURNED	06-Apr-2020

GENERAL COMMENTS	All points raised in the previous review were fully adressed by the authors. Thank you.

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