

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Traumatic Brain Injury in England and Wales: prospective audit of epidemiology, complications and standardised mortality
<b>AUTHORS</b>	Lawrence, Thomas; Helmy, Adel; Bouamra, Omar; Woodford, Maralynn; Lecky, Fiona; Hutchinson, Peter

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Bernhard Walder Division of Anaesthesiology Departement of Anaesthesiology, Intensive Care and Clinical Pharmacology University Hospitals of Geneva Switzerland
<b>REVIEW RETURNED</b>	22-Apr-2016

<b>GENERAL COMMENTS</b>	<p>Major comments</p> <ol style="list-style-type: none"> <li>1. The authors presented a prospective observational and epidemiological study on moderate to severe TBI (based on AIS of head region (HAIS)) in England and Wales conducted between April 2014 and June 2015. Epidemiological studies are rare in this setting despite a high death rate. Repeated investigations in this domain are needed related to demographic changes (more older patients with TBI) and the changes of procedures and structures in high income countries (use of helicopters and establishment of trauma systems including trauma regions and dedicated trauma centres with neurosurgery).</li> <li>2. The study has some strengths. The most important is the use of a standardised mortality based on data collected between 2012 and 2015. A limitation is that this “prediction” model has not been validated in an external data base; but it seems to be a promising prediction model with very good ability of discrimination. A figure with the calibration of this prediction model would be a highly welcomed supplement.</li> <li>3. The actual presentation of the study has, however, some limitations and I propose to check the website “EQUATOR Network” and to use, for instance, the STROBE Statement for this study: 1. The method section must be structured, 2. Recruitments of patients should be described in more details, 3. Variables must be clearly defined (initial GCS is not a definition) and 4. The outcome must be clearly defined.</li> <li>4. There is a mix of two definitions to identify patients and to grade the severity of trauma: HAIS and GCS (initial?). The authors included, based on HAIS classification patients with serious, severe, critical and maximum TBI. Thereafter, the authors report on mild TBI (based on GCS criteria). This is very confusing! GCS has major limitations in the early management of TBI (Reith F 2015 and 2016,</li> </ol>
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	<p>or Zürcher M 2009) and I propose to present the data based on the HAIS classification. This would also avoid the problem of missing GCS data of about 5% and increase the validity of the presented data.</p> <p>5. The outcome was short-term mortality; a very important and highly valid outcome for the estimation of the quality of a trauma system. Two definitions were used (Figure 1): mortality at discharge or mortality at 30 days. It would be highly preferable to have only 1 clear definition, for instance, mortality at 30 days. At least, in the method section, the reader should be informed that X patients were followed up until discharge and Y patients until 30 days. Furthermore, length of hospital stay should be reported. The overall crude mortality of the included cohort should be reported as a post-traumatic complication (before standardisation); of interest would also be the mortality per HAIS 3, HAIS 4, HAIS 5 and 6 (if the authors change the concept of manuscript as proposed in point 4). The reporting of the crude mortality would increase comparison with other epidemiological studies performed recently in Europe.</p> <p>6. The discussion section needs to be structured based on established guidelines (website “EQUATOR Network” and to use, for instance, the STROBE Statement): a short paragraph on the key results (what is really your key results of your study?), interpretation of the data compared with other studies in similar settings in other high income countries (please, do not focus on the local British situation – BMJ online is an international journal). The paragraph on limitation should be more detailed and more complete. New results should not be presented in the discussion section (recruitment of patients).</p> <p>Minor comments</p> <p>1. Title: Based on the HAIS classification the authors included no patients with mild TBI. Therefore, my proposition is. Moderate to severe traumatic brain injury ....</p> <p>2. Introduction, first paragraph: There are published data suggesting that there is no improvement in outcome in the last years in the TBI setting (Stein SC, 2010). Please, add a sentence that balances your statement on improvement.</p> <p>3. Methods, results and discussion see points 3-6.</p>
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<b>REVIEWER</b>	Monish Maharaj Prince of Wales Hospital New South Wales Australia
<b>REVIEW RETURNED</b>	29-Apr-2016

<b>GENERAL COMMENTS</b>	<p>This Audit on adherence to guidelines in the setting of TBI across England and Wales is well written and I would recommend it for publication should some minor modifications be made.</p> <p>The attached file goes through my personal suggestions.</p>
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<b>REVIEWER</b>	Dr. Patrick Czorlich Department of Neurosurgery University Medical Centre Hamburg-Eppendorf Martinstr. 52
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	20246 Hamburg Germany
<b>REVIEW RETURNED</b>	04-May-2016

<b>GENERAL COMMENTS</b>	<p>Lawrence et al. present a comprehensive evaluation on traumatic brain injury (TBI) in England and Wales based on data taken from the Trauma Audit and Research Network (TARN) in a 15 month period. In my opinion, these kinds of reports are indispensable to evaluate the effectiveness of TBI treatment in connected regions and countries and therefore this work should be of particular interest to any physician dealing with TBI patients, especially in England and Wales.</p> <p>The manuscript is overall well written and I only have some minor points to address that might improve the manuscript:</p> <ol style="list-style-type: none"> <li>1) The authors describe in an appropriate way the evaluation and results of the Ps14n-Model. I think the manuscript could benefit from another table that summarizes the overall mortality (in total numbers and in percentages) in comparison to the expected mortality, providing the reader this additional important information.</li> <li>2) Abstract – Setting: I would add some more aspects the authors focused on and harmonize it with the results section of the abstract like the Ps14n model etc.</li> <li>3) Page 9 of 23, Line 18: I guess it should be Figure 4 instead of Figure 2.</li> <li>4) The manuscript is entitled “Traumatic Brain Injury in England and Wales....”. In some parts of the manuscript like the beginning of the discussion (Page 9 of 23, line 40) the authors talk about the United Kingdom (UK). The authors should harmonize this throughout the manuscript.</li> <li>5) The authors describe the very important aspect of inpatient complications. A description of the definitions and diagnostic pathways of aspiration or bronchopneumonia etc. in the methods section should be given to compare these findings with data from other trauma networks.</li> </ol> <p>I’m looking forward to upcoming future publications from the Trauma and Audit Research Network as the presented data have the potential to investigate a lot more associations in TBI research.</p>
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### VERSION 1 – AUTHOR RESPONSE

#### REVIEWER 1

##### Major comments

1. The authors presented a prospective observational and epidemiological study on moderate to severe TBI (based on AIS of head region (HAIS)) in England and Wales conducted between April 2014 and June 2015. Epidemiological studies are rare in this setting despite a high death rate. Repeated investigations in this domain are needed related to demographic changes (more older patients with TBI) and the changes of procedures and structures in high income countries (use of helicopters and establishment of trauma systems including trauma regions and dedicated trauma centres with neurosurgery).

2. The study has some strengths. The most important is the use of a standardised mortality based on data collected between 2012 and 2015. A limitation is that this “prediction” model has not between

validated in an external data base; but it seems to be a promising prediction model with very good ability of discrimination. A figure with the calibration of this prediction model would be a highly welcomed supplement.

Thank you for highlighting the importance of validation of the model. We have incorporated an additional figure in the appendix that addresses the quality of calibration.

3. The actual presentation of the study has, however, some limitations and I propose to check the website “EQUATOR Network” and to use, for instance, the STROBE Statement for this study: 1. The method section must be structured, 2. Recruitments of patients should be described in more details, 3. Variables must be clearly defined (initial GCS is not a definition) and 4. The outcome must be clearly defined.

Thank you for this helpful suggestions. We have updated the manuscript methods section to incorporate additional comments from the STROBE guidelines e.g. comment on bias. We have explicitly defined GCS and have added some detail on the outcome metrics.

4. There is a mix of two definitions to identify patients and to grade the severity of trauma: HAIS and GCS (initial?). The authors included, based on HAIS classification patients with serious, severe, critical and maximum TBI. Thereafter, the authors report on mild TBI (based on GCS criteria). This is very confusing! GCS has major limitations in the early management of TBI (Reith F 2015 and 2016, or Zürcher M 2009) and I propose to present the data based on the HAIS classification. This would also avoid the problem of missing GCS data of about 5% and increase the validity of the presented data. We agree that we have complicated the selection of patients by incorporating a two stage identification of patients. Head AIS is used in the first instance as we have complete data on AIS in TARN. This makes it explicit and transparent how many TBI patients we have in the TARN registry. However, GCS is the clinically relevant metric that clinicians are familiar with and on which they base decisions. The limitations of GCS are well rehearsed in the literature and we comment on them specifically in the limitations section of the discussion, nevertheless, it remains the established and pragmatic method for stratifying TBI severity. Furthermore, it is a key component of our standardized mortality model and limiting ourselves to head AIS data would not therefore solve the issue of missing data.

5. The outcome was short-term mortality; a very important and highly valid outcome for the estimation of the quality of a trauma system. Two definitions were used (Figure 1): mortality at discharge or mortality at 30 days. It would be highly preferable to have only 1 clear definition, for instance, mortality at 30 days. At least, in the method section, the reader should be informed that X patients were followed up until discharge and Y patients until 30 days. Furthermore, length of hospital stay should be reported. The overall crude mortality of the included cohort should be reported as a post-traumatic complication (before standardisation); of interest would also be the mortality per HAIS 3, HAIS 4, HAIS 5 and 6 (if the authors change the concept of manuscript as proposed in point 4). The reporting of the crude mortality would increase comparison with other epidemiological studies performed recently in Europe.

Tables of crude mortality by GCS definition are provided – we have also provided this by Head AIS in appendix. We hope this provides the necessary transparency and clarity required.

6. The discussion section needs to be structured based on established guidelines (website “EQUATOR Network” and to use, for instance, the STROBE Statement): a short paragraph on the key results (what is really your key results of your study?), interpretation of the data compared with other studies in similar settings in other high income countries (please, do not focus on the local British situation – BMJ online is an international journal). The paragraph on limitation should be more detailed and more complete. New results should not be presented in the discussion section (recruitment of patients).

The key results are summarized in the ‘Article Summary’ as per BMJ open author guidelines. We

presume the reviewer refers to Walder et al J Neurotrauma 2013, and have included this reference.

#### Minor comments

1. Title: Based on the HAIS classification the authors included no patients with mild TBI. Therefore, my proposition is. Moderate to severe traumatic brain injury ....

As commented on above, although we accept that GCS has its various limitations, it remains the clinically relevant parameter. On this basis we are including patients with mild TBI (GCS 14,15).

2. Introduction, first paragraph: There are published data suggesting that there is no improvement in outcome in the last years in the TBI setting (Stein SC, 2010). Please, add a sentence that balances your statement on improvement.

Many thanks for pointing out this paper. We have read it carefully, however, it reinforces the secular trend in reduced mortality from TBI over time. We have referenced it as suggested.

3. Methods, results and discussion see points 3-6.

#### REVIEWER 2

Setting: Please add the number of centres across England and Wales that data was collected from. The data presented is from 187 hospitals of which 26 are neurosurgical centres on which the funnel plot is based. This is made explicit in manuscript.

Results: Line 21 there is an extra space after "...3 hours."

Thank you.

Conclusion: Line 26, there is a double space in between "...and suggests equity" and then again between "...in England."

Thank you.

#### Manuscript

Introduction: No changes necessary.

Materials and Methods: No changes necessary Results:

With the significant proportion of patients aged 80-90, I would like to see the impact of age on transfer times and complications rates (ideally stratifying the data into groups), similar to what is done with the GCS figures provided. As you have mentioned the elderly population are more likely to develop complications and in general have poorer complications – is this the case with the dataset?

We have provided additional data in the supplementary information to address this point, with a breakdown of transfer time and complications by age bracket. This demonstrates that older patients are not delayed in their transfer, and that younger patients (0-10 years) are delayed but have fewer complications.

If it is possible, I believe a comparison of the complication rates with the non-transferred patients would also supplement the recommendations given by the present NICE guidelines.

We have provided this additional information in the supplementary data.

In terms of complication rates, it is necessary to report the number of patients who suffered multiple complications, as there is a chance that the majority of patients with complications actually suffer from multiple complications (eg, bronchopneumonia and sepsis). Consider reporting the median number of complications suffered stratified by both age/severity.

Discussion:

The majority of the discussion is well written. Pg 10

1. Line 22 – Sentence beginning “A recent publication.”

a. Please expand on the findings of this study and their methodology (eg. What were the parameters they analysed?)

2. Line 55 – “...CT brain scan for medium risk GCS15 patients:

a. Please define “medium risk”

This is a specific reference to the classification within the NICE head injury guidelines for CT imaging (referenced). We have removed the word ‘medium’ in case this is not widely understood outside the UK.

Further questions to answer in discussion:

1. Are there any limitations considering the data is limited to patients with a hospital stay >3d? Could this be contributing to why the majority of centres fall slightly below the expected outcome on the funnel plot?

The initial data used to generate the model is collected in the same fashion (ie in those with >3d hospital stay. This is not a reason for expected outcomes to fall outside the funnel plot. As the funnel plot illustrates 95% and 99.7% confidence intervals, we would expect 5% of units to lie between the 2sd and 3sd lines.

The 3 day stipulation applies to survivors and those not transferred and admitted to critical care

2. I would like to see more information about the impact of indirect patients (patients entered into the dataset that are not transferred). Is there any evidence that they do poorer across

complications rates? This could raise questions regarding the necessity of transfer in the first place, as most of these smaller facilities do still have access to a MDT.

We have provided a breakdown of complications in those patient’s transferred and not transferred.

The complications are higher in the transferred group is higher, however, this is confounded by the likelihood that these patients were more unwell and therefore required specialist intervention.

3. There needs to be further discussion surrounding the funnel plot. Why do the majority of centres fall below the expected outcome?

This is an important point, that we are unable to definitively address based on the data we present. Even if there are changes in referral patterns over time, one would expect the multivariate model to account for strong predictors of mortality. If one excludes the low volume centres to the left of the funnel plot, it appears that the centres on the right are more closely clustered, and the differences are likely to be statistical noise.

4. I would also like a short statement regarding the contents of the NICE guidelines, do the authors recommend any modifications to improve the state of TBI care?

We have included a statement reflecting this point. The purpose of the NICE guidelines is to encompass as wide a range of presentations as possible and provide safe advice to those who may have little or no specialist knowledge. This includes all head injury rather than specifically Traumatic Brain Injury (TBI). It makes recommendations about time to CT and transfer of severe TBI to specialist care and we have presented the relevant adherence figures within this report. NICE is yet to develop a guideline for the more specific aspects of TBI care (time to craniotomy, ICP) but may do so in the future.

Conclusions:

You have mentioned the CRASH and IMPACT studies in the conclusion with no formal discussion of them prior throughout the manuscript. As they are significant studies, please share their findings and design in the background section of the manuscript.

We have incorporated this suggestion into the background section.

REVIEWER 3

Please leave your comments for the authors below

Lawrence et al. present a comprehensive evaluation on traumatic brain injury (TBI) in England and Wales based on data taken from the Trauma Audit and Research Network (TARN) in a 15 month period. In my opinion, these kinds of reports are indispensable to evaluate the effectiveness of TBI treatment in connected regions and countries and therefore this work should be of particular interest to any physician dealing with TBI patients, especially in England and Wales.

The manuscript is overall well written and I only have some minor points to address that might improve the manuscript:

1) The authors describe in an appropriate way the evaluation and results of the Ps14n-Model. I think the manuscript could benefit from another table that summarizes the overall mortality (in total numbers and in percentages) in comparison to the expected mortality, providing the reader this additional important information.

Overall mortality is now provided in the supplementary information.

2) Abstract – Setting: I would add some more aspects the authors focused on and harmonize it with the results section of the abstract like the Ps14n model etc.

Thank you.

3) Page 9 of 23, Line 18: I guess it should be Figure 4 instead of Figure 2.

Thank you.

4) The manuscript is entitled “Traumatic Brain Injury in England and Wales....”. In some parts of the manuscript like the beginning of the discussion (Page 9 of 23, line 40) the authors talk about the United Kingdom (UK). The authors should harmonize this throughout the manuscript.

Thank you. In some circumstances, UK is the appropriate designation, for example for SBNS membership.

5) The authors describe the very important aspect of inpatient complications. A description of the definitions and diagnostic pathways of aspiration or bronchopneumonia etc. in the methods section should be given to compare these findings with data from other trauma networks.

These complications were submitted by the local hospitals. No over-arching definition was provided. This is not designated as ‘self-reported’ in the manuscript.

I’m looking forward to upcoming future publications from the Trauma and Audit Research Network as the presented data have the potential to investigate a lot more associations in TBI research.

Thank you.

**VERSION 2 – REVIEW**

<b>REVIEWER</b>	Monish Maharaj Coffs Harbour Base Hospital, Australia
<b>REVIEW RETURNED</b>	03-Jul-2016

<b>GENERAL COMMENTS</b>	<p>Thank you for addressing prior concerns regarding the manuscript. I am satisfied with the current submission and recommend its acceptance for publication.</p> <p>Out of interest I would like some basic analysis on the impact of direct admission vs transfer on the complication rates. This is of particular importance as if those admitted directly have superior outcomes across all domains (complication rates, LOS etc) your publication could be used as evidence for future health policy advocating immediate transfer to specialised neurosurgical units - as</p>
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	is seen in some countries with spinal cord injuries.
<b>REVIEWER</b>	Patrick Czorlich University Medical Center Hamburg-Eppendorf Department of Neurosurgery Martinistr. 52 20246 Hamburg Germany
<b>REVIEW RETURNED</b>	19-Jun-2016

<b>GENERAL COMMENTS</b>	<p>The authors present a thorough revision of the manuscript responding to nearly all aspects mentioned by the reviewers.</p> <p>Nevertheless I still have some points to address:</p> <p>1) The point of time of assessment of the GCS has to be clear (i.e. at place of accident, at admission to trauma centre). This aspects seems very important to me.</p> <p>2) Thank you for presenting additional information on mortality in relation to the GCS and HAIS in Table 5 of the supplementary files. In severe TBI (GCS and HAIS) the observed mortality was certainly statistical significant higher than the predict mortality. The authors should respond to these findings in the discussion section. What might be the reasons for this finding? Might pre-hospital intubation has any influence mortality and early outcome like discussed by recently published studies?</p> <p>3) Like reviewer 1 I think to assess the short-term outcome is very important. The authors should consider if the manuscript would benefit by removing the 30-day outcome as these data are only available when patients are alive (see Table 5). The length of hospital stay and assessment of early outcome at discharge is practice in other TBI databases.</p> <p>Once again I´m looking forward for upcoming manuscripts from TARN.</p>
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### VERSION 2 – AUTHOR RESPONSE

Reviewer: 3

The authors present a thorough revision of the manuscript responding to nearly all aspects mentioned by the reviewers.

Nevertheless I still have some points to address:

1) The point of time of assessment of the GCS has to be clear (i.e. at place of accident, at admission to trauma centre). This aspects seems very important to me.

This is at the time of admission to the emergency department and has been made clear in the manuscript.

2) Thank you for presenting additional information on mortality in relation to the GCS and HAIS in Table 5 of the supplementary files. In severe TBI (GCS and HAIS) the observed mortality was certainly statistical significant higher than the predict mortality. The authors should respond to these

findings in the discussion section. What might be the reasons for this finding? Might pre-hospital intubation have any influence on mortality and early outcome like discussed by recently published studies?

The reviewer is correct to identify that the predicted mortality is 36% and the actual value is 40% (38.7 – 42.1% 95% CI). This may well be an artefact of the model as the model is calibrated to work across the entire population, hence the similarity between the expected and predicted values overall however it is not calibrated for specific groups (there's also an excess of survivors in the mild TBI group). We have clarified this in the appendix to incorporate your suggestion.

3) Like reviewer 1 I think to assess the short-term outcome is very important. The authors should consider if the manuscript would benefit by removing the 30-day outcome as these data are only available when patients are alive (see Table 5). The length of hospital stay and assessment of early outcome at discharge is practice in other TBI databases.

Please accept our apologies for not making this clearer. The outcome is measured at 30 days or discharge, whichever is sooner. We have stated this explicitly at the end of the methods section.

Once again I'm looking forward for upcoming manuscripts from TARN.

Reviewer: 2

Reviewer Name  
Monish Maharaj

Institution and Country  
Coffs Harbour Base Hospital, Australia

Please state any competing interests or state 'None declared':  
none declared

Please leave your comments for the authors below  
Thank you for addressing prior concerns regarding the manuscript. I am satisfied with the current submission and recommend its acceptance for publication.

Out of interest I would like some basic analysis on the impact of direct admission vs transfer on the complication rates. This is of particular importance as if those admitted directly have superior outcomes across all domains (complication rates, LOS etc) your publication could be used as evidence for future health policy advocating immediate transfer to specialised neurosurgical units - as is seen in some countries with spinal cord injuries.

We have added an additional table (6) to the supplementary information that compares complication rates in these two groups, and referenced it in the main text of the manuscript.