PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Prognostication in critically ill patients with severe traumatic brain injury: The TBI-Prognosis multicenter feasibility study
AUTHORS	Turgeon, Alexis; Lauzier, François; Zarychanski, Ryan; Fergusson, Dean; Leger, Caroline; McIntyre, Lauralyn; Bernard, Francis; Rigamonti, Andrea; Burns, Karen E. A.; Griesdale, Donald; Green, Robert; Scales, Damon; Meade, Maureen; Savard, Martin; Shemilt, Michele; Paquet, Jérome; Gariépy, Jean-Luc; Lavoie, André; Reddy, Kesh; Jichici, Draga; Pagliarello, Giuseppe; Zygun, David; Moore, Lynne

VERSION 1 - REVIEW

REVIEWER	David Harrison, Senior Statistician Intensive Care National Audit & Research Centre, UK
REVIEW RETURNED	30-Sep-2016

GENERAL COMMENTS	The authors are to be congratulated on achieving such high levels of adherence and 100% follow-up of neurological outcomes to 6 months in such a difficult patient population. As such they have clearly demonstrated that the planned study is feasible. The introduction would benefit from a brief overview of the organisation of major trauma care, neurosurgery and neurocritical care in Canada. Given the high level of follow-up achieved, the methods would benefit from some expansion to describe how this was achieved and the workload involved. How many phone calls were required? Were these made by a single central team or by the individual sites? Were phone calls made during working hours only or also out-of-hours and at weekends? Importantly, as this is a feasibility study, will the approach be scalable to the larger study? The main implication of the study is in the potential impact of non-recruitment of patients presenting out-of-hours and at weekends - both in terms of the speed of recruitment to the larger study and also on the representativeness of the population recruited to the future study if this is not addressed. We have previously demonstrated (in the UK) substantial variation in the epidemiology of patients presenting to critical care following acute TBI by day and time of presentation [Harrison D et al. Health Technol Assess 2013; 17(23)]. Minor comments 1. The STROBE statement recommends that dates of recruitment should be reported and not just duration

	2. The text states that GCS was assessed at ICU admission but in Table 1 this is described as "GCS in ER" - could you clarify? 3. The text states that "Compliance to tests was measured according to the survival status during the time window in which the test was scheduled", however all reported compliance figures appear to have a denominator of 50. Do you therefore mean by this that dead patients were reported to be compliant? Would it not be a fairer evaluation of compliance to also remove dead patients from the denominator? 4. You say that using deferred consent in all centers is "one of the avenues considered" to address 24/7 recruitment in the larger study. However, you also state that the larger study is ongoing so did you do this or not do this?

REVIEWER	ZHANGJIE SU 1. Department of Neurosurgery, University Hospitals Birmingham NHS Foundation Trust, UK 2. School of Clinical and Experimental Medicine, University of Birmingham, UK
REVIEW RETURNED	17-Oct-2016

GENERAL COMMENTS	Outcome prediction has been a challenging filed in traumatic brain injury (TBI) and numerous studies has tried to address this issue but with results of wide variation. Currently the most recognized and widely applied prognostic calculators are the CRASH and IMPACT models. This study assessed the feasibility of conducting a large, multicentre prospective study to develop a prognostic model to inform long-term functional outcome in patients with severe TBI. Comments: In Introduction: References #11-13 for “Serious concerns have been expressed regarding early decisions made to withdraw life-sustaining therapies in absence of evidence-based prognostic information” are all quite old (1995, 1999 and 2001). Are there any more up-to-date literature expressing these concerns since now we have more evidence-based prognostic models such as CRASH and IMPACT calculators? Reference #26 did consider secondary brain injury in TBI so please remove it from the reference list for “retrospective studies that did not consider secondary brain injury. [3, 16-20, 22, 23, 26-28]”. I appreciate that “The development of appropriate prognosis tools and models is necessary to help guide the decision making process with families”. Now that we have the CRASH and IMPACT prognostic calculators established and widely applied, could you please indicate the difference between the ongoing large-scale, multicentre study and those established prognostic models (i.e. CRASH and IMPACT), and the potential changes in practice or outcome prediction you envisage based on this difference? In Methods: Did you recruit TBI patients with blunt-force trauma only?

	"Data were collected daily from intensive care unit admission". Those data that were collected daily in ICU, were they the pupillary reactivity, corneal reflex, episodes of increased ICP, hypoxemia and hypotension, or anything else? If so, could you please indicate the daily frequency of such data collection in the Methods session, and also mention any missed collection/reporting of those in the Results session? In Results: Please also indicate at which time point(s) blood sampling and blood sample shipment were missed. As previously mentioned in the Abstract "The overall study adherence was 96%", please elaborate how this was calculated because it was not detailed in the Results session. In Interpretation: As "personnel oversight" was the other main reason for non-enrollment, could you please elaborate on this and mention anything implemented to overcome such oversight in order to improve enrollment? Please indicate the estimated sample size and how it was calculated for completing the ongoing "large multicentre prospective cohort study informed by the results of this pilot feasibility study". The sample size and completing time frame for the large study should be realistic and practically achievable base on the enrollment rate and protocol compliance or study adherence from this pilot study.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name
David Harrison, Senior Statistician

Institution and Country
Intensive Care National Audit & Research Centre, UK

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

Please leave your comments for the authors below
The authors are to be congratulated on achieving such high levels of adherence and 100% follow-up of neurological outcomes to 6 months in such a difficult patient population. As such they have clearly demonstrated that the planned study is feasible.

The introduction would benefit from a brief overview of the organisation of major trauma care, neurosurgery and neurocritical care in Canada.
-We thank the reviewer and added a sentence describing the Canadian health care system in which the study was conducted (see end of the introduction section: 'The study was conducted in the Canadian health care system in which trauma, neurosurgery and critical care are part of a public system with universal health care coverage for all citizens.').

Given the high level of follow-up achieved, the methods would benefit from some expansion to describe how this was achieved and the workload involved. How many phone calls were required? Were these made by a single central team or by the individual sites? Were phone calls made during working hours only or also out-of-hours and at weekends? Importantly, as this is a feasibility study, will the approach be scalable to the larger study?
-We appreciate the comment from the reviewer and added a section in the methods to describe the research team at participating centers. A research team at each center was responsible for the coordination of the study locally, including follow-ups. We did not collect the granular information on the number of phone calls required or the exact time of these phone calls. However, we know that the majority were done during working hours. We added this information in the manuscript. See new sections: 'research team at participating centers'; 'start-up meeting'; 'central coordination and data monitoring', and additios/changesn in the 'data collection' section.

The main implication of the study is in the potential impact of non-recruitment of patients presenting out-of-hours and at weekends - both in terms of the speed of recruitment to the larger study and also on the representativeness of the population recruited to the future study if this is not addressed. We have previously demonstrated (in the UK) substantial variation in the epidemiology of patients presenting to critical care following acute TBI by day and time of presentation [Harrison D et al. Health Technol Assess 2013; 17(23)].
-Indeed, the impact of non-recruitment of patients presenting out-of-hours and on week-ends is an important observation made in our feasibility study. We added the reference to the above mentioned study in the manuscript (new reference # 39).

Minor comments

1. The STROBE statement recommends that dates of recruitment should be reported and not just duration
-Dates of recruitment were added to the manuscript.

2. The text states that GCS was assessed at ICU admission but in Table 1 this is described as "GCS in ER" - could you clarify?
-We agree that the information was misleading and have corrected the manuscript. The GCS was considered following resuscitation and stabilization. We removed the mention to the ER to avoid confusion. See 'eligibility criteria' section.

3. The text states that "Compliance to tests was measured according to the survival status during the time window in which the test was scheduled", however all reported compliance figures appear to have a denominator of 50. Do you therefore mean by this that dead patients were reported to be compliant? Would it not be a fairer evaluation of compliance to also remove dead patients from the denominator?
-The goal of this feasibility study was not to evaluate whether patients survived long enough to get all tests performed, but rather to ensure the feasibility of performing these planned tests when alive.

4. You say that using deferred consent in all centers is "one of the avenues considered" to address 24/7 recruitment in the larger study. However, you also state that the larger study is ongoing so did you do this or not do this?
-Using a deferred consent approach in all centers for the large-scale study was one of the avenues considered and the one we chose.

Reviewer: 2

Reviewer Name
ZHANGJIE SU

Institution and Country
1. Department of Neurosurgery, University Hospitals Birmingham NHS Foundation Trust, UK
2. School of Clinical and Experimental Medicine, University of Birmingham, UK

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

Please leave your comments for the authors below
Outcome prediction has been a challenging filed in traumatic brain injury (TBI) and numerous studies has tried to address this issue but with results of wide variation. Currently the most recognized and widely applied prognostic calculators are the CRASH and IMPACT models. This study assessed the feasibility of conducting a large, multicentre prospective study to develop a prognostic model to inform long-term functional outcome in patients with severe TBI.

Comments:

In Introduction:

References #11-13 for “Serious concerns have been expressed regarding early decisions made to withdraw life-sustaining therapies in absence of evidence-based prognostic information” are all quite old (1995, 1999 and 2001). Are there any more up-to-date literature expressing these concerns since now we have more evidence-based prognostic models such as CRASH and IMPACT calculators?
-These references are among the first ones having expressed these concerns and highlight the fact that this issue has not been taken care of for years. We kept these references but added a recent one (new ref # 14 – Muehlschlegel et al. Neurocrit Care 2016).

Reference #26 did consider secondary brain injury in TBI so please remove it from the reference list for “retrospective studies that did not consider secondary brain injury. [3, 16-20, 22, 23, 26-28]”.
-We thank the reviewer for his thorough review. Reference 26 has been removed from the reference list.

I appreciate that “The development of appropriate prognosis tools and models is necessary to help guide the decision making process with families”. Now that we have the CRASH and IMPACT prognostic calculators established and widely applied, could you please indicate the difference between the ongoing large-scale, multicentre study and those established prognostic models (i.e. CRASH and IMPACT), and the potential changes in practice or outcome prediction you envisage based on this difference?
-The CRASH and IMPACT prognostic models were not designed to help guiding the decision-making process. These models were designed using data from admission or data collected within the very early phase of injury thus not considering secondary cerebral injuries. The models also used limited prognostic indicators (limited clinical data, no MRI, no electrophysiological tests, no serum biological marker). As such, these models are suboptimal to be used as part of the clinical decision making process on level of care at the bedside. A multimodal approach using different prognostic tests (including imaging and electrophysiology), the evolution of this data over time, the performance of the tests according to a structured planned schedule not as per clinical indication, will allow reaching a greater level of accuracy, but more so, will better represent the clinical environment when assessing prognosis in critically ill patients with severe TBI.

In Methods:

Did you recruit TBI patients with blunt-force trauma only?
-Yes.

"Data were collected daily from intensive care unit admission". Those data that were collected daily in ICU, were they the pupillary reactivity, corneal reflex, episodes of increased ICP, hypoxemia and hypotension, or anything else? If so, could you please indicate the daily frequency of such data collection in the Methods session, and also mention any missed collection/reporting of those in the Results session?
-We clarified the daily data collection process in this section. We added information on the collection of clinical daily data in the results section. See new section in the results: 'compliance to the daily clinical data collection'

In Results:

Please also indicate at which time point(s) blood sampling and blood sample shipment were missed.
-We added this information in the results section. There was one missing blood sample at day 7. See section 'compliance to the test procedures'.

As previously mentioned in the Abstract "The overall study adherence was 96%", please elaborate how this was calculated because it was not detailed in the Results session.
-We removed this sentence in the abstract since it was confusing with the compliance to the protocol of tests.

In Interpretation:

As "personnel oversight" was the other main reason for non-enrollment, could you please elaborate on this and mention anything implemented to overcome such oversight in order to improve enrollment?
-The oversight by the personnel was something we did not expect and it was attributed to the important workload or late admissions to the ICU (only noticed the following day). To avoid this situation, we ensured that the screening process was done more than once a day and highlighted the importance of organizing workload to not miss patients.

Please indicate the estimated sample size and how it was calculated for completing the ongoing "large multicentre prospective cohort study informed by the results of this pilot feasibility study". The sample size and completing time frame for the large study should be realistic and practically achievable base on the enrollment rate and protocol compliance or study adherence from this pilot study.
- The purpose of this feasibility study was to evaluate the feasibility of conducting a larger scale study based on the compliance to the schedule of tests, which we considered the main potential barrier to achieving a multicenter study. We added information on the sample size of the large-scale TBI-Prognosis study and the planned period of enrolment in the discussion section (see end of the discussion section). The larger scale study will be presented in more details in a future manuscript.

VERSION 2 – REVIEW

REVIEWER	David Harrison, Senior Statistician Intensive Care National Audit & Research Centre, UK
REVIEW RETURNED	09-Dec-2016

GENERAL COMMENTS	I thank the authors for addressing my previous comments. The manuscript is much improved. I have a couple of points outstanding, where perhaps I could have been clearer in the original review: 1. With regard to the organisation of trauma services, I am aware that Canada has a publicly funded healthcare system and was rather seeking further information on trauma services specifically. For example, in England, major trauma services, including neurosurgery, are regionalised and delivered through a network of 26 designated Major Trauma Centres. In sites providing neurosurgery, neurocritical care is delivered either in a dedicated neurocritical care unit (approximately half of sites) or in a combined neuro/general critical care unit. 2. With regard to compliance, I was not suggesting that patients who had died should be considered non-compliant with the measurement schedule but rather that they should be removed from the calculation of compliance entirely, i.e. compliance = number of patients who had the measurement performed divided by total number of patients alive at that time point. For example, it appears from Fig 3 that for MRI, in addition to the 3 patients for whom the test was missed, a further 9 patients had died. Therefore the compliance would be 38/41=93% and not 96% as reported.

REVIEWER	ZHANGJIE SU 1. Department of Neurosurgery, University Hospitals Birmingham NHS Foundation Trust, UK 2. School of Clinical and Experimental Medicine, University of Birmingham, UK
REVIEW RETURNED	27-Dec-2016

GENERAL COMMENTS	The authors have addressed all my comments appropriately. Some minor revisions are required, such as the incomplete sentence "This study was conducted" in Study Design under Methods, and the reference format of citation number 14 in the Reference section.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Harrison, David
ICNARC

Please leave your comments for the authors below
I thank the authors for addressing my previous comments. The manuscript is much improved. I have a couple of points outstanding, where perhaps I could have been clearer in the original review:

1. With regard to the organisation of trauma services, I am aware that Canada has a publicly funded healthcare system and was rather seeking further information on trauma services specifically. For example, in England, major trauma services, including neurosurgery, are regionalised and delivered through a network of 26 designated Major Trauma Centres. In sites providing neurosurgery, neurocritical care is delivered either in a dedicated neurocritical care unit (approximately half of sites) or in a combined neuro/general critical care unit.

-We agree with the reviewer that this information is very relevant. The Canadian trauma system is an

integrated system with care delivered through 10 provincial health care systems. ICUs are mainly combined neuro/general units. We added a few sentences in the methods to better reflect this reality.

2. With regard to compliance, I was not suggesting that patients who had died should be considered non-compliant with the measurement schedule but rather that they should be removed from the calculation of compliance entirely, i.e. compliance = number of patients who had the measurement performed divided by total number of patients alive at that time point. For example, it appears from Fig 3 that for MRI, in addition to the 3 patients for whom the test was missed, a further 9 patients had died. Therefore the compliance would be 38/41=93% and not 96% as reported.

-We agree with the reviewer that there are different ways of presenting this data. For clarity and ease of comprehension, we prefer presenting the data using the whole denominator for each test in the manuscript. We however present the data in figure 3 thus allowing the reader to appreciate the whole dataset.

Reviewer: 2
Su, Zhangjie
Queen Elizabeth Hospital Birmingham, Neurosurgery

Please leave your comments for the authors below
The authors have addressed all my comments appropriately. Some minor revisions are required, such as the incomplete sentence "This study was conducted" in Study Design under Methods, and the reference format of citation number 14 in the Reference section.

-Thanks for notifying this. We made the changes in both the methods and for ref 14.