STUDY PROTOCOL

REVISED An international, prospective observational study on traumatic brain injury epidemiology study protocol: *GEO-TBI: Incidence*

[version 2; peer review: 2 approved]

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Abstract

Background

The epidemiology of traumatic brain injury (TBI) is unclear – it is estimated to affect 27–69 million individuals yearly with the bulk of the TBI burden in low-to-middle income countries (LMICs). Research has highlighted significant between-hospital variability in TBI outcomes following emergency surgery, but the overall incidence and epidemiology of TBI remains unclear. To address this need, we established the Global Epidemiology and Outcomes following Traumatic Brain Injury (GEO-TBI) registry, enabling recording of all TBI cases requiring admission irrespective of surgical treatment.

Objective

The GEO-TBI: Incidence study aims to describe TBI epidemiology and outcomes according to development indices, and to highlight best practices to facilitate further comparative research.

Design

Multi-centre, international, registry-based, prospective cohort study.

Subjects

Any unit managing TBI and participating in the GEO-TBI registry will be eligible to join the study. Each unit will select a 90-day study period. All TBI patients meeting the registry inclusion criteria (neurosurgical/ICU admission or neurosurgical operation) during the selected study period will be included in the GEO-TBI: Incidence.

Open Peer Review

Approval Status ✓ ✓

	1	2
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Any reports and responses or comments on the article can be found at the end of the article.

Methods

All units will form a study team, that will gain local approval, identify eligible patients and input data. Data will be collected via the secure registry platform and validated after collection. Identifiers may be collected if required for local utility in accordance with the GEO-TBI protocol.

Data

Data related to initial presentation, interventions and short-term outcomes will be collected in line with the GEO-TBI core dataset, developed following consensus from an iterative survey and feedback process. Patient demographics, injury details, timing and nature of interventions and post-injury care will be collected alongside associated complications. The primary outcome measures for the study will be the Glasgow Outcome at Discharge Scale (GODS) and 14-day mortality. Secondary outcome measures will be mortality and extended Glasgow Outcome Scale (GOSE) at the most recent follow-up timepoint.

Keywords
epidemiology, global, registry, traumatic brain injury

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REVISED **Amendments from Version 1**

We have made the amendments suggested by the reviewers' expert comments on our manuscript as well as some minor typographical changes. Most notably, the site questionnaire (Table 1) was updated to assess the availability of intracranial pressure monitoring and hypertonic fluids in the management of TBI patients.

Any further responses from the reviewers can be found at the end of the article

Introduction

Traumatic brain injury (TBI) is a growing global health concern due to increasing and ageing populations in LMICs and high-income countries (HICs) respectively[1]. Despite the importance of TBI epidemiology in informing health service planning, research priorities, and public health policy, this remains poorly understood. TBI is estimated to affect 27–69 million people every year, although data from LMICs is scarce[1,2].

The Global Neurotrauma Outcomes Study (GNOS) has recently demonstrated country- and hospital-level differences in the case mix, management, and outcomes of surgically treated TBI[3]. Of note, outcome variability between countries was almost entirely accounted for by their human development index (HDI). Highlighting opportunities to influence outcomes by identification and replication of best practice, significant between-hospital outcome variation was described within countries[3].

To elucidate the observed differences in TBI epidemiology, case-mix and outcomes, and to pave the way for comparative effectiveness research, systematic data collection of all TBI patients is needed[4]. To address this need, the Global Epidemiology and Outcomes following Traumatic Brain Injury (GEO-TBI) registry has been established. The registry is an international collaboration for recording TBI, with the core dataset focusing on injury mechanisms, initial presentation, interventions, and short-term outcomes. Any centre treating TBI is welcome to join the registry, and further information on protocols and documentation is available on the registry website.

The *GEO-TBI: Incidence* is the first collaborative study to run on the GEO-TBI registry. It is a multi-centre, international, prospective observational study, that aims to describe global TBI epidemiology based on real-world clinical data using the core dataset of the GEO-TBI registry via a snapshot design – all TBI patients admitted to the local hospital during a 90-day window will be included in the study. It is expected that data collection will be continued after the conclusion of the initial collection period as part of the GEO-TBI registry collaborative.

Objectives

Primary objective

1) Describe the epidemiology of TBI using primary clinical data and compare outcomes of TBI between Human Development Index (HDI) tiers.

Secondary objectives

2) Examine differences in patient demographics, mechanisms of injury, and baseline clinical characteristics alongside indications, means and outcomes of TBI management.

3) Establish an international benchmark as a basis to compare outcomes in future clinical audits, epidemiological and intervention effectiveness research.

4) Compare the settings and resources of TBI management with regard to development indices.

5) Demonstrate the feasibility of collaborative registry data collection in an international setting and encourage ongoing prospective data collection.

6) Expand and empower the international network of neurotrauma professionals to conduct collaborative TBI research.

Roles, responsibilities and authorship

Central study team

A team of lead investigators from the NIHR Global Health Research Group on Neurotrauma will be responsible for co-ordinating the *GEO-TBI: Incidence* study.

Local study team

Each participating institution will form a local study team consisting of the senior study lead, data collectors, optional additional members and an independent data validator. The validator will work independently to the rest of the local team and will perform local data validation after its collection as outlined under *Data capture and validation*. Local teams may consist of a mix of surgeons, physicians, research associates and/or trainees. On centre registration, a Data Sharing Agreement outlining data processing will be formulated and the participant site profile questionnaire (Table 1) will be completed by the centres.

Authorship

The GEO-TBI registry follows the International Committee of Medical Journal Editors criteria for authorship. In addition, all members of the local study teams will be listed individually as PubMed-citable GEO-TBI collaborators in any central reporting output. In any other manuscripts arising from the GEO-TBI dataset (such as participant centre-initiated projects), members of the local teams who participated in the corresponding project should be listed as authors or PubMed-citable collaborators. In any publications arising from GEO-TBI-based data, it is expected that the GEO-TBI collaboration is acknowledged.

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Table 1. Participant site profile questionnaire.

Centre details	
Institution name:	
Institution address:	
Institution country:	
Local registry team members	Local registry lead/contact person
	Full name:
	E-mail:
	Contact number:
	Local data validator
	Full name:
	E-mail:
	Contact number:
	Full names and e-mails of other local team members:
Centre characteristics	
Healthcare level of your centre:	Primary/Secondary/Tertiary
Do you consider your hospital rural or urban?	Rural/Urban
Does your centre manage only adults, only children, or both?	Adults only/Children only/Both
Do patients have to pay for the care they receive at your centre?	Yes, all of it/Yes, some of it/No, none of it
Early management of TBI	
How do TBI patients arrive to your hospital?	Ambulance (including HEMS), staffed by doctor(s) Ambulance (including HEMS), staffed by paramedics Ambulance (including HEMS), staffed by non-medical practitioners Car, staffed by non-medical practitioners Other, what?
Does your centre have a trauma team who immediately assesses seriously injured patients upon their arrival to your hospital?	All of the time Most of the time Some of the time Never
Do you have at least one CT scanner in your hospital?	Yes No
Is there constant access to a CT scanner in your hospital?	Yes No If no: is there a nearby institution you can send patients to for emergency CT imaging? Yes No
In your hospital, TBI is managed by: (tick all that apply)	Neurosurgeons General surgeons NCCU/ICU/anaesthetists General practitioners Other, who?

Operative management of TBI				
How many fully trained neurosurgeons are employed by your institution?				
How many cranial neurosurgical procedures are performed in your institution per year?				
Do you have access to the following in cranial neurosurgery?	Yes, for all cases	Yes, for most cases	Yes, for some cases	Never
High-speed drill				
Diathermy (monopolar and/or bipolar)				
Haemostatic agents				
Perioperative management of TBI				
Does your centre have an intensive care unit (ICU)?	Yes No			
Number of ICU beds for adult neurosurgery patients (if your institute only treats paediatric patients, enter 0)				
Number of ICU beds for paediatric neurosurgery patients (if your institute only treats adult patients, enter 0)				
How would you best describe the ICU that TBI patients are admitted to in your institution?	Neurosurgical ICU Neurotrauma ICU Neurological/neurosciences ICU Trauma ICU Surgical ICU Medical ICU General ICU			
Does your institution have a separate paediatric ICU?	Yes No, paediatric TBI patients are managed in the same ICU as adult patients We do not manage paediatric TBI			
Do you have access to an ultrasound machine in your ICU?	Yes No			
How often are the following available for the treatment of TBI patients in your hospital?	All of the time	Most of the time	Some of the time	None of the time
Invasive intracranial pressure monitoring				
External ventricular drain (ventriculostomy)				
Mechanical ventilator				
Invasive blood pressure monitoring (arterial line)				
Central venous pressure monitoring (central line)				
End-tidal CO_2 monitoring (capnography)				
Intravenous fluids				
Hypertonic saline				
Mannitol				
Other hypertonic solutions				
Do you have a preferred hypertonic solution, i.e., do you only use one/several hypertonic solution(s) over the others for TBI patients?				
Tranexamic acid				

Sedatives				
Muscle relaxants				
Opiates				
Anticonvulsants				
Vasopressors				
Inotropes				
Red blood cell transfusion				
Platelet transfusion				
Arterial blood gas testing				
Blood electrolyte testing				
Full blood count				
Clotting tests				
Chest radiograph				
Parenteral feeding				
Enteral feeding (NGT or PEG)				
TBI rehabilitation				
Do TBI patients have access to the following during their rehabilitation phase?	All of the time	Most of the time	Some of the time	None of the time
Physiotherapist				
Occupational therapist				
Neuropsychologist				
Speech and language therapist				
Dietician				
Rehabilitation medicine physician				
Do TBI patients undergo follow-up in your hospital?	Yes No If Yes, how many TBI patients are followed up? 0–25% 25–50% 50–75% 75–100%			
Who conducts TBI patients' follow-up?	Neurosurgeons NCCU/ICU/anaesthetists Trauma surgeons General surgeons Neurologists General practitioners Other, who?			

Volume data	
Catchment population	
Catchment area	km^2
Estimated admissions per year due to: Mild TBI Moderate TBI Severe TBI Estimated operations per year due to TBI:	

Menon, Midhun Mohan, Wellingson Paiva, Kee Park, Andres Rubiano, Vijaya Sekhar, Hamisi Shabani, Kachinga Sichizya, Davi Solla, Manjul Tripathi, Abenezer Tirsit, Sara Venturini

- Honorary Advisory Panel – Bart Depreitere, Corrado Iaccarino, Laura Lippa, Andrew Reisner, Gail Rosseau, Franco Servadei, Rikin Trivedi, Vicknes Waran

Data ownership, processing and storage

Data ownership remains with the participating centres in accordance with the GEO-TBI protocol. As per the GEO-TBI protocol, data is processed on behalf of the participating unit by Orion MedTech CIC (a not-for-profit organisation) independently of the central study team. Data will be collected and stored on a secure online platform (https://orion.net) aggregate data will be shared with the central study team to enable analysis as outlined in the Data Sharing Agreement. Collection of identifiable data is supported by the platform, but not required in order to participate to *GEO-TBI: Incidence* or the GEO-TBI registry in general. If identifiable data is decided to be collected by the participating units, any identifying data will be kept strictly confidential and accessible only for local use. A detailed explanation is available in the GEO-TBI registry protocol.

Local collaborators will be given access to their own data after completion of the study to enable comparison of local practice with regional or international standards. Named collaborators will be able to request access to the entire data set or a subset of the data to perform post-hoc analyses to answer a defined research question. The study dataset will also be included in the aggregated core registry data reports and benchmarking.

Methods

Inclusion criteria

Centre inclusion criteria

Any hospital or clinic worldwide offering acute TBI treatment (surgical and/or non-surgical) and participating in the GEO-TBI registry will be eligible to join the study.

Patient inclusion criteria

All adult and paediatric patients admitted to the participating institution with a traumatic brain injury during the selected 90-day inclusion period are eligible for inclusion in the *GEO-TBI: Incidence* study. The inclusion criteria are the GEO-TBI core registry criteria:

- Clear history of recent trauma leading to TBI

AND at least one of:

- Neurosurgical admission with TBI
- Intensive care unit (ICU) admission with TBI
- Neurosurgical procedure(s) for TBI

Patient exclusion criteria

Patients receiving elective (planned admission) procedures or admission.

Data set

The GEO-TBI registry core dataset (Table 2) will be collected on all patients admitted to the participating unit due to TBI during in the study period. The collected data consists of 3 sub-sections – injury/admission data, operative data and outcome data. The dataset was formed via an international iterative consensus-based approach comprising an initial face-to-face meeting between a network of neurotrauma professionals from LMICs and HICs, an international survey to ensure usefulness and feasibility of the dataset in a variety of healthcare settings, and a final consensus meeting to define the final dataset. A publication outlining this process and the registry protocol is currently under peer review.

Each institution lead will be asked to fill out a questionnaire on resources available for neurotrauma care and rehabilitation in their healthcare setting. Finally, the data will be validated by the local independent validator as described under *Data capture and validation*.

Duration of study

Local study teams can select any 90-day period as their data input period. From the date of their injury, teams must follow patients up for a minimum of two weeks. For example, if a team selects the 1st of March 2023 as their start date then they must include all patients who meet the inclusion criteria between then and the 30th of April 2023. Functional outcomes at the date of last follow-up will also be included as a secondary measure.

Table 2. The Global Epidemiology and Outcomes following Traumatic Brain Injury (GEO-TBI) Case Report Form.

Demographic data	
Name	Surname, forename
Date of birth	dd.mm.yyyy
Sex	Male/female
Unique patient ID number	CHI number/NHS number/National patient identifier
Hospital	Choose from participating hospitals
Injury data	
Date and time of injury	dd.mm.yyyy, hh:mm
Mechanism of injury	Select one: Fall: level/<2m/≥2m Vehicle collision: car/motorcycle/pedestrian/bicycle/other Assault: firearm/blade/blunt Blast Not otherwise specified: occupational/recretional/self-harm/other/unknown
Primary intracranial injury	Select one: Scalp injury Fracture of skull vault Base of skull fracture Compound fracture of skull Concussion Diffuse brain injury Focal brain injury or contusion Extradural haematoma Acute subdural haematoma Chronic subdural haematoma Traumatic subarachnoid haemorrhage Traumatic intraventricular haemorrhage Injury to cranial nerve Unspecified injury to head No secondary intracranial injury
Secondary intracranial injury	
Presence of major extracranial injury	Yes/No
Initial GCS *	Eye, Verbal, Motor: 1–4, 1–5, 1–6, respectively
Pupil reactivity *	Left, right: Yes/No/Unassessable
Focal neurological deficit	Yes/No/Unassessable
ASA grade	I–V
Secondary transfer	Yes/No
Systolic blood pressure prior to resuscitation	Millimetres of mercury, option for unknown
SpO2 prior to resuscitation	%, option for unknown

Imaging data	
No imaging performed	Tick if no imaging
	If imaging performed:
Date of initial CT head	dd.mm.yyyy
Imaging pathology present	Select if present:
	Extradural haematoma Subdural haematoma Contusion Fracture Intraventricular blood Traumatic subarachnoid haemorrhage
Midline shift on initial CT	Millimetres
Obliteration of basal cisterns	Select one: Normal Compressed Absent
Admission data	
Date and time of hospital admission	dd.mm.yyyy, hh:mm
Pre-hospital intubation	Yes/No
Treatment	Non-operative management only If operatively managed, select if conducted: Washout or debridement (including penetrating injury) ICP monitoring EVD Burrhole(s) Fracture elevation Craniotomy Craniectomy Posterior fossa decompression Other surgical procedure
Intracranial infection during admission	Yes/No
Intubation †	Yes/No If Yes: Dates of intubation & extubation or tracheostomy (dd.mm.yyyy) Extubation Tick one: Independent ventilation/tracheostomy/terminal
Intensive care unit admission	Yes/No If Yes: Dates of ICU admission & discharge dd.mm.yyyy
In-hospital mortality	Yes/No If No: Glasgow Coma Scale at hospital discharge Eye, Verbal, Motor: 1–4, 1–5, 1–6, respectively

Glasgow Outcome at Discharge Scale	1-8
Date of hospital discharge	dd.mm.yyyy
Outcome data	
Date of assessment	dd.mm.yyyy
Extended Glasgow Outcome Scale	1–8

* Initial GCS and pupil status: after resuscitation, pre-intubation or at presentation if not intubated.

† Intubation other than solely for surgery. For example, if the patient was only intubated for intraoperative anaesthesia (e.g. surgery of subdural and epidural haematomas causing only mild neurological impairment). If the patient was kept intubated postoperatively, they should be recorded as intubated.

Outcome measures

Primary outcome

The primary outcome measures for the study will be 14-day mortality and the Glasgow Outcome Scale at Discharge (GODS)[5]. The GNOS study demonstrated 14-day mortality as a useful and feasible outcome measure for data collection in a comparable setting comprising both LMICs and HICs[3], and the GODS system has been validated by McMillan and colleagues to be a robust predictor of post-discharge recovery with capability to compensate for loss to follow-up[5].

Secondary outcomes

Glasgow Coma Scale (GCS) at hospital discharge.

Intracranial infections during the admission.

Length of stay in hospital and intensive care.

GOSE at latest follow-up.

Data capture and validation

Data capture

Collected data will be stored exclusively on a secure web-based registry system within the Orion platform described earlier The platform enables the secure data collection, validation and storage in a standard (SQL) format and is compliant with NHS security standards (including the Information Governance toolkit). The feasibility of data collection was confirmed in an internal pilot.

Data validation

Data validation will occur by two mechanisms:

- Web-based forms in the registry will contain fixed options at the point of data entry to maximise the likelihood of accurate and complete data capture from the outset.
- A local data validator independent of the local study team will be appointed at every participating site. After the 90-day study period chosen by the local team has ended, the data validator will be asked to retrospectively identify all patients admitted to their hospital during the 90-day period and complete the Data Validation Form (Table 3).

Table 3. Data validation form. To ensure the epidemiological quality of the GEO-TBI data, the local data validator is requested to fill the below fields using an alternative information source such as hospital records, theatre logbooks or institutional reports.

Centre name:	
Number of admissions due to TBI during the year:	
Number of operations due to TBI during the year:	
Source of information:	

Standards of care

Epidemiology

The overall mortality after surgically and non-surgically managed TBI is not well known. Studies with differing methodologies suggest highly varying estimates of the worldwide yearly TBI incidence. Extrapolating data from road traffic injuries, Dewan *et al.* suggest that between 64–74 million TBIs occur yearly with the highest incidence in Northern America and Europe, whereas the absolute TBI burden was found to be highest in resource-poorer regions[2]. A review based on the Global Burden of Disease Study 2016 suggested a TBI incidence of 27 million/year, but noted that this is probably an underestimate, as the results were derived predominantly from hospital-based sources[1]. Indeed, 70–90% of treated TBI (presenting to secondary care) is of mild severity, which probably represents 17–30% of all mild TBI[6,7]. A survey study showed that the incidence of TBI varied from <1% in China to almost 15% in Mexico suggesting a broad range of incidence rates across both LMICs and HICs[8]. There is a consensus that the incidence of TBI is likely increasing – in HICs due to population ageing[9], and in LMICs due to increasing motorisation leading to more road traffic injury-related TBIs[10]. The Lancet Neurology Commission on TBI reported that an international consensus is needed on standardised epidemiological monitoring of TBI to allow the measurement of its incidence and mortality as well as comparison of access to care[11]. The GEO-TBI collaboration is a step towards this direction.

Mortality

Data on TBI outcomes in relation to development indices is scarce. Data from GNOS confirmed previous reports indicating that most surgically managed TBIs in HICs are severe, but mild-to-moderate TBI is more prevalent in the medium and low HDI tier countries[3]. Furthermore, the pathologies varied in relation to the HDI tiers, patient age and injury mechanisms. Surgeries in very high and high HDI tier countries were conducted more commonly due to acute subdural haematomas, whereas epidural haematomas and skull fractures were more common in medium and low HDI tier countries, respectively.

Correspondingly, patients were oldest in higher HDI countries and youngest in low HDI countries – falls were the most common cause of injuries in HICs, whereas road traffic accidents and violence were the prominent mechanisms in medium and low HDI tiers, respectively[3], which corresponds with research discussed under *Epidemiology*. Most between-country variation in TBI surgery outcomes was explained by HDI[3].

In GNOS, fourteen-day mortality following emergency surgery for severe TBI was 33% in very high HDI tier countries, 31% in high HDI tier, 43% in medium HDI tier and 27% in low HDI tier countries[3], which is in line with previous research suggesting a long-term mortality of 30% in HICs, but in contrast to earlier results indicating a mortality of 51% in LMICs for severe TBI[12]. The mechanism behind this difference is unclear – it is possibly related to country-level differences in patient selection for surgery and pre-hospital management of TBI. This highlights the rationale for the *GEO-TBI: Incidence* study to help elucidate the basis for this discrepancy.

Incidence of TBI in individual unit catchment areas during a consecutive 90-day period will be determined. To account for case mix and interventions, a logistic regression model will be constructed. In the model, patient-, institution- and country-level confounders are adjusted for. Patient-level confounders include age, GCS, pupillary reactivity, major extracranial injury; the hospital in which the patient is managed is the institution-level confounder; and country-level confounders include the country and its HDI tier.

Time from injury to imaging

The UK National Institute of Clinical Excellence (NICE) guidelines for investigation of suspected clinically significant acute head injuries suggests that such patients should be assessed on arrival in the emergency department, and a CT head should be conducted within one hour of arrival[13]. A large European dataset showed that a shorter time from TBI leading to GCS 9-12 to CT head scan was associated with reduced time to intervention and ED stay times, but not with mortality or worse outcomes[14].

Time from injury to intervention

Mortality after trauma craniotomy increases sharply, if the procedure is conducted more than four hours after injury[15,16]. In GNOS, the median delay from injury to intervention was eight hours. The median delays from injury to admission, admission to operation and injury to operation were highest in low HDI tier countries, and lowest in high HDI tier countries with significant HDI tier-related variation. Importantly, even in the very high HDI tier, the time from injury to surgery exceeded four hours in half of such cases – in the low HDI tier, the lower quartile times in all of the above categories were four hours or longer[3].

Infections

Post-craniotomy infection rates in recent large studies have been reported to be 5–7%[17,18]. In GNOS, the surgical site infection rate was 3%, though the 14-day follow-up period is probably not sufficient to characterise the total incidence of surgical site infections.

GOSE

The GOSE is not a sufficient measure of neurological outcome after the 14-day follow-up applied in the *GEO-TBI: Incidence* study. On the other hand, long-term follow-up may be altogether infeasible in certain settings. Therefore, the GOSE will be measured at the most recent available follow-up as a secondary outcome. GOSE scores typically increase within the first year after moderate-to-severe TBI patients[19], but seem to plateau in longer-term follow-up[20].

Analysis

Statistical advice was provided by the MRC Biostatistics Unit, University of Cambridge. We plan to stratify the countries in which the participating units are situated in relation to their HDI index (very high, high, medium and low) as defined by the United Nations[21] and successfully applied in the GNOS and the GlobalSurg studies[3,22,23]. The HDI is a tri-dimension composite measure comprising life expectancy index, education index and gross national income index, that consist of life expectancy at birth, expected and mean years of schooling, and GNI per capita, respectively.

Participating centres will be stratified based on their country into four groups based on their Human Development Index (HDI) rank, similar to the approach successfully used by the GlobalSurg studies[16,17]. The Human Development Index is calculated for each country based on life expectancy at birth, years of schooling, years of schooling and gross national income (GNI) per capita.

Limitations

The GNOS highlighted disparities in case-mix and outcomes after emergency surgery for TBI, but it was not designed to assess the epidemiology of TBI, an area deficit of robust information. Data on TBI epidemiology may be used to inform different stakeholders, such as patients, care providers and policymakers, and to eventually guide data-driven decision-making and funding allocation. Indeed, the unavailability of data may impede funding opportunities as reports are commonly required by international funding providers and universities. Furthermore, the *GEO-TBI: Incidence* will form a basis for ongoing auditing and research intiatives as part of the GEO-TBI registry, and aims to provide insight to guide comparative effectiveness research. However, the methodology of the *GEO-TBI: Incidence* will not allow for evaluation of TBI that does not result in a hospital admission.

All data and results must be interpreted in the context of the participating units' healthcare setting – for example, long-term follow-up may not be feasible in all settings. The epidemiological representativeness of the data depends on case ascertainment into the online registry. As such, the dataset was formed following an international consensus of neurotrauma care providers and it was kept sufficiently concise, while still capturing the most pertinent variables.

Approval

This study, as well as the GEO-TBI registry, will measure current practice and will not introduce any changes to current patient care. A part of the GEO-TBI registry, local

approvals for the reporting of anonymised aggregate data will already be in place as part of the core registry enrolment process.

Data availability

No data are associated with this article.

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Open Peer Review

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Version 1

Reviewer Report 07 September 2023

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✔ **Ping K Yip**
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The proposed study by Joannides and colleagues is the creation of an epidemiological international, prospective observation study on traumatic brain injury (TBI), termed GEO-TBI. The idea is good and currently, different countries collect data that are too variable to be meaningful for cross comparison, so this will benefit an understudied and underfunded medical issue that affects millions worldwide. There are some comments suggested to my opinion would improve the study:

1. If the study intents to obtain a global representation of patients, I suggest they should include a representative from east Asia countries such as China, Mongolia, Taiwan, Japan or South Korea as there are no authors located in these countries. China is particularly important as they have a population of over a 1.4 billion.

2. In table 1, there seems to be a missing intracranial-pressure (ICP) monitoring and EVD listing. Chestnut et al., (DOI: 10.1056/NEJMoa1207363) questioned the need for ICP monitoring at 20 mmHg or less, so this study would be able to examine this.

3. In table 1, authors should split mannitol and hypertonic saline into 2 separate rows as still unsure which is better. This would provide opportunity to examine this information.

4. In table 2, sex was labelled male and female. How about transgender person?

5. In table 2, does the table allow for multiple intracranial injury to be selected? Important as some patients may experience multiple intracranial injuries.

6. In table 2, suggest adding an extra row for pre-injury medications (if known) such as anticoagulants as drug and/or disease (e.g. diabetes) can exacerbate the brain injury that could contribute to unfavourable outcomes.

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Yes

Are the datasets clearly presented in a useable and accessible format?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: I have over 65 peer-reviewed publications in the field of neuroinjury in in vitro, in vivo and human studies. One of my current research fields is on traumatic brain injury, involving animal models, patient biosamples, and analysis of large clinical data sets.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 24 Apr 2024

Tommi Kalevi Korhonen

We thank the reviewer for their insightful comments on our study protocol. We have actioned their suggestions in the registry project. These improvements will undoubtedly enhance the quality of the Incidence study, as well as future collaborative research conducted on the GEO-TBI platform.

1. The GEO-TBI: Incidence study aims to obtain a view of the global TBI burden. We agree that participation from East Asia will significantly benefit the study. We are happy to announce that three units in China have expressed interest in participating in the study. We would like to note that the author list and registry working group includes representation from Malaysia and the Philippines. We are continuing efforts to further promote this co-operative project to other Asian as well as African and South American centres, and warmly welcome interested clinicians and researchers to join the collaboration.

2. We thank the reviewer for this accurate remark – ICP monitoring is perhaps the most central modality in current neurointensive care of TBI, and its availability should be included in the site questionnaire. We have added the availability of ICP monitoring and EVD to Table 1 as well as to the electronic site questionnaire sent to each centre at the commencement of data collection.

3. We thank the reviewer for this suggestion, which will increase the granularity of data collection on hyperosmolar therapy following TBI. We have divided the Hypertonic solutions variable to *Hypertonic saline*, *Mannitol* and *Other hypertonic solutions* in Table 1 and the electronic site questionnaire. This will provide important contextual

information on availability of the solutions, which is particularly interesting with regard to the ongoing Sugar or Salt (SOS) trial.

4. The GEO-TBI registry objectives, inclusion criteria and variables were chosen in a consensus-based process (1). *Gender* was suggested to be added to the registry dataset in the GEO-TBI establishment survey (Supplementary Table 1 in (1)) – wording was evaluated in detail in the scoping workshop and the registry consensus meeting. The variable was changed to *sex* to explicitly refer to sex assigned at birth due to the difficulty in accurately recording *gender* from potentially unconscious TBI patients, which would be based on external characteristics and thus potentially inaccurate.

   We agree that it would be interesting to study gender-related differences in TBI epidemiology and the GEO-TBI would be a natural framework for such research – proposed research questions are warmly welcomed to the participant-initiated GEO-TBI research arm.

5. Only one type of primary intracranial injury and secondary intracranial injury can be chosen in the *Injury* form to describe the respective clinical significance of different types of simultaneous TBI. All (one or more) types of TBI independent of their clinical significance are recorded in the *Imaging* form to describe the extent of radiological TBI. Both the *Injury* and *Imaging* forms are described in Table 2 under the respective subheadings.

6. We agree with the reviewer that prior medications may be important confounding factors for TBI outcomes. However, given the difficulty of accurately recording pre-injury medications in the contemporary medical practice especially in LMICs, these variables were voted out from being included in the registry during the registry establishment consensus survey (1), and as such were not included in the study dataset.

We have added a reference to the recently published GEO-TBI registry core protocol (1) to the Introduction section.

References:
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Competing Interests: No competing interests were disclosed.

Reviewer Report 03 August 2023

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This paper describes the protocol for an international, prospective observation study on traumatic brain injury epidemiology. The paper is well written and the rationale and justification for the study is clear and well reasoned. The study methodology is sound and aligns with the objectives of the study. The description of the study protocol is explained well and will provide a useful scaffold for future work. My only feedback pertains to the structure of the study. I note that in the statistical analyses section, the authors outline current evidence pertaining to the epidemiology of TBI. I thought that this content was better suited in the introduction which provides the reader with more understanding of the current state of knowledge in this area.

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Yes

Are the datasets clearly presented in a useable and accessible format?
Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Traumatic brain injury

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 24 Apr 2024

Tommi Kalevi Korhonen

We thank the editor and the reviewer for their comprehensive assessment of the GEO-TBI: Incidence study protocol. We believe the reviewer's suggestions have led to substantial improvements in the protocol and will benefit the eventual results of the study.

As the reviewer correctly points out, we had outlined current TBI epidemiology and

standards of care under the *Statistical analysis* section. We have changed the order of these sections and renamed them more accurately as *Standards of care* and *Analysis* in the most recent version of the manuscript.

Competing Interests: No competing interests were disclosed.