BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-060679
Article Type:	Protocol
Date Submitted by the Author:	29-Dec-2021
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Keywords:	NEUROSURGERY, ACCIDENT & EMERGENCY MEDICINE, Neuroradiology < NEUROLOGY, Neurological injury < NEUROLOGY, Computed tomography < RADIOLOGY & IMAGING

Stockholm score of lesion development on computed tomography following mild traumatic brain injury (SELECT-TBI): study protocol for a multi-centre, population-based, retrospective cohort study

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Abstract

Introduction: Mild traumatic brain injury (mTBI) is one of the most common reasons for emergency department (ED) visits. A portion of mTBI patients will develop an intracranial lesion that might require medical or surgical intervention. In these patients, swift diagnosis and management is paramount. Several guidelines have been developed to help direct these patients for head computed tomography (CT) scanning, but they lack specificity, focus on ruling out lesions, and do not estimate the probability of lesion development. In light of this, the aim of this study is to create a risk stratification score that predicts the probability of intracranial lesion development in patients with mTBI who present to the ED.

Methods and analysis: This will be a retrospective population-based cohort study conducted at all emergency department (ED) hospitals in Stockholm, Sweden. Eligible patients are adults (≥ 15 years) with mTBI who presented to the ED within 24 hours of injury and performed a CT scan. The primary outcome will be a traumatic lesion on head CT. The secondary outcomes will be any clinically significant lesion, defined as an intracranial

finding that led to neurosurgical intervention, discontinuation or reversal of anticoagulant or antiplatelet medication, hospital admission ≥ 48 hours due to the TBI, or death. Machine-learning models will be applied to create scores predicting the primary and secondary outcomes. An estimated 20,000 patients will be included.

Ethics and dissemination: The study has been approved by the Swedish Ethical Review Authority (Dnr: 2020-05728) and is registered with ClinicalTrials.gov (NCT04995068). The research findings will be disseminated through peer-reviewed scientific publications and presentations at international conferences.

Trial registration number: ClinicalTrials.gov (NCT04995068).

Keywords: traumatic brain injury, mild TBI, head injury, computed tomography

Article summary

Strengths and limitations of this study

- This will be the first study to estimate the probability of intracranial lesion development in mild traumatic brain injury.
- The population-based study setting means that all patients who sought emergency care for a mild TBI during the time period will be assessed for eligibility – reducing selection bias.
- An estimated 20,000 patients will be included, allowing for robust conclusions and the opportunity to analyse presumed risk factors that are very rare.
- Machine-learning models will be applied to create scores predicting the primary and secondary outcomes.
- Data collectors will not be blinded to outcome data.

Introduction

With over 60 million annual cases worldwide [1], traumatic brain injury (TBI) is one of the most common reasons behind emergency department (ED) visits [2]. The vast majority are mild (mTBI) with an admission Glasgow Coma Scale (GCS) of 13-15 [3], of whom 5-10 % will develop an intracranial lesion that might require medical or surgical management [4,5].

Several decision aids have been developed to identify patients in whom a head computed tomography (CT) should be performed. These include the Canadian CT Head Rule (CCHR) [5], New Orleans Criteria (NOC) [6], National Institute of Health and Care Excellence (NICE) guidelines [7], CT in Head Injury Patients (CHIP) Prediction Rule [8], and the Scandinavian Neurotrauma Committee (SNC) guidelines [9,10]. These commonly provide algorithms to help clinicians decide on care-pathways and if to perform a CT scan. The Brain Injury Guidelines (BIG) and the Mild TBI Risk Score have also been developed to help determine which patients are suitable for discharge once the CT has been performed [11,12], and hence do not primarily focus on stratifying the risk of lesion development.

While the above-described algorithms have a high sensitivity for identifying those with intracranial lesions, they share two flaws. To begin, they have low specificity [13], resulting in CT overuse with unnecessarily high radiation exposure, ED overcrowding and higher costs [14,15]. Secondly, they don't provide a case-by-case probability of lesion development. This can be contrasted to the HEART score, which provides risk stratification for major cardiac events in patients with chest-pain [16], CHA_2DS_2-VASc, which gives an annual risk of stroke in those with atrial fibrillation [17], and Wells score to predict deep vein thrombosis [18]. These types of prediction models tailored to a patient's specific features is increasingly becoming a part of modern-precision "personalized medicine" [19], but have yet to be implemented in the management of patients presenting with mTBI.

Objective

The aim of this study is to create a risk stratification score that predicts the probability of intracranial lesion development in patients with mTBI who present to the ED.

Methods and analysis

Study setting

This will be a retrospective cohort study designed to develop a clinical prediction score for physicians evaluating adults with mTBI in the ED setting. We will focus on information available to the ED physician when making the decision of whether to perform a head CT scan or not. Thus, the model will incorporate predictors from the patient's history, physical examination and laboratory results. The study will follow the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guidelines [20], and has been registered at ClinicalTrials.gov (NCT04995068).

Study population

The goal is to conduct the study at all hospitals with an ED in Stockholm, Sweden (Karolinska University Hospital Huddinge, Karolinska University Hospital Solna, S:t Göran's Hospital, Stockholm South General Hospital, Norrtälje Hospital, Danderyd's Hospital and Södertälje Hospital), which serve a catchment area of more than 2.4 million people. All hospitals share the same pre-hospital TBI management protocol [21], and adhere to the SNC guidelines for initial management of minimal, mild and moderate head injuries [10]. Since 2014, the Karolinska University Hospital Solna, S:t Göran's Hospital and Stockholm South General Hospital have also had the capabilities to sample the brain biomarker S100B, thus adhering to the updated SNC guidelines from 2013 [9]. Included patients will be adults (≥ 15 years) with mTBI (GCS 13-15) who presented to the ED within

24 hours of injury between 2010-2020 (Table 1). Inclusion years will depend on the availability of digital hospital charts, which became centralized during the 2010s throughout Region Stockholm, but the focus will be on the last six years (2015-2020) when data will be available from all hospitals. Patients have been identified by a systemwide search in the electronic medical records software for ICD-10 codes for intracranial injury (S06X) and fracture of skull and facial bones (S02X), as well as the ED admissions codes for "head injury". An estimated 20,000 patients will be included.

Table 1: Inclusion and exclusion criteria

Inclusion criteria	Adult (≥ 15 years) Presented within 24 hours of TBI between 2010-2020 GCS 13-15 at presentation to the emergency department
Exclusion criteria	No CT scan performed Patient from another region in Sweden or another country Penetrating TBI Secondary transfer from other ED Medical record missing

Abbreviations: CT = computed tomography; ED = emergency department; GCS = Glasgow Coma Scale; TBI = traumatic brain injury

Data collection

Clinical variables will be retrospectively collected by, or closely supervised by, trained physicians using standardised review protocols. Review will be conducted by members of the direct care team in the different hospitals included. Clinical data will be collected from the health record software TakeCare (CompuGroup Medical Sweden AB, Farsta, Sweden), Melior (Siemens, Stockholm, Sweden) and Cosmic (Cambio Healthcare Systems, Stockholm, Sweden), while imaging data will be collected from the radiological management software

Sectra Picture Archiving and Communication System (PACS) (Sectra AB, Linköping, Sweden). The data will be entered into anonymized case report forms (CRF) (Additional file 1) in the electronic data capture system REDCap [22], which can be accessed by the authors AFS and EPT. We will not be able to blind assessors from outcome data.

The primary outcome will be any traumatic lesion on head CT, defined as a cerebral haematoma, subdural haematoma, epidural haematoma, subarachnoid haemorrhage, intraventricular haemorrhage, diffuse axonal injury, skull fracture, traumatic infarction or sinus thrombosis. The secondary outcome will be any clinically significant lesion, defined as a traumatic intracranial finding that led to neurosurgical intervention, discontinuation or reversal of anticoagulant or antiplatelet medication, hospital admission ≥ 48 hours due to the TBI, or death due to TBI. We will use the 48-hour cut-off to exclude overnight admissions for minor CT findings that did not result in any further treatment. Due to the retrospective nature of the study, each patient has already been assessed at their index ED visit by a physician who decided the need for a head CT in accordance with the SNC guidelines [9], and the results of the CT scans have been interpreted by site faculty radiologists (including a board certified radiologist).

Supplementary file 1 details the CRF that will be used to collect inputs for the model. The variables have been chosen due to their previously demonstrated relationship to intracranial lesion development following TBI [5–9,11,12], and their number has been limited to ensure the practical applicability of the prediction model.

Statistics

A separate statistical analysis plan, together with pilot results, will be published following completion of the first 3,000-5,000 patients from the Karolinska University Hospital.

Ethics and dissemination

The study has been approved by the Swedish Ethical Review Authority (Dnr: 2020-05728) who waived the need for informed consent. Each hospital in the Stockholm Region will certify that local regulations are adhered to. The research findings will be disseminated through publications in international, peer-reviewed scientific publications, and presentations at conferences.

Patient and public involvement statement

As this is a retrospective observational cohort study, patients and the public are not involved in the design, conduct, or reporting of this study.

Discussion

While there are several guidelines to help direct mTBI patients for CT scanning, this will be the first study to create a score predicting the probability of intracranial lesion development, including those with a clinically significant lesion. Earlier identification of patients with lesions requiring treatment may decrease time to intervention [23]. The large cohort will allow for robust conclusions from the statistical methods, and will also provide us with the opportunity analyse presumed risk factors that are very rare, such as intraventricular shunts and haemostatic disorders. Hopefully, we will also be able to increase model specificity compared to previous decision tools. The population-based study setting also means that all patients in the Stockholm region who sought emergency care for a mTBI during the time period will be assessed for eligibility.

There are some limitations to bear in mind. As all patients do not undergo a CT scan, there will be those with undiagnosed intracranial lesions. In one study, 0.8 % of elderly TBI patients who did not undergo a head CT were diagnosed with intracranial bleeding within 6

weeks, as compared to 0.6 % of patients with an initial negative CT scan [24]. To minimize this potential bias, we will scan medical records to make sure that the patient did not return to the ED within 30 days with a positive CT scan. The imperfect reference standard bias, introduced with differential testing depending on the emergency physician CT request, might also inflate the strength of association between predictor variables which are commonly used to determine the need for CT in the SNC guidelines (such as of loss of consciousness or anticoagulation use) [9,10]. Assessors will also not be blinded to outcome data.

Trial status

Patient recruitment was commenced on 2021-09-01 and the study is estimated to be completed by 2023-12-31.

Abbreviations

CCHR	Canadian CT Head Rule
CHIP	CT in Head Injury Patients
CRF	Case report form
CT	Computed tomography
ED	Emergency department
GCS	Glasgow Coma Scale
NICE	National Institute of Health and Care Excellence
NOC	New Orleans Criteria
SNC	Scandinavian Neurotrauma Committee
TBI	Traumatic brain injury

Author contributions: Study design: AFS, ET. Draft of manuscript: AFS. Approval of manuscript: All authors. Study supervision: ET.

Funding: AFS acknowledges funding support from the Swedish Brain Foundation (#FO2019-0006) and Region Stockholm (Research Internship). EPT acknowledges funding support from StratNeuro (Karolinska Institutet), The Erling-Persson Family Foundation, Region Stockholm (Clinical Research Appointment) and the Swedish Brain Foundation (#FO2019-0006). The funders had no role in the design or conduct of this research.

Competing interests: The authors declare that they have no competing interests.

Acknowledgements: Not applicable

Data statement: Not applicable (study protocol)

Word count: 1,400

Additional material

File name: Additional file 1

Fil format: pdf

Title: Case report form

Description: Case report form that will be used for data collection

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SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section	Item No	Description	Location
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	p. 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	p. 3
	2b	All items from the World Health Organization Trial Registration Data Set	p. 3
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	p. 9
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	N/A
	5b	Name and contact information for the trial sponsor	N/A
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	p. 3-4
	6b	Explanation for choice of comparators	N/A
Objectives	7	Specific objectives or hypotheses	p. 4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	p. 5-7
Methods: Participants, interventions, and outcomes			

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	p. 5-7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	p. 6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	N/A
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	p. 6-7
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	p. 8
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	p. 6
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	p. 6
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A

Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	p. 7
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	p. 6-7
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	p. 7
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	p. 7
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A

Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	p. 7
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	N/A
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	p. 6
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	p. 9
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	p. 6
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	p. 7
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Variable list

Patient ID	_____
Hospital	◯ Danderyds Sjukhus ◯ Karolinska Universitetssjukhuset Solna ◯ Karolinska Universitetssjukhuset Huddinge ◯ Norrtälje Sjukhus ◯ S:t Görans Sjukhus ◯ Södertälje Sjukhus ◯ Södersjukhuset (Hospital where the emergency department was located)
Sex	◯ Male ◯ Female
Age	_____ (Years)
Date of trauma	_____ (YYYY-MM-DD (if unknown, leave blank))
Time of trauma	_____ (HH:MM (if unknown, leave blank))
Emergency department admission date	_____ (YYYY-MM-DD (if unknown, leave blank))
Emergency department admission time	_____ (HH:MM (if unknown, leave blank))
Time from injury to emergency department admission	◯ 0-3 hours ◯ 3-6 hours ◯ 6-12 hours ◯ 12-24 hours ◯ Unknow
Doctor assessment date	_____ (YYYY-MM-DD (if unknown, leave blank))
Doctor assessment time	_____ (HH:MM (if unknown, leave blank))
Date of discharge from emergency room	_____ (YYYY-MM-DD (if unknown, leave blank))

Time of discharge from emergency room	_____ (HH:MM (if unknown, leave blank))
Comorbidities	☐ None of the below ☐ Dementia ☐ Alcoholism ☐ Liver cirrhosis ☐ Chronic renal impairment ☐ Intraventricular shunt ☐ Anticoagulation treatment ☐ Antiplatelet treatment ☐ Bleeding disorder (Select all that apply)
If "anticoagulation treatment" = yes, specify type(s)	☐ Warfarin ☐ Apixaban (Eliquis) ☐ Rivaroxaban (Xarelto) ☐ Dabigatran (Pradaxa) ☐ Edoxaban (Lixiana) ☐ LMWH (low-molecular-weight heparin) ☐ Other (Select all that apply)
If "antiplatelet treatment" = yes, specify type(s)	☐ ASA (Trombyl) ☐ Clopidogrel (Plavix) ☐ Ticagrelor (Brilique) ☐ Prasugrel (Effient) ☐ Dipyridamole (Persantin) ☐ Ticlopidine (Ticlid) ☐ Eptifibatide (Integrilin) ☐ Other (Select all that apply)
If "bleeding disorder" = yes, specify type	_____
Trauma mechanism	◯ Low energy fall (same level) ◯ High energy fall (> 1 meter or > 5 steps) ◯ Motor vehicle accident (not motorcycle) ◯ Motorcycle accident ◯ Bicycle accident ◯ Pedestrian hit by traffic ◯ Other traffic accident ◯ Shot by gun ◯ Stabbed by sharp object ◯ Struck by blunt object ◯ Blast injury (e.g. explosion) ◯ Other ◯ Unknown
Multitrauma	◯ Yes ◯ No (Defined as radiology ordered for body part other than brain / cervical spine due to suspicion of traumatic injury)

If "multitrauma" = yes, specify	☐ Thorax ☐ Abdomen ☐ Spine (thoracic or lumbar) ☐ Upper Extremity ☐ Lower Extremity (Select all that apply)
GCS = 15 before injury	◯ Yes ◯ No ("No" means that the patient was GCS 14 or below prior to injury (e.g. dementia))
GCS on emergency department admission	◯ GCS = 15 ◯ GCS = 14 ◯ GCS = 13 (GCS when the physician performed the first assessment of the patient)
GCS eye score	◯ 4 (eyes open spontaneously) ◯ 3 (eyes open to verbal command) ◯ 2 (eyes open to pain) ◯ Unknown
GCS verbal score	◯ 5 (orientated to time, person, place) ◯ 4 (confused) ◯ 3 (innapropriate words) ◯ Unknown
GCS motor score	◯ 6 (obeys command) ◯ 5 (moves to localised pain) ◯ 4 (flex to withdraw from pain) ◯ Unknown
Deterioration in GCS after first assessment	◯ Yes ◯ No (Deteriorated in GCS after initial assessment of GCS)
Intoxicated	◯ Yes ◯ No (Intoxicated on assessment (e.g. alcohol))
If "intoxicated" = yes, specify substance(s)	☐ Alcohol ☐ Central stimulants (e.g. amphetamines, cocaine, LSD, ecstasy) ☐ Anxiolytics (e.g. benzodiazepines) ☐ Cannabis ☐ Opioids ☐ Other ☐ Unknown (Select all that apply)
Pupilary status	◯ Normal ◯ Unilateral dilation ◯ Bilateral dilation (If not detailed, choose "normal")
If abnormal pupilary status - reactive to light?	◯ Yes ◯ No

Post-traumatic neurological deficit	☐ None of the below ☐ Weakness in extremity ☐ Numbness in extremity ☐ Diplopia (double-vision) ☐ Blurry vision ☐ Dysphasia (problems with speech) ☐ Dizziness / loss of balance ☐ Loss of coordination ☐ Other (Select all that apply. Do NOT check if patient had impairment prior to injury (e.g. already paralyzed patient))
If "other deficit" = yes, specify	_____
Other worrysome factors	☐ None of the below ☐ Amnesia ☐ Confirmed loss of consciousness ☐ Suspected loss of consciousness (e.g. if patient is unsure) ☐ Vomiting ☐ Persistent headache ☐ Seizure ☐ Scalp wound that needed suturing (excl. face) ☐ Suspected open or depressed skull fracture ☐ Sign(s) of skull base fracture (Select all that apply)
If "amnesia" = yes, specify type(s)	◯ Retrograde (can't recall entire traumatic event) ◯ Anterograde (can't remember new information) ◯ Combined retrograde and anterograde ◯ Unknown / missing
If "loss of consciousness" = yes, specify if it was due to the head injury (i.e. not syncope / fainting)	◯ Yes ◯ No ◯ Unclear
If "vomiting" = yes, specify amount	◯ Once ◯ More than once ◯ Unknown / missing
If "sign(s) of skull base fracture" = yes, specify	☐ Racoon-eyes (bruising around eye - "black eye", "brillenhematoma") ☐ Battle's sign (bruising of the mastoid process behind ear) ☐ Rhinnorea (CSF-leak from nose) ☐ Otorrhea (CSF-leak from ear) ☐ Anosmia (loss of smell) ☐ Hematotympanon (blood behind ear drum) ☐ Deafness ☐ Nystagmus ☐ Fascial nerve paralysis ☐ Other
If "other sign(s) of skull base fracture" = yes, specify	_____
Lab sampled	◯ Yes ◯ No

Date of lab sampling (first test)	_____ (YYYY-MM-DD)
Time of lab sampling (first test)	_____ (HH:MM)
S100B	_____ (µg/L)
PK(INR)	_____
APT-time	_____ (seconds)
Hemoglobin (Hb)	_____ (g/L)
Platelet count	_____ (150 x 10^9/L)
Serum ethanol	_____ (mmol/L)
Alcohol promille level (breathalyzer)	_____ (promille)
Date of CT scan	_____ (YYYY-MM-DD)
Time of CT scan	_____ (HH:MM)
Intracranial lesion on CT	◯ Yes ◯ No
If "intracranial lesion on CT" = yes, specify type(s)	☐ Cerebral contusion ☐ Traumatic subarachnoid haemorrhage ☐ Epidural hematoma ☐ Acute subdural hematoma ☐ Chronic subdural hematoma ☐ Intraventricular hematoma ☐ Diffuse axonal injury ☐ Sinus thrombosis ☐ Traumatic infarct ☐ Skull fracture (neurocranium, not face) (Select all that apply)

If "skull fracture" = yes, specify type(s)	☐ Linear fracture with impression ☐ Linear fracture without impression ☐ Crush fracture with impression ☐ Crush fracture without impression ☐ Other
If "intracranial lesion on CT" = yes, specify management	☐ None (sent home from emergency department) ☐ Admission < 48 hours due to TBI ("overnight observation") ☐ Admission > 48 hours due to TBI ☐ Paus or reversal of anticoagulants or antiplatelets ☐ Intubated due to TBI ☐ Transfer to neurosurgical department ☐ Death due to TBI (Select all that apply)
If patient was admitted due to TBI, specify amount of days in hospital	_____
Follow-up CT performed	◯ Yes ◯ No
If "follow-up CT performed" = yes, specify reason(s)	☐ Decided on admission regardless of neurology ☐ Decreased consciousness ☐ Increased headache ☐ New neurological abnormality ☐ Vomiting ☐ Other ☐ Unclear / unknown
If "follow-up CT performed" = yes, specify if the lesion progressed	◯ Yes ◯ No
Re-admission within 30 days with CT-verified intracranial lesion	◯ Yes ◯ No

BMJ Open

Stockholm score of lesion detection on computed tomography following mild traumatic brain injury (SELECT-TBI): study protocol for a multi-centre, retrospective, observational cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-060679.R1
Article Type:	Protocol
Date Submitted by the Author:	19-Jun-2022
Complete List of Authors:	Fletcher-Sandersjöö, Alexander ; Karolinska University Hospital, Department of Neurosurgery; Karolinska Institutet, Department of Clinical Neuroscience Tatter, Charles; Karolinska University Hospital, Department of Neurosurgery; Karolinska Institutet, Department of Clinical Neuroscience Yang, Li; Södersjukhuset, Department of Emergency Medicine; Karolinska Institutet, Department of Clinical Science and Education Pontén, Emeli; Capio S:t Görans Hospital Boman, Magnus; KTH Royal Institute of Technology, Department of Software and Computer Systems; Karolinska Institutet, Department of Learning, Informatics Lassarén, Philipp; Karolinska Institutet, Department of Clinical Neuroscience Forsberg, Sune; Karolinska Institutet Department of Medicine Solna Grönlund, Ingrid; Danderyds Hospital, Department of Emergency Medicine Tidehag, Viktor; Danderyds Hospital, Department of Emergency Medicine Rubenson-Wahlin, Rebecka; Södersjukhuset, Department of Emergency Medicine; Karolinska Institutet, Department of Clinical Science and Education Strömmer, Lovisa; Capio S:t Görans Hospital, Department of Surgery; Karolinska Institutet, Division of Surgery, Department of Clinical Science, Intervention and Technology (CLINTEC) Westberg, Karin; Danderyds Hospital, Department of Emergency Medicine Ängeby, Kristian; Södersjukhuset, Department of Emergency Medicine; Karolinska Institutet, Department of Clinical Science and Education Djärv, Therese; Karolinska University Hospital, Department of Emergency Medicine Lundblad, Olof; Karolinska University Hospital, Department of Emergency Medicine Bartek, Jiri; Karolinska University Hospital, Department of Neurosurgery Thelin, Eric; Karolinska Institutet, Department of Clinical Neuroscience
Primary Subject Heading:	Emergency medicine

Secondary Subject Heading:	Neurology
Keywords:	NEUROSURGERY, ACCIDENT & EMERGENCY MEDICINE, Neuroradiology < NEUROLOGY, Neurological injury < NEUROLOGY, Computed tomography < RADIOLOGY & IMAGING

Stockholm score of lesion detection on computed tomography following mild traumatic brain injury (SELECT-TBI): study protocol for a multi-centre, retrospective, observational cohort study

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Abstract

Introduction: Mild traumatic brain injury (mTBI) is one of the most common reasons for emergency department (ED) visits. A portion of mTBI patients will develop an intracranial lesion that might require medical or surgical intervention. In these patients, swift diagnosis and management is paramount. Several guidelines have been developed to help direct mTBI patients for head computed tomography (CT) scanning, but they lack specificity, do not consider the interactions between risk factors, and do not provide an individualised estimate of intracranial lesion risk. The aim of this study is to create a model that estimates individualised intracranial lesion risks in patients with mTBI who present to the ED.

Methods and analysis: This will be a retrospective cohort study conducted at emergency department (ED) hospitals in Stockholm, Sweden. Eligible patients are adults (≥ 15 years) with mTBI who presented to the ED within 24 hours of injury and performed a CT scan. The primary outcome will be a traumatic lesion on head CT. The secondary outcomes will be any clinically significant lesion, defined as an intracranial finding that led to neurosurgical

intervention, hospital admission ≥ 48 hours due to TBI, or death due to TBI. Machine-learning models will be applied to create scores predicting the primary and secondary outcomes. An estimated 20,000 patients will be included.

Ethics and dissemination: The study has been approved by the Swedish Ethical Review Authority (Dnr: 2020-05728) and is registered with ClinicalTrials.gov (NCT04995068). The research findings will be disseminated through peer-reviewed scientific publications and presentations at international conferences.

Trial registration number: ClinicalTrials.gov (NCT04995068).

Keywords: traumatic brain injury, mild TBI, head injury, computed tomography

Article summary

Strengths and limitations of this study

- This will be the first study to assess the interactions between risk factors, both in terms of synergism and antagonistic effects, to provide an individualised estimate of intracranial lesion risk following mild traumatic brain injury.
- An estimated 20,000 patients will be included, allowing for robust conclusions and the opportunity to analyse presumed risk factors that are very rare.
- Machine-learning models will be applied to create scores predicting the primary and secondary outcomes.
- Data collectors will not be blinded to outcome data.

Introduction

With over 60 million annual cases worldwide [1], traumatic brain injury (TBI) is one of the most common reasons behind emergency department (ED) visits [2]. The vast majority are

mild (mTBI) with an admission Glasgow Coma Scale (GCS) of 13-15 [3], of whom 5-10 % develop an intracranial lesion that might require medical or surgical management [4,5].

Several decision aids have been developed to identify patients in whom a head computed tomography (CT) should be performed. These include the Canadian CT Head Rule (CCHR) [5], New Orleans Criteria (NOC) [6], National Institute of Health and Care Excellence (NICE) guidelines [7], CT in Head Injury Patients (CHIP) Prediction Rule [8], the National Emergency X-Radiography Utilization Study II (NEXUS II) criteria [9], and the Scandinavian Neurotrauma Committee (SNC) guidelines [10,11], all of which allow for more selective use of CT scanning in patients with mild TBI. The Brain Injury Guidelines (BIG) and the Mild TBI Risk Score have also been developed to help determine which patients are suitable for discharge once the CT has been performed [12,13], and hence do not primarily focus on stratifying the risk of lesion detection.

While the above-described algorithms have a high sensitivity for identifying those with intracranial lesions, they share some flaws. To begin, they have low specificity [14], resulting in CT overuse with unnecessarily high radiation exposure, ED overcrowding and higher costs [15,16]. For example, in a recent prospective, multicentre, external validation of the CHIP Prediction Rule, NOC, CCHR, and NICE guidelines, 82% of patients who presented to the ED with a mild TBI underwent a CT scan and 8% had a traumatic intracranial finding. While the sensitivity ranged from 73% to 99%, specificity ranged from only 4% (NOC) to 61% (NICE) [17]. These finding were corroborated in another prospective validation of CCHR, NOC and NEXUS II, where 93% of patients underwent CT scanning and specificity ranged from 16% (NOC) to 52% (NEXUS II) [18]. Another important limitation is the lack of interaction assessments between risk factors, both in terms of synergism and antagonistic effects, to better estimate intracranial lesion risk. In addition, some novel parameters are not present or detailed specifically in the present guidelines, for example warfarin vs direct oral

anticoagulants or which specific "neurological deficits" that are high risk. Lastly, the available decision aids don't provide an individualised probability of lesion development. This can be contrasted to the HEART score, which provides risk stratification for major cardiac events in patients with chest-pain [19], CHA_2DS_2-VASc, which gives an annual risk of stroke in those with atrial fibrillation [20], and Wells score to predict deep vein thrombosis [21]. [22]

Objective

The aim of this study is to create a model that estimates individualised intracranial lesion risks in patients with mTBI who present to the ED.

Methods and analysis

Study setting

This will be a retrospective cohort study of adults with mTBI in the ED setting. We will focus on information available to the ED physician when making the decision of whether to perform a head CT scan or not. Thus, the model will incorporate predictors from the patient's history, physical examination and laboratory results. The study will follow the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guidelines [23], and has been registered at ClinicalTrials.gov (NCT04995068).

Study population

The study will include all patients who sought ED care for a mTBI at the Karolinska University Hospital Huddinge, Karolinska University Hospital Solna, Stockholm South General Hospital, Norrtälje Hospital, Danderyd's Hospital and Södertälje Hospital. Together these hospitals serve a catchment area of more than 2 million people in Stockholm, Sweden.

All hospitals share the same pre-hospital TBI management protocol [24], and adhere to the SNC guidelines for initial management of minimal, mild and moderate head injuries [11]. The Karolinska University Hospital Solna, S:t Göran's Hospital and Stockholm South General Hospital also have the capabilities to sample the brain biomarker S100B, thus adhering to the updated SNC guidelines from 2013 [10]. Included patients will be adults (≥ 15 years) with mTBI (GCS 13-15) who presented to the ED within 24 hours of injury between 2010-2020 (Table 1). Inclusion years will depend on the availability of digital hospital charts, which became centralized during the 2010s throughout the Stockholm Regional Council, but the focus will be on the last six years (2015-2020) when data will be available from all hospitals. Patients have been identified by a systemwide search in the electronic medical records software for ICD-10 codes for intracranial injury (S06X) and fracture of skull and facial bones (S02X), as well as the ED admissions codes for "head injury".

Table 1: Inclusion and exclusion criteria

Inclusion criteria	Adult (≥ 15 years) Presented within 24 hours of TBI between 2010-2020 GCS 13-15 at presentation to the emergency department
Exclusion criteria	No CT scan performed Patient from another region in Sweden or another country Penetrating TBI Secondary transfer from other ED Medical record missing Already performed CT scan for other TBI within 30 days

Abbreviations: CT = computed tomography; ED = emergency department; GCS = Glasgow Coma Scale; TBI = traumatic brain injury

Data collection

Clinical variables will be retrospectively collected by, or closely supervised by, trained physicians using standardised review protocols. Review will be conducted by members of the direct care team at the different study hospitals. Clinical data will be collected from the health record software TakeCare (CompuGroup Medical Sweden AB, Farsta, Sweden), while imaging data will be collected from the radiological management software Sectra Picture Archiving and Communication System (PACS) (Sectra AB, Linköping, Sweden). The data will be entered into anonymized case report forms (CRF) (Additional file 1) in the electronic data capture system REDCap [25], which can be accessed by the authors AFS and EPT. We will not be able to blind assessors from outcome data.

The primary outcome will be any traumatic lesion on head CT, defined as a cerebral haematoma, subdural haematoma, epidural haematoma, subarachnoid haemorrhage, intraventricular haemorrhage, diffuse axonal injury, depressed skull fracture, traumatic infarction or sinus thrombosis. The secondary outcome will be any clinically significant lesion, defined as a traumatic intracranial finding that led to neurosurgical intervention, hospital admission ≥ 48 hours due to the TBI, or death due to TBI. We will use the 48-hour cut-off to exclude overnight admissions for minor CT findings that did not result in any further treatment. Due to the retrospective nature of the study, each patient has already been assessed at their index ED visit by a physician who decided the need for a head CT in accordance with the SNC guidelines [10], and the results of the CT scans have been interpreted by site faculty radiologists (including a board certified radiologist).

Additional file 1 details the CRF that will be used to collect inputs for the model. The candidate variables have been chosen due to their previously demonstrated relationship to intracranial lesion risk in the mTBI decision rules CCHR [5], NOC [6], NICE guidelines [7], CHIP Prediction Rule [8], NEXUS II criteria [9], SNC guidelines [10,11], BIG [12], the Mild

TBI Risk score [13], as well as others which we believe have clinical grounds to be predictive.

Statistics

An estimated 20,000 patients will be included, which represents all patients treated between 2015 – 2020 who fulfil the inclusion criteria. This means that even in an extreme case of modelling predictors with a total of 100 degrees of freedom, there will still be around 200 patients per predictor parameter. The model will also identify the most important predictors early on, leading to a large sample size for estimating coefficients. A separate statistical analysis plan, together with pilot results, will be published following completion of the first 5,000 patients. This will help us to better estimate how many patients are needed to adequately assess the clinical impact of presumed risk factors that are more rare (for example dual antiplatelet therapy and ventriculoperitoneal shunt).

In order to identify relevant predictors, a regularized regression approach will be attempted. Cross validation will be used for variable selection. Missing data might be imputed if it is missing at random or completely at random, assuming that the missing rate is within reasonable bounds. We already know that there will be missing S100B values from certain hospitals, and two parallel might will be developed: a "core" model with variables available at all hospitals, and an additional model with S100B data from the hospitals that use extended laboratory testing. Interaction terms will be used when clinically or statistically motivated. Area under the receiver operating characteristic curve (AUC) will be used to asses model performance. The dataset will be randomly divided into a derivation- and a validation dataset, allowing for internal validation. Overfitting will be avoided by using regularized regression, which will eliminate poorly performing predictors. Furthermore, the validation set will give a non-biased estimate of the final score's performance internally.

Ethics and dissemination

The study has been approved by the Swedish Ethical Review Authority (Dnr: 2020-05728) who waived the need for informed consent. Each hospital in the Stockholm Region will certify that local regulations are adhered to. The research findings will be disseminated through publications in international, peer-reviewed scientific publications, and presentations at conferences.

Patient and public involvement statement

Patients and members of the public were not involved in the design of this study.

Discussion

Potential clinical benefits

While there are several guidelines to help direct mTBI patients for CT scanning, this will be the first study to provide an individualised estimate of intracranial lesion risk following mild traumatic brain injury, including those with a clinically significant lesion. The large cohort will allow us to analyse presumed risk factors that are very rare, such as intraventricular shunts and haemostatic disorders. In addition, novel parameters that are not present or detailed specifically in the present guidelines will be included, for example warfarin vs direct oral anticoagulants or which specific "neurological deficits" that are high risk. Applying a machine-learning algorithm on a large sample size will also allow us to explore the combined effects of predictive or protective factors, both in terms of synergism and antagonistic effects. Together, we believe this will allow us to increase model specificity, without compromising sensitivity, compared to previous decision tools.

Study limitations

There are some limitations to bear in mind. As all patients do not undergo a CT scan, there will be those with undiagnosed intracranial lesions. In one study, 0.8 % of elderly TBI patients who did not undergo a head CT were diagnosed with intracranial bleeding within 6 weeks, as compared to 0.6 % of patients with an initial negative CT scan [26]. This also means that we will only be able to determine SNC-guideline compliance with regards to overtriage, but not undertriage, which might impact the characteristics of the study population. Thus, the derived model will not be applicable to mTBI patients who have not undergone CT scans. However, to mitigate this, the Swedish National Patient Register [27] will be used to detect if any excluded patient was diagnosed with an intracranial lesion within 30 days of their index ED visit. This will also allow us to calculate the incidence of delayed intracranial haemorrhage among the patients with initial normal CT scans. The imperfect reference standard bias, introduced with differential testing depending on the emergency physician CT request, might also inflate the strength of association between predictor variables which are commonly used to determine the need for CT in the SNC guidelines (such as of loss of consciousness or anticoagulation use) [10,11]. Lastly, the model will be developed based on patients seeking medical care in Stockholm, Sweden. This means that the generalisability of the data outside of Stockholm can be questioned, and the score will need to undergo prospective validation in other regions prior to potential clinical implementation. Assessors will also not be blinded to outcome data.

Trial status

Patient recruitment was commenced on 2021-09-01 and the study is estimated to be completed by 2023-12-31.

Abbreviations

AUC	Area under the receiver operating characteristic curve
CCHR	Canadian CT Head Rule
CHIP	CT in Head Injury Patients
CRF	Case report form
CT	Computed tomography
ED	Emergency department
GCS	Glasgow Coma Scale
NEXUS II	National Emergency X-Radiography Utilization Study II
NICE	National Institute of Health and Care Excellence
NOC	New Orleans Criteria
SNC	Scandinavian Neurotrauma Committee
TBI	Traumatic brain injury

Author contributions: Study design: AFS, ET. Draft of manuscript: AFS. Approval of manuscript: AFS, CT, LY, EP, MB, PL, SF, IG, VT, RRW, LS, KW, KÄ, TD, OL, JB, ET. Study supervision: ET.

Funding: AFS acknowledges funding support from the Swedish Brain Foundation (#FO2019-0006) and Region Stockholm (Research Internship). EPT acknowledges funding support from StratNeuro (Karolinska Institutet), The Erling-Persson Family Foundation, Region Stockholm (Clinical Research Appointment) and the Swedish Brain Foundation (#FO2019-0006). The funders had no role in the design or conduct of this research.

Competing interests: The authors declare that they have no competing interests.

Acknowledgements: Not applicable

Data statement: Not applicable (study protocol)

Word count: 1,400

Additional material

File name: Additional file 1

Fil format: pdf

Title: Case report form

Description: Case report form used for data collection

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Variable list

Patient ID	_____
Hospital	◯ Danderyds Sjukhus ◯ Karolinska Universitetssjukhuset Solna ◯ Karolinska Universitetssjukhuset Huddinge ◯ Norrtälje Sjukhus ◯ S:t Görans Sjukhus ◯ Södertälje Sjukhus ◯ Södersjukhuset (Hospital where the emergency department was located)
Sex	◯ Male ◯ Female
Age	_____ (Years)
Date of trauma	_____ (YYYY-MM-DD (if unknown, leave blank))
Time of trauma	_____ (HH:MM (if unknown, leave blank))
Emergency department admission date	_____ (YYYY-MM-DD (if unknown, leave blank))
Emergency department admission time	_____ (HH:MM (if unknown, leave blank))
Time from injury to emergency department admission	◯ 0-3 hours ◯ 3-6 hours ◯ 6-12 hours ◯ 12-24 hours ◯ Unknow
Doctor assessment date	_____ (YYYY-MM-DD (if unknown, leave blank))
Doctor assessment time	_____ (HH:MM (if unknown, leave blank))
Date of discharge from emergency room	_____ (YYYY-MM-DD (if unknown, leave blank))

Time of discharge from emergency room	_____ (HH:MM (if unknown, leave blank))
Comorbidities	☐ None of the below ☐ Dementia ☐ Alcoholism ☐ Liver cirrhosis ☐ Chronic renal impairment ☐ Intraventricular shunt ☐ Anticoagulation treatment ☐ Antiplatelet treatment ☐ Bleeding disorder (Select all that apply)
If "anticoagulation treatment" = yes, specify type(s)	☐ Warfarin ☐ Apixaban (Eliquis) ☐ Rivaroxaban (Xarelto) ☐ Dabigatran (Pradaxa) ☐ Edoxaban (Lixiana) ☐ LMWH (low-molecular-weight heparin) ☐ Other (Select all that apply)
If "antiplatelet treatment" = yes, specify type(s)	☐ ASA (Trombyl) ☐ Clopidogrel (Plavix) ☐ Ticagrelor (Brilique) ☐ Prasugrel (Effient) ☐ Dipyridamole (Persantin) ☐ Ticlopidine (Ticlid) ☐ Eptifibatide (Integrilin) ☐ Other (Select all that apply)
If "bleeding disorder" = yes, specify type	_____
Trauma mechanism	◯ Low energy fall (same level) ◯ High energy fall (> 1 meter or > 5 steps) ◯ Motor vehicle accident (not motorcycle) ◯ Motorcycle accident ◯ Bicycle accident ◯ Pedestrian hit by traffic ◯ Other traffic accident ◯ Shot by gun ◯ Stabbed by sharp object ◯ Struck by blunt object ◯ Blast injury (e.g. explosion) ◯ Other ◯ Unknown
Multitrauma	◯ Yes ◯ No (Defined as radiology ordered for body part other than brain / cervical spine due to suspicion of traumatic injury)

If "multitrauma" = yes, specify	☐ Thorax ☐ Abdomen ☐ Spine (thoracic or lumbar) ☐ Upper Extremity ☐ Lower Extremity (Select all that apply)
GCS = 15 before injury	◯ Yes ◯ No ("No" means that the patient was GCS 14 or below prior to injury (e.g. dementia))
GCS on emergency department admission	◯ GCS = 15 ◯ GCS = 14 ◯ GCS = 13 (GCS when the physician performed the first assessment of the patient)
GCS eye score	◯ 4 (eyes open spontaneously) ◯ 3 (eyes open to verbal command) ◯ 2 (eyes open to pain) ◯ Unknown
GCS verbal score	◯ 5 (orientated to time, person, place) ◯ 4 (confused) ◯ 3 (innapropriate words) ◯ Unknown
GCS motor score	◯ 6 (obeys command) ◯ 5 (moves to localised pain) ◯ 4 (flex to withdraw from pain) ◯ Unknown
Deterioration in GCS after first assessment	◯ Yes ◯ No (Deteriorated in GCS after initial assessment of GCS)
Intoxicated	◯ Yes ◯ No (Intoxicated on assessment (e.g. alcohol))
If "intoxicated" = yes, specify substance(s)	☐ Alcohol ☐ Central stimulants (e.g. amphetamines, cocaine, LSD, ecstasy) ☐ Anxiolytics (e.g. benzodiazepines) ☐ Cannabis ☐ Opioids ☐ Other ☐ Unknown (Select all that apply)
Pupilary status	◯ Normal ◯ Unilateral dilation ◯ Bilateral dilation (If not detailed, choose "normal")
If abnormal pupilary status - reactive to light?	◯ Yes ◯ No

Post-traumatic neurological deficit	☐ None of the below ☐ Weakness in extremity ☐ Numbness in extremity ☐ Diplopia (double-vision) ☐ Blurry vision ☐ Dysphasia (problems with speech) ☐ Dizziness / loss of balance ☐ Loss of coordination ☐ Other (Select all that apply. Do NOT check if patient had impairment prior to injury (e.g. already paralyzed patient))
If "other deficit" = yes, specify	_____
Other worrysome factors	☐ None of the below ☐ Amnesia ☐ Confirmed loss of consciousness ☐ Suspected loss of consciousness (e.g. if patient is unsure) ☐ Vomiting ☐ Persistent headache ☐ Seizure ☐ Scalp wound that needed suturing (excl. face) ☐ Suspected open or depressed skull fracture ☐ Sign(s) of skull base fracture (Select all that apply)
If "amnesia" = yes, specify type(s)	◯ Retrograde (can't recall entire traumatic event) ◯ Anterograde (can't remember new information) ◯ Combined retrograde and anterograde ◯ Unknown / missing
If "loss of consciousness" = yes, specify if it was due to the head injury (i.e. not syncope / fainting)	◯ Yes ◯ No ◯ Unclear
If "vomiting" = yes, specify amount	◯ Once ◯ More than once ◯ Unknown / missing
If "sign(s) of skull base fracture" = yes, specify	☐ Racoon-eyes (bruising around eye - "black eye", "brillenhematoma") ☐ Battle's sign (bruising of the mastoid process behind ear) ☐ Rhinnorea (CSF-leak from nose) ☐ Otorrhea (CSF-leak from ear) ☐ Anosmia (loss of smell) ☐ Hematotympanon (blood behind ear drum) ☐ Deafness ☐ Nystagmus ☐ Fascial nerve paralysis ☐ Other
If "other sign(s) of skull base fracture" = yes, specify	_____
Lab sampled	◯ Yes ◯ No

Date of lab sampling (first test)	_____ (YYYY-MM-DD)
Time of lab sampling (first test)	_____ (HH:MM)
S100B	_____ (µg/L)
PK(INR)	_____
APT-time	_____ (seconds)
Hemoglobin (Hb)	_____ (g/L)
Platelet count	_____ (150 x 10^9/L)
Serum ethanol	_____ (mmol/L)
Alcohol promille level (breathalyzer)	_____ (promille)
Date of CT scan	_____ (YYYY-MM-DD)
Time of CT scan	_____ (HH:MM)
Intracranial lesion on CT	◯ Yes ◯ No
If "intracranial lesion on CT" = yes, specify type(s)	☐ Cerebral contusion ☐ Traumatic subarachnoid haemorrhage ☐ Epidural hematoma ☐ Acute subdural hematoma ☐ Chronic subdural hematoma ☐ Intraventricular hematoma ☐ Diffuse axonal injury ☐ Sinus thrombosis ☐ Traumatic infarct ☐ Skull fracture (neurocranium, not face) (Select all that apply)

If "skull fracture" = yes, specify type(s)	☐ Linear fracture with impression ☐ Linear fracture without impression ☐ Crush fracture with impression ☐ Crush fracture without impression ☐ Other
If "intracranial lesion on CT" = yes, specify management	☐ None (sent home from emergency department) ☐ Admission < 48 hours due to TBI ("overnight observation") ☐ Admission > 48 hours due to TBI ☐ Paus or reversal of anticoagulants or antiplatelets ☐ Intubated due to TBI ☐ Transfer to neurosurgical department ☐ Death due to TBI (Select all that apply)
If patient was admitted due to TBI, specify amount of days in hospital	_____
Follow-up CT performed	◯ Yes ◯ No
If "follow-up CT performed" = yes, specify reason(s)	☐ Decided on admission regardless of neurology ☐ Decreased consciousness ☐ Increased headache ☐ New neurological abnormality ☐ Vomiting ☐ Other ☐ Unclear / unknown
If "follow-up CT performed" = yes, specify if the lesion progressed	◯ Yes ◯ No
Re-admission within 30 days with CT-verified intracranial lesion	◯ Yes ◯ No

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section	Item No	Description	Location
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	p. 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	p. 3
	2b	All items from the World Health Organization Trial Registration Data Set	p. 3
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	p. 11
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	p. 1
	5b	Name and contact information for the trial sponsor	N/A
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	p. 4-5
	6b	Explanation for choice of comparators	N/A
Objectives	7	Specific objectives or hypotheses	p. 5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	p. 5-8
Methods: Participants, interventions, and outcomes			

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	p. 5-7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	p. 6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	N/A
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	p. 7
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	p. 10
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	p. 8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	p. 8
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A

Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	p. 8
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	p. 6-7
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	p. 8
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	p. 8
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A

Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	p. 9
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	N/A
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	p. 7
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	p. 11
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	p. 7
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	p. 9
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.