Diagnostic and Prognostic Research

Mild Traumatic Brain Injury with CT scan abnormality: which patients are safe for discharge? A protocol for the development of a prediction model in a retrospective cohort.

--Manuscript Draft--

Manuscript Number:	DAPR-D-17-00028R1
Full Title:	Mild Traumatic Brain Injury with CT scan abnormality: which patients are safe for discharge? A protocol for the development of a prediction model in a retrospective cohort.
Article Type:	Protocol
Funding Information:	Research Trainees Coordinating Centre (DRF-2016-09-086) — Dr Carl Marincowitz
Abstract:	Background: Head injury is an extremely common clinical presentation to hospital Emergency Departments (ED). Nine-five percent of patients present with an initial Glasgow Coma Scale (GCS) score of 13-15, indicating a normal or near normal conscious level. In this group around 7% of patients have brain injuries identified by CT imaging but only 1% of patients have life-threatening brain injuries. It is unclear which brain injuries are clinically significant, so all patients with brain injuries identified by CT imaging are admitted for monitoring. If risk could be accurately determined in this group admissions for low-risk patients could be avoided and resources could be focused on those with greater need. This study aims to: (a) estimate the proportion of GCS13-15 patients with traumatic brain injury identified by CT imaging admitted to hospital who clinically deteriorate (b) develop a prognostic model highly sensitive to clinical deterioration which could help inform discharge decision making in the ED. Methods: A retrospective case note review of 2000 patients with an initial GCS13-15 and traumatic brain injury identified by CT imaging (2007-2017) will be completed in two English major trauma centres. The prevalence of clinically significant deterioration including death, neurosurgery, intubation, seizures or drop in GCS by more than 1 point will be estimated. Candidate prognostic factors have been identified in a previous systematic review. Multivariable logistic regression will be used to derive a prognostic model and its sensitivity and specificity to the outcome of deterioration will be explored. Discussion: This study will potentially derive a statistical model that predicts clinically relevant deterioration and could be used to develop a clinical risk-tool guiding need for hospital admission in this group.
Corresponding Author:	Carl Marincowitz Hull York Medical School York, UNITED KINGDOM
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Hull York Medical School
Corresponding Author's Secondary Institution:	
First Author:	Carl Marincowitz, MB BChir, MSc, BA
First Author Secondary Information:	

Order of Authors:	Carl Marincowitz, MB BChir, MSc, BA
	Fiona Lecky, MB Ch B, FRCS, DA, MSc, PhD, FCEM
	William Townend, MD FRCS FCEM
	Victoria Allgar, PhD, BSc PhD C StatCSi
	Andrea Fabbri, MD
	Trevor Sheldon, MSc, MSc, DSc, FMedSci
Order of Authors Secondary Information:	
Response to Reviewers:	DAPR-D-17-00028 Mild Traumatic Brain Injury with CT scan abnormality: which patients are safe for discharge? A protocol for the development of a prediction model in a retrospective cohort. Dear Editor of Diagnostic and Prognostic Research, Thank you for the time that the reviewers have taken in considering our manuscript and their useful comments. We outline how we have addressed their comments below and have highlighted the changes to the manuscript using tack changes. Yours sincerely, Carl Marincowitz Reviewer 1 Main issues: - In exclusion criteria, why do you exclude patients that are transferred from other EDs when they diagnosed an injury? Or you doing this as to avoid having more "severe" TBIs in your group? The prognostic model that we are attempting to derive is aimed at helping clinicians in the emergency department assess whether alert patients that have traumatic brain injuries identified by CT imaging on first presentation need hospital admission. Patients transferred to neurosurgery centres (such as the 2 sites at which data collection is occurring) for admission under specialist neurosurgical care are not first presentation and represent a different and more severely injured population of patients. Their inclusion therefore would make the derived model less applicable to the population of interest. - Why "intravenous therapy" as an outcome metric? What is "intravenous therapy" here? Osmotic agents to reduce intracranial pressure or are we talking about nutrition? I know many centers who have it as standard therapy of fasting patients with TBI as they "might" need surgery, is this why? Please elaborate. We agree that intravenous therapy is too general and that the use of osmotic agents is clinically variable. We have therefore removed this from our outcome measure. - Marshall CT classification was constructed on patients that were unconscious when they arrived to the hospital (thus not optimal for your study), and is not an ordinal score that is suitable for outcome prediction. If you are thinking of including the rather outdated Marshall, I would strongly include other CT classification systems such as the Rotterdam-, Helsinki- and Stockholm CT scores as they have shown to be better outcome predictors (PLoS Med 2017; 14(8):e1002368). We need a CT classification system that can be derived from the available written CT reports to include in the modelling in order to assess the prognostic value of injury severity. Study investigators have been trained in abbreviated injury scale coding of injuries on CT brain scans by the Trauma Audit and Research Network, which is an accredited trainer, to ensure a reliable and reproducible injury scale coding of CT reports. We have added to the section entitled “Research Team Undertaking

	Screening and Data Extraction" to emphasise this. There is an established method of mapping from brain injury scale coding to the Marshall Classification system derived from the UK trauma registry.1 We are unaware of an equivalent method for mapping between injury severity coding and other CT classification systems. To apply a different CT classification system, therefore, the CT scans would have to be re-assessed and reported again with a classification score assigned. This is beyond the resources available for this study. However, we will consider how the assigned brain injury scale codes and severity scores map to the Rotterdam and Helsinki scores during the study and see if they improve the prognostic model. Although the Marshall classification was derived in patients with lower GCS scores than in our study it was used as a common CT scoring system in the validation of the IMPACT and CRASH prognostic studies, both of which included patients that were conscious, and is well validated.2 The use of the Marshal Classification as an ordinal prognostic scale has been described in the literature.3 We are collecting data on the additional factors, such as the presence of traumatic subarachnoid haemorrhage, found to improve the predictive value of newer but less widely validated classification systems.4 - You are likely to have problems scoring "frailty" index in these patients, with a lot of missing variables (similar with Charlson Comomorbidity Index). There is also a strong likelihood that there will be confounding factors towards patients that were admitted for a longer period of time or that have comorbidities requiring previous hospitalization to have notes that will allow you to calculate these scores. Younger patients with no or little time spent in the emergency department will probably have a lot of missing/uncertain data here. Will you do a subcohort analysis of elderly patients for your frailty index? The standard care for all patients with brain injuries identified by CT imaging in the UK currently is inpatient hospital admission for a period of observation. Therefore, for the vast majority of patients an inpatient hospital clerking is available and this contains both an assessment of comorbidities and functional status. This will allow an assessment of frailty on almost all patients. Missing data will prevent an assessment only for the small number of patients that self-discharge or are discharged erroneously from the Emergency Department. It is true that more information to make an assessment of frailty may be available for (frailer) patients with more frequent recent hospital admissions. This may result in there being more accurate frailty scoring of frail patients with increased admissions. However, we don't believe that this confounds the relationship between frailty and the outcomes of interest which are independent of such previous hospital admissions. - I would recommend that a special group of investigators assess the CT scans and that this group is blinded to outcome, as this would increase the quality and decrease the risk of bias in the study. The CT scans have all been reported by neuro-radiologists at the time of injury for clinical purposes. The reporting radiologists, therefore, were in effect blinded to the outcomes that we are interested in. The CT scans are not being re-assessed for the purposes of this study. The use of available CT reports is pragmatic as it is directly applicable to information available during clinical care. Any variability in the accuracy of clinical CT reports will introduce random error (rather than bias) and will potentially lead to more conservative estimates of effect.5 We are reassured by a recent Cochrane review assessing the value of central study adjudication which found little deviation between treatment effect estimates for subjective outcomes derived local assessors and those assigned by central study adjudicators.6 We also do not have the resources to undertake the re-assessment of all CT scans included in the study. Minor issues: Abstract: Page 2, Line 14: Remove "and" (or "so"). This change has been made.

Introduction: Page 3, Line 19: I would include in regards to clinical deterioration "due primarily to intracranial hematoma progression"

This change has been made.

M&M: Page 5, Line 17: "whist" = whilst

This change has been made.

Limitations: Page 10, Line 28: "Prevalence of.", the sentence suddenly ends.

This sentence has been changed to: This may underestimate deterioration following discharge especially if patients die in the community or deteriorate and are readmitted to a different hospital.

Reviewer 2

1)In the inclusion criteria please elaborate on the definition of traumatic brain injury. Be more specific about the mechanism of trauma and the CT findings that were deemed eligible. Also you mention in the exclusion criteria that you excluded spontaneous intracranial hemorrhage. How was that ascertained? Moreover, please give more details on which type of pre-existing brain pathologies you excluded.

We have amended the sections entitled inclusion and exclusion criteria to make these definitions more specific. In the section entitled inclusion criteria we explicitly state that all patients with brain injuries identified by CT that can only be traumatic in origin are included. In the section entitled exclusion criteria we now outline that patients with intracranial bleeds that could either be spontaneous or traumatic in aetiology without a documented mechanism of injury that could result in head trauma or without physical evidence of head injury are excluded on the basis that they have spontaneous bleeds. In the section entitled exclusion criteria we now list the pre-existing brain pathologies that we exclude if they prevent the timing of injury.

2)In the study outcome you mention as part of the composite endpoint "intravenous therapy whilst an inpatient". Please clarify what type of treatment that includes eg antibiotics, antiepileptic medication

In light of this comment and a similar comment from Reviewer 1 we have removed as an outcome measure.

3)Page 8, line 2 : you mention that predictors that you will retain in the multivariate model prediction having great clinical relevance. Do you mean that this is true even if they don't fulfill the p-value criterion? What is your rationale for that?

Our sample size and estimated prevalence of outcomes means that we can assess up to 20 factors in a multivariable model. We are collecting data on more than 20 factors and will have to choose which factors to assess in the multivariable model to undergo backward elimination. This will be in part determined by the univariable associations that we find but we will also initially include factors that are clinically relevant, irrespective of univariable statistical significance. They will not be retained following backward elimination if they are not statistically predictive of the outcomes of interest. The second paragraph of the section entitled model development has been changed to clarify this.

4)You mention that according to your sample size and the expected prevalence of the outcome that allows the model to include 20 variables. However this is a very big number of variables for a model to allow application in acute care settings. A prediction model that is intended for use in the emergency department should include a small number of factors, that are easily and quickly measured.

The quoted 20 variables that can be included in the model simply represents the largest number of variables that be included in the modelling process at the same time and have enough statistical power based on our sample size calculation.

We agree that a parsimonious model that includes the smallest number of easily obtained factors would be desirable and the most practically applicable within the clinical context of the Emergency Department. We will include up to 20 factors as our starting point and then reduce the number of included variables whilst optimising the prognostic model's sensitivity to the outcome of interest.

5)Please specify the method you will use for imputation of missing values

Missing data will be addressed based on a missing at random assumption using multiple imputation using STATA.7 The exact methods will be determined by the amount, type and distribution of missing data and therefore we cannot describe the methods precisely until data collection is complete. However, we will adhere to guidelines published in the BMJ regarding the use and reporting of methods to deal with missing data.8 The section entitled missing data has been modified to clarify this.

6)If you have access in the Italian cohort why not perform external validation then? Why did you decide to compare results only?

The Italian cohort represents a modestly sized group (approximately 700) of eligible patients in which not all the factors that we are assessing have been measured. We therefore felt that it may not be possible to validate the model in this cohort and if it were possible the estimated precision would be limited by the sample size. We therefore decided to only undertake the outlined exploratory analysis and plan to validate the derived model in larger and more comprehensive Center TBI study data.

7)Page 10, patagraph 2nd of limitations please rephrase the paragraph, it is very difficult to comprehend

This paragraph has been rephrased as follows:

"Outcomes will only be assessed during hospital admission and for those who re-attend the study hospitals following discharge. This may underestimate deterioration following discharge especially if patients die in the community or deteriorate and are readmitted to a different hospital. We will estimate the effect of this possible bias by conducting a sensitivity analysis using data for the sub-set of patients registered on the Trauma and Audit Network Database where complete data following discharge is available."

8)Figure 1: I would propose one column with the factors and group them by source of inclusion
Table 1 has been modified accordingly

9)Comment on midline shift and size of bleed are two factors that suffer greatly from lack of interobserver agreement. How will this be assessed, qualitatively or quantitatively?

The size of the largest bleed and presence of midline shift will be taken from the written CT reports provided by a neuro-radiologist at the time of injury. We agree there may be some inter-observer variation between individual neuro-radiologists in assessing these factors that may introduce random error. This reflects real clinical practice and so makes the use of variables derived in this way more practically applicable. Random error may reduce the effect estimates but will not bias the results.5

10)When you mention CT head report as a factor what do you mean? How is that assessed?
This was included in error and has been removed.

11)GCS as a variable in the final model is dependent on the eligibility criteria you set and has low variability. I would propose to omit it as a variable.

In our recently published systematic review assessing prognostic factors in GCS13-15 patients with injuries identified by CT imaging we found that even in this small range initial GCS was highly predictive of clinical deterioration so we think it should be retained initally.9 If it does not add significant independent predictive value then it will

	be removed from the model. 12)Please add in table 1 for each candidate factor how it will be handled (as a categorical or continuous variable) Table 1 has been amended accordingly. 1. Lesko MM, Woodford M, White L, et al. Using Abbreviated Injury Scale (AIS) codes to classify Computed Tomography (CT) features in the Marshall System. BMC Med Res Methodol 2010;10:72. doi: 10.1186/1471-2288-10-72 2. Roozenbeek B, Lingsma HF, Lecky FE, et al. Prediction of outcome after moderate and severe traumatic brain injury: External validation of the International Mission on Prognosis and Analysis of Clinical Trials (IMPACT) and Corticoid Randomisation after Significant Head injury (CRASH) prognostic models. Critical Care Medicine 2012;40(5):1609-17. 3. Saatman KE, Duhaime AC, Bullock R, et al. Classification of traumatic brain injury for targeted therapies. J Neurotrauma 2008;25(7):719-38. doi: 10.1089/neu.2008.0586 [published Online First: 2008/07/17] 4. Thelin EP, Nelson DW, Vehvilainen J, et al. Evaluation of novel computerized tomography scoring systems in human traumatic brain injury: An observational, multicenter study. PLoS Med 2017;14(8):e1002368. doi: 10.1371/journal.pmed.1002368 [published Online First: 2017/08/05] 5. Flegal KM, Brownie C, Haas JD. The effects of exposure misclassification on estimates of relative risk. Am J Epidemiol 1986;123(4):736-51. [published Online First: 1986/04/01] 6. Ndounga Diakou LA, Trinquart L, Hrobjartsson A, et al. Comparison of central adjudication of outcomes and onsite outcome assessment on treatment effect estimates. Cochrane Database Syst Rev 2016;3:MR000043. doi: 10.1002/14651858.MR000043.pub2 [published Online First: 2016/03/11] 7. Royston P. Multiple imputation of missing values: update. The Stata Journal 2005;5(2):1-14. 8. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ 2009;338:b2393. doi: 10.1136/bmj.b2393 [published Online First: 2009/07/01] 9. Marincowitz C, Lecky FE, Townend W, et al. The Risk of Deterioration in GCS13-15 Patients with Traumatic Brain Injury Identified by Computed Tomography Imaging: A Systematic Review and Meta-Analysis. J Neurotrauma 2018;35(5):703-18. doi: 10.1089/neu.2017.5259 [published Online First: 2018/01/13]
Additional Information:	
Question	**Response**

Mild Traumatic Brain Injury with CT scan abnormality: which patients are safe for discharge? A protocol for the development of a prediction model in a retrospective cohort.

Carl Marincowitz[1] MB BChir, MSc, BA

Fiona E. Lecky[2] MB Ch B, FRCS, DA, MSc, PhD, FCEM

William Townend[3] MD FRCS FCEM

Victoria Allgar[4] PhD, BSc PhD C StatCSi

Andrea Fabbri[5] MD

Trevor A. Sheldon[6] MSc, MSc, DSc, FMedSci

1. **Corresponding Author.** Hull York Medical School, Allam Medical Building, University of Hull, Hull HU6, UK 7RX, Fax: +44 (0) 1482 464705 Tel +44 (0) 870 1245500 Email:carl.marincowitz@hyms.ac.uk

2. School of Health and Related Research, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA, UK, Fax: +44 (0)114 222 0749 Tel: (+44) (0)114 222 4345, Email: f.e.lecky@sheffield.ac.uk

3. Emergency Department, Hull and East Yorkshire NHS Trust, Anlaby Road, Hull, HU3 2JZ, UK, Fax: (+44) (0) 1482 477857 Tel: (+44) (0) 1482 623065, Email: William.Townend@hey.nhs.uk

4. Hull York Medical School, John Hughlings Jackson Building, University of York, Heslington, York YO10 5DD Tel: 0870 124 5500, Email: Victoria.Allgar@hyms.ac.uk

5. Head of Emergency Unit, Presidio Ospedaliero Morgagni-Pierantoni, AUSL della Romagna, via Forlanini 34, 47121 Forlì (FC), Italy Tel +390543735156, email: andrea.fabbri@auslromagna.it

6. Department of Health Sciences, University of York, Alcuin Research Resource Centre , Heslington, York, YO10 5DD, Tel +44 (0) 1904 321344, Fax: +44 (0) 1904 32 3433, e-mail: trevor.sheldon@york.ac.uk

Abstract:

Background:

Head injury is an extremely common clinical presentation to hospital Emergency Departments (ED). Nine-five percent of patients present with an initial Glasgow Coma Scale (GCS) score of 13-15, indicating a normal or near normal conscious level. In this group around 7% of patients have brain injuries identified by CT imaging but only 1% of patients have life-threatening brain injuries. It is unclear which brain injuries are clinically significant, ~~and~~ so all patients with brain injuries identified by CT imaging are admitted for monitoring. If risk could be accurately determined in this group admissions for low-risk patients could be avoided and resources could be focused on those with greater need.

This study aims to: (a) estimate the proportion of GCS13-15 patients with traumatic brain injury identified by CT imaging admitted to hospital who clinically deteriorate (b) develop a prognostic model highly sensitive to clinical deterioration which could help inform discharge decision making in the ED.

Methods:

A retrospective case note review of 2000 patients with an initial GCS13-15 and traumatic brain injury identified by CT imaging (2007-2017) will be completed in two English major trauma centres. The prevalence of clinically significant deterioration including death, neurosurgery, intubation, seizures or drop in GCS by more than 1 point will be estimated. Candidate prognostic factors have been identified in a previous systematic review. Multivariable logistic regression will be used to derive a prognostic model and its sensitivity and specificity to the outcome of deterioration will be explored.

Discussion:

This study will potentially derive a statistical model that predicts clinically relevant deterioration and could be used to develop a clinical risk-tool guiding need for hospital admission in this group.

Key Words:

Mild Traumatic Brain Injury; Prognosis; Predictive model; Intra-cranial haemorrhage; Minor Head Injury

Background:

There are 1.4 million annual attendances to Emergency Departments in England and Wales following a head injury.[1] Approximately 95% of patients present with an initial score of 13-15 ~~-~~on the Glasgow Coma Scale (indicating a normal or mildly impaired conscious level) and are defined as having a "minor head injury".[2] Minor head injured patients have a 1% risk of life threatening traumatic brain injury (TBI).[3] In the UK head injury guidelines are used to triage CT imaging in this large patient population with the aim of identifying all life-threatening injuries.[1, 4] Adult guidelines are based on the internationally used and validated Canadian CT Head Rule and are applied to patients aged ≥16.[3, 5] Around 7% of patients have TBI identified by CT imaging.[6] ~~and~~ ~~-~~Aa~~ll~~ of these patients are admitted to hospital in the UK due to fears about the risk of ~~clinical~~ deterioration due primarily to intra-cranial haematoma progression, but these risks are not well characterised (fig. 1).~~[6]~~

The management of GCS13-15 patients with CT identified TBI is controversial with some advocating admission to higher levels of care and mandatory repeat CT imaging due to the risk of deterioration.[7] Others argue that some patients are at low enough risk to be discharged safely from the ED after a short period of observation, a model of care adopted in a level 1 trauma centre in Arizona.[8] The UK NICE guidelines (published 2004, 2007 and 2014) state that all patients with significant brain injuries identified by CT imaging should be admitted to hospital, but do not qualify what constitutes such injuries.[1]

In our recent systematic review ~~we conducted~~, we estimated a pooled risk of neurosurgery in GCS13-15 patients with injuries identified by CT imaging of 3.5% (95% C.I. 2.2-4.9%) from the results of 36 studies.[9] A risk of clinical deterioration, such that patients would benefit from inpatient hospital admission, of 11.7% (95% C.I 11.7-15.8%) was derived from 18 studies. There was significant variation in estimates of these outcomes across individual studies and no studies were conducted in the UK where NICE guidelines are used so relevant risk factors were not considered. Following the introduction of the NICE guidelines hospital admissions for head injury increased in England.[10] It is thought this may be due to more injuries of less clinical significant being identified due to increased CT imaging of minor head injured patients.[10] Research is required to estimate the risks of adverse outcomes in GCS13-15 patients with injuries identified by CT imaging in the UK.

GCS13-15 patients with brain injuries identified by CT imaging have a small but clinically important risk of significant adverse outcomes. Well conducted prognostic research could

generate models which allow the identification of low-risk patients who could be safely discharged from ED and high-risk patients who would benefit from more aggressive management. Our review identified 41 factors in 21 studies that had been assessed as potentially affecting the risk of adverse outcomes in this group.[9] None of this research was conducted in the UK and no multivariable models were identified that could be used to accurately identify patients at sufficiently low-risk of deterioration to be discharged from the ED. Prognostic research conducted within the context of NHS care is required to assess the extent to which GCD13-15 patients with CT identified TBI can be stratified by risk. This will help refine the NICE guidelines and potentially allow better resource allocation in the management of these patients by identifying those who do not require hospital admission.

Aims:

1) Estimate the prevalence of clinical deterioration in initial GCS13-15 adult patients with brain injuries identified by CT imaging.
2) Develop a multivariable model that accurately identifies adult patients of sufficiently low-risk of clinical deterioration that they could be discharged from the ED.

Methods:

Study Design:

This a retrospective and consecutive cohort observational study. The proportion of the cohort that clinically deteriorate will be estimated and a multivariable prognostic model that predicts deterioration will be developed. The study will be conducted and reported in accordance with the TRIPOD recommendations.[11, 12]

Patients will be identified through retrospective case note review over a 10-year period from 2007-2017 at Hull Royal Infirmary and Salford Royal Hospital, two English major trauma centres.

Participants:

Inclusion criteria: Patients aged ≥16 admitted to hospital, with an initial GCS of 13 or more on presentation to the ED and traumatic brain injury identified definitively by CT head imaging. All patients with epidural haemorrhage, subdural haemorrhage, subarachnoid haemorrhage, intra-cerebral haemorrhage, intra-cerebral contusion, skull fractures and any combination of these injuries will be considered for inclusion. All patients with injuries

identified by CT that could only be traumatic in aetiology including skull fractures, extradural haemorrhages and subdural haemorrhages will be counted as having traumatic brain injury. Where patients have intracranial haemorrhage identified that could be either traumatic or spontaneous patients will only be included if they have either a documented mechanism or evidence of head injury. This will apply to intra-cerebral and subarachnoid haemorrhages.~~This definition of TBI includes any type of traumatic intra-cranial haemorrhage, skull fracture, contusion or combination of these injuries.~~ Included mechanisms are falls, assault, road traffic collision, sport and any other mechanism that could result in blunt trauma above the clavicles. Evidence of head trauma includes bruising, wounds or injuries above the clavicles including facial and skull fractures identified radiologically.

Exclusion criteria:

Patients with obvious penetrating head injury or with spontaneous intra-cranial haemorrhage. Patients will be categorised as having a spontaneous intra-cranial haemorrhage if the haemorrhage could occur spontaneously or traumatically and they have no documented preceding mechanism or evidence of head injury or if the CT report states that the pattern of intra-cranial haemorrhage indicates a spontaneous event. Patients with pre-existing brain injuries or other pathology that makes the interpretation of timing of injury difficult and this includes patients with haemorrhagic brain tumours, chronic subdural haemorrhage or hygromas and other types of pre-existing intra-cranial bleeds. Patients with isolated occipital condyle fractures are excluded as these are treated as cervical spine injuries. Patients transferred from other EDs following identification of a brain injury will also be excluded.

Study outcome:

The outcome of interest is a composite measure of clinical deterioration such that inpatient hospital admission was warranted, this includes: death due to TBI or neurosurgery within 30 days of attendance, ~~intravenous therapy whilst an inpatient,~~ ICU intervention whilst an inpatient, seizure activity whilst inpatient, drop in GCS by 2 or more points whilst an inpatient, or a readmission to hospital within 30 days of injury related to TBI.

Candidate prognostic factors:

Potential candidate factors have been selected a priori by: identification of factors that individually predict deterioration in the study population in our systematic review, inclusion of additional factors that predict adverse outcomes in prognostic models for patients with

more severe TBI and trauma and inclusion of factors that represent NICE guideline standards and criteria for treatment and investigation of head injury and TBI.[1, 9, 13-15] All factors being considered for inclusion in the final model are presented in Table 1 with the reason for their inclusion.

Comorbidities will be measured using a trauma modified Charlson Comorbidity Index. Brain injury severity, as shown on CT scan, will be stratified using the Marshal Classification, which will be calculated from Abbreviated Injury Severity (AIS) codes for TBI using the method described by Lesko et al.[16, 17] The Charlson Comorbidity Index, AIS and Marshal Classification are internationally validated prognostic scoring systems.[18, 19] Frailty will be assessed using the clinical frailty scale described by Rockwood et al.[20]

Data collection:

Screening:

A database of all emergency department CT brain requests and reports for patients aged 16 and over between 2007-2017 will be generated at the 2 sites from the electronic requesting and reporting system. This will be screened to identify potentially eligible patients with CT requests related to head injury and CT scans with reported abnormalities related to TBI or intra-cranial haematomas (Fig. 2). Patients identified in this way will be matched to electronic ED case notes, reports and discharge summaries to identify the subset of patients potentially admitted with an initial GCS13-15.

Data Extraction:

The full case records of patients identified through screening as potentially meeting the inclusion criteria will be retrieved (Fig. 2). In patients who are confirmed to meet the inclusion criteria all a priori candidate prognostic factors will be extracted from the case records. Demographic information will be extracted from data recorded at the time of presentation to the ED following head injury. Comorbidities, frailty and pre-injury medication use will be extracted from that recorded in the ED attendance and subsequent inpatient hospital admission documentation. Co-morbidities recorded in the inpatient notes up to 1 year prior to the presentation following head trauma will be included in accordance with the method of data collection in a recent update of the Charlson comorbidity index.[19]

The full inpatient records will be interrogated for evidence of intervention or clinical deterioration that would meet the composite outcome measure. Recorded patient ED and

hospital admissions after discharge following the relevant admission for traumatic brain injury will be assessed for evidence of deterioration, intervention or readmission in the 30 days following the initial ED attendance.

Patients who were included in the national Trauma Audit and Research network (TARN) registry will be identified locally. Using an anonymous TARN study number we will assess for any deaths recorded on the TARN registry within 30 days of admission.

~~The electronic data extraction proforma is presented in Appendix 1.~~

Research Team Undertaking Screening and Data Extraction:

Members of the direct Emergency Department care team at each NHS trust will undertake the screening of electronic records for patients admitted following head injury and data extraction from case notes. Staff undertaking data extraction will undergo data extraction training and this includes training in abbreviated injury scale coding of injuries on CT brain scans by the Trauma Audit and Research Network (TARN) which is an Association for the Advancement of Automotive Medicine accredited trainer to ensure the use of AIS dictionary in a reliable and reproducible fashion. ~~and~~ D~~d~~ata extraction will be piloted over a 1-month period. Hypothetical and non-identifiable training samples of potential patient records will be generated at both sites during the training period and will be used to check the quality of, and validate, data-extraction in the research team. The research team will not be blinded to outcomes. However, most prognostic variables being collected are demographic and other factors not subject to interpretation. Patients are also not being allocated to treatment groups and therefore data collection is less likely to be biased in favour of a specific outcome.

Sample Size:

Sample size of a prognostic study is informed by 3 factors: anticipated prevalence of the outcome (in this study clinical deterioration), desired sensitivity of the model to the outcome and the precision of the 95% confidence interval around the sensitivity of the model.[12]

We have based our sample size on a 10% estimated prevalence of clinical deterioration in our systematic review and our desired precision of the sensitivity of the derived model for this outcome.[9] Research into discharge decision making in patients presenting to the ED with chest pain, indicated that a 1/100 risk of a patient being discharged who subsequently had a significant cardiac event, may be an acceptable risk threshold to both patients and

clinicians.[21] Therefore, we will aim for 99% sensitivity for clinical deterioration as this may correspond to a clinically acceptable level of model accuracy.

A sample size of approximately 2000 patients is required, based upon the desired 99% sensitivity in order that the maximum marginal error of the estimate does not exceed 1.4% with a 95% confidence interval.[22] Based upon previous data collection we estimate at least 100 patients will be eligible for inclusion per year at each site of data collection over the 10 year period of interest.[23]

Statistical analysis:

Outcome Estimate:

The proportion of patients that fulfil the composite measure of deterioration will be estimated. A sample size of 2000 patients will allow us to estimate the prevalence of clinically significant deterioration with a 1.3% margin of error at a 95% confidence level.

Model Development:

Multivariable logistic regression with backward stepwise selection will be used to find the best combinations of candidate factors highly sensitive for detecting deterioration while achieving the maximum possible specificity. This approach is favoured as all correlations between predictors are considered in the modelling procedure and there is easier transparency of reporting.[12]

Candidate prognostic factors with a P value greater than 0.~~1~~05 will be selected for removal. Forced variables (predictors) that we consider as having ~~great~~ clinical relevance, as indicated in our systematic review and the NICE guidelines, will initially also~~also~~ be considered for inclusion in our model and retained in the initial steps of backwards elimination. In the final model all factors that do meet the significance level will be removed.

The sample size of 2000, with an anticipated prevalence of clinical deterioration of around 10%, will allow the model to include 20 variables, based on the rule of at least 10 outcome events per parameter estimated.

Continuous factors will not be categorised initially to avoid a loss of power.[24, 25] Calibration (the agreement between outcome predictions from the model and the observed outcomes) will be tested with the Hosmer–Lemeshow test. We will assess the apparent performance of the fitted models for discrimination using the C-statistic (equal to the area

under the receiver-operating characteristic curve) and the sensitivity for clinically significant deterioration.[26]

Internal validation using the bootstrap validation approach will be undertaken to evaluate the performance and optimism of the developed model.[27] This will allow the use of the complete data set for model development and provide a mechanism to account for model overfitting or uncertainty in the model development process. We will quantify any optimism in the final prediction model and estimate a so-called "shrinkage factor" that can be used to adjust the regression coefficients and apparent performance for optimism. This will lead to a new final model being produced in each of the bootstrap samples. We will average the difference in the performance of the models to obtain a single estimate of optimism for the C-statistic.

Missing Data:

As data are to be extracted from clinical records, missing variable data will inevitably occur. Although it is possible to verify the data to judge whether missing data are missing completely at random (MAR) or associated with observed variables, it is generally impossible to prove that data are indeed MAR or whether they are not missing at random. (MNAR).[24] Multiple imputation will be used to impute ~~,~~ with the number of imputations determined by the amount of missing data~~10 imputations~~, under a missing at random assumption, ~~missing values~~ so as to avoid excluding patients from the analysis. This will be completed using STATA with the exact method determined by the amount, type and distribution of the missing data and we will adhere to recognised guidelines for appropriate use and reporting of methods to deal with missing data.[28, 29] After imputation, a sensitivity analysis will be undertaken to determine how the substantive results depend on the multiple imputation method employed. This is consistent with the TRIPOD recommendations with the handling of missing data in prognostic studies.[12]

Model Accuracy:

The sensitivity and specificity of the model for detecting patients at low-risk of deterioration will be calculated comparing the classification of each patient by the model with whether they actually deteriorated. To assess how informative lack of deterioration is, the model will be derived again for those patients who do not deteriorate within 24 hours. We will determine whether a more accurate model can be produced for those still in hospital after 24 hours.

A Receiver Operating Characteristic (ROC) curve for both models will be plotted and the trade-off between the sensitivity and specificity of the model explored.[30] As indicated previously a 1/100 risk of deterioration following discharge may be clinically acceptable and therefore our model will aim for at least a 99% sensitivity to deterioration.[21]

Sensitivity analysis:

The 10-year period of data collection represents a long-time period over which clinical practice and outcomes may have changed. To assess for this, we will estimate the yearly prevalence of clinical deterioration and note any statistically significant changes in outcome over time. In addition, because NICE guidelines were updated in 2014 (with minor changes to the indications for CT brain imaging) the prognostic model will be estimated solely for the time-period 2014-2017 and compared to the model estimated for the whole-time period.[1]

Exploratory Analysis:

Individual patient data from a prospective Italian cohort study is available to the research team.[31] The variables collected in the Italian study and how they compare to the variables being collected in our study are shown in Table 2. If most factors present in the multivariable model developed in our study are present in the Italian data set then we will assess the effect of these factors on the risk of deterioration in a multivariable model derived in the Italian data set. If the effect estimates are similar to those estimated in the data collected in England then we will combine the individual patient data of the 2 data sets to improve the precision of the model estimates.

Discussion:

Strengths:

To the authors' knowledge this will be the largest cohort study conducted that assesses clinical deterioration in GCS13-15 patients with brain injuries identified by CT imaging. We are collecting data from multiple sites and potentially incorporating data from a different European country. The definition of clinical deterioration is wide and defined to encompass potential benefits of hospital admission from the ED. This outcome is one that can be used to help inform clinical decision making regarding the selection of patients in this group that would benefit from hospital admission.

Limitations:

Data collection is retrospective and will be limited by the nature and accuracy of the data clinically recorded. However, such data are likely to be applicable and implementable in current routine practice. Given the large sample size required for this study and the challenges of prospectively recruiting patients in the ED, a retrospective method for data collection represents a feasible and pragmatic data collection strategy.

~~In the primary data collection at the 2 sites in the UK, O~~outcomes will only be assessed during hospital admission and for those who re-attend the study hospitals following discharge. This may underestimate deterioration following discharge especially if patients ~~and not those who~~ die in the community or deteriorate and are readmitted to a different hospital ~~in~~. ~~This will potentially underestimate the prevalence of.~~ We will estimate the effect of this possible bias by conducting a sensitivity analysis using data for the sub-set of patients registered on the Trauma and Audit Network Database where complete data following discharge is available.

Further Research:

Prognostic models tend to perform optimistically using the data from which they were derived and therefore their accuracy requires external validation in separate data sets.[12] There are different strategies for this and we will attempt to validate the model derived from this study in a sub-population of a European prospective cohort of TBI patients that is currently ongoing (CENTER-TBI), with data expected to be available in 2018.[32, 33] Our validation study will be subject to a separate protocol. If the model appears sufficiently accurate at identifying low-risk TBI patients could be safely discharged implementation will be tested prospectively in the context of the NHS.

Abbreviations:

AIS: Abbreviated Injury Severity Score; CT: Computed Tomography; GCS: Glasgow Coma Scale; NICE: National Institute for Health and Clinical Excellence; ROC: Receiver Operating Curve; TBI: Traumatic Brain Injury; TARN: The Trauma Audit and Research Network

Declarations:

Ethics Approval and consent to participate:

This study received ethical approval from the West of Scotland NHS Research Ethics Committee 4, reference 17/WS/0204.

Patient and Public Involvement:

The Hull and East Yorkshire NHS hospital trust have a patient public involvement group, The Trans-Humber-Research Panel, that includes current and previous patients and carers. This group has helped formulate the research aims and protocol for this project. They will have an ongoing role in the project.

The Headway Charity have been consulted in formulating the project aims and will be involved in dissemination of the project findings.

Consent for publication:

Not applicable.

Availability of data and materials:

Not applicable.

Competing interests:

The authors declare that they have no competing interests.

Funding:

Carl Marincowitz is funded by a National Institute for Health Research Doctoral Fellowship.

This protocol presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Authors' contributions:

This idea for the study was conceived by Carl Marincowitz with help from all the co-authors. Trevor Sheldon and Fiona Lecky provided specialist advice regarding methodology and the design of the methods. Victoria Allgar provided specialist advice regarding statistical analysis. Will Townend provided specialist clinical context.

Acknowledgements:

Not applicable.

1. NICE, *National Clinical Guidance Centre. (2014). CG 176 Head Injury Triage, assessment, investigation and early management of head injury in children, young people and adults. National Institute for Health and Care Excellence.*, NICE, Editor. 2014, DOH: UK.

2. Miller, J.D., *Minor, moderate and severe head injury.* Neurosurg Rev, 1986. **9**(1-2): p. 135-9.
3. Stiell, I.G., et al., *The Canadian CT Head Rule for patients with minor head injury.* Lancet, 2001. **357**(9266): p. 1391-6.
4. Network, S.I.G., *Guideline 110: Early management of patients with a head injury*. 2009.
5. Smits, M., et al., *External validation of the Canadian CT Head Rule and the New Orleans Criteria for CT scanning in patients with minor head injury.* JAMA, 2005. **294**(12): p. 1519-25.
6. Haydel, M.J., et al., *Indications for computed tomography in patients with minor head injury.* N Engl J Med, 2000. **343**(2): p. 100-5.
7. Thorson, C.M., et al., *Repeat head computed tomography after minimal brain injury identifies the need for craniotomy in the absence of neurologic change.* Journal of Trauma & Acute Care Surgery, 2013. **74**(4): p. 967-975.
8. Joseph, B., et al., *The BIG (brain injury guidelines) project: defining the management of traumatic brain injury by acute care surgeons.* J Trauma Acute Care Surg, 2014. **76**(4): p. 965-9.
9. Marincowitz, C., et al., *The Risk of Deterioration in GCS13-15 Patients with Traumatic Brain Injury Identified by Computed Tomography Imaging: A Systematic Review and Meta-Analysis.* J Neurotrauma, 2018. **35**(5): p. 703-718.~~Marincowitz, C.F.E.L., William Townend, Aditya Borakati, Andrea Fabbri, Trevor A. Sheldon6, *The risk of deterioration in GCS13-15 patients with traumatic brain injury identified by CT imaging. A systematic review and meta-analysis.* Journal of Neurotrauma, 2017. **In press**.~~
10. Goodacre, S., *Hospital admissions with head injury following publication of NICE guidance.* Emerg Med J, 2008. **25**(9): p. 556-7.
11. Royston, P., et al., *Prognosis and prognostic research: Developing a prognostic model.* BMJ, 2009. **338**: p. b604.
12. Moons, K.G., et al., *Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration.* Ann Intern Med, 2015. **162**(1): p. W1-73.
13. Steyerberg, E.W., et al., *Predicting outcome after traumatic brain injury: Development and international validation of prognostic scores based on admission characteristics.* PLoS Medicine, 2008. **5**(8): p. 1251-1261.
14. Roozenbeek, B., et al., *Prediction of outcome after moderate and severe traumatic brain injury: external validation of the International Mission on Prognosis and Analysis of Clinical Trials (IMPACT) and Corticoid Randomisation After Significant Head injury (CRASH) prognostic models.* Crit Care Med, 2012. **40**(5): p. 1609-17.
15. Lesko, M.M., et al., *Models of mortality probability in severe traumatic brain injury: results of the modelling by the UK trauma registry.* J Neurotrauma, 2013. **30**(24): p. 2021-30.
16. Lesko, M.M., et al., *Using Abbreviated Injury Scale (AIS) codes to classify Computed Tomography (CT) features in the Marshall System.* BMC Med Res Methodol, 2010. **10**: p. 72.
17. Bouamra, O., et al., *Prediction modelling for trauma using comorbidity and 'true' 30-day outcome.* Emerg Med J, 2015. **32**(12): p. 933-8.
18. Raabe, A., et al., *Correlation of computed tomography findings and serum brain damage markers following severe head injury.* Acta Neurochirurgica, 1998. **140**(8): p. 787-792.
19. Quan, H., et al., *Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries.* Am J Epidemiol, 2011. **173**(6): p. 676-82.
20. Rockwood, K., et al., *A global clinical measure of fitness and frailty in elderly people.* CMAJ, 2005. **173**(5): p. 489-95.
21. Hess, E.P., et al., *Shared decision making in patients with low risk chest pain: prospective randomized pragmatic trial.* BMJ, 2016. **355**: p. i6165.
22. Hajian-Tilaki, K., *Sample size estimation in diagnostic test studies of biomedical informatics.* J Biomed Inform, 2014. **48**: p. 193-204.

23. Marincowitz, C., V. Allgar, and W. Townend, *CT head imaging in patients with head injury who present after 24 h of injury: a retrospective cohort study.* Emerg Med J, 2016. **33**(8): p. 538-42.
24. Little RJA, R.D., *Statistical analysis with missing data.* 2nd Edition ed. 2002, New York: John Wiley.
25. Royston, P. and W. Sauerbrei, *Building multivariable regression models with continuous covariates in clinical epidemiology--with an emphasis on fractional polynomials.* Methods Inf Med, 2005. **44**(4): p. 561-71.
26. Steyerberg, E.W. and Y. Vergouwe, *Towards better clinical prediction models: seven steps for development and an ABCD for validation.* Eur Heart J, 2014. **35**(29): p. 1925-31.
27. Harrell, F.E., Jr., K.L. Lee, and D.B. Mark, *Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors.* Stat Med, 1996. **15**(4): p. 361-87.
28. Royston, P., *Multiple imputation of missing values: update.* The Stata Journal, 2005. **5**(2): p. 1-14.
29. Sterne, J.A., et al., *Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls.* BMJ, 2009. **338**: p. b2393.
30. Florkowski, C.M., *Sensitivity, specificity, receiver-operating characteristic (ROC) curves and likelihood ratios: communicating the performance of diagnostic tests.* Clin Biochem Rev, 2008. **29 Suppl 1**: p. S83-7.
31. Fabbri, A., et al., *Observational approach to subjects with mild-to-moderate head injury and initial non-neurosurgical lesions.* J Neurol Neurosurg Psychiatry, 2008. **79**(10): p. 1180-5.
32. Maas, A.I., et al., *Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI): a prospective longitudinal observational study.* Neurosurgery, 2015. **76**(1): p. 67-80.
33. Altman, D.G., et al., *Prognosis and prognostic research: validating a prognostic model.* BMJ, 2009. **338**: p. b605.

Figures:

Figure 1: Current management of minor head injured patients

Figure 2: Population screening and selection

Table 1: Prognostic factors being investigated

Factors from Systematic Review	Type of Data	Factors from NICE guidelines	Type of Data	Factors from TARN TBI/trauma model	Type of Data
Age	Continuous	1st neurological examination in ED	Categorical	Admission Hb	Continuous
Sex	Categorical	Equal Pupils 1st examination	Categorical	Admission Platelets	Continuous
Pre-injury anti-coagulant use	Categorical	Both Pupils reactive 1st examination	Categorical	Charlson Trauma Modified Comorbidity index	Continuous
Pre-injury anti-platelet use	Categorical	SIGN of Skull fracture 1st examination	Categorical	Admission BM	Continuous
GCS on arrival to ED	Categorical	Seizures in ED	Categorical	Frailty Score	Continuous
BP on arrival ED	Continuous	Vomiting in ED	Categorical		
HAIS	Continuous	An occupant ejected from a motor vehicle	Categorical		
Marshall Classification	Categorical	Mechanism of Injury	Categorical		
Single Injury	Categorical	Amnesia	Categorical		
Comment on Midline shift	Categorical	Intoxicated EToH time of injury	Categorical		
Comment on size of bleed		Seizures before arrival ED	Categorical		
Additional Injuries	Categorical	Vomiting before arrival ED	Categorical		
Sats on arrival ED	Continuous	A pedestrian or cyclist struck by a motor vehicle	Categorical		
		A fall from height of > than 1 metre or 5 stairs	Categorical		

Table 2: Comparison between Italian data set and data being collected

Factor	**In Italian Data**	**Factor**	**In Italian Data**
Age	Yes	Equal Pupils 1st examination	Yes
Sex	Yes	Both Pupils reactive 1st examination	Yes
Pre-injury anti-coagulant use	Yes	SIGN of Skull fracture 1st examination	No
Pre-injury anti-platelet use	No	Seizures in ED	No
Charlson Trauma Modified Comorbidity index	Yes	Vomiting in ED	No
A pedestrian or cyclist struck by a motor vehicle	Yes	HAIS	No
An occupant ejected from a motor vehicle	Yes	Marshall Classification	Yes
A fall from height of > than 1 metre or 5 stairs	Yes	Single Injury and type of injury	Yes
Mechanism of Injury	No	Comment on Midline shift	No
Amnesia	Yes	Comment on size of bleed	No
Loss of Consciousness	Yes	Frailty Score	No
Intoxicated time of injury	No	Admission Hb	No
Seizures before arrival ED	Yes	Admission Platelets	No
Vomiting before arrival ED	Yes	Admission BM	No
GCS on arrival to ED	Yes	Additional Injuries	Yes
BP on arrival ED	No		

Figure 1

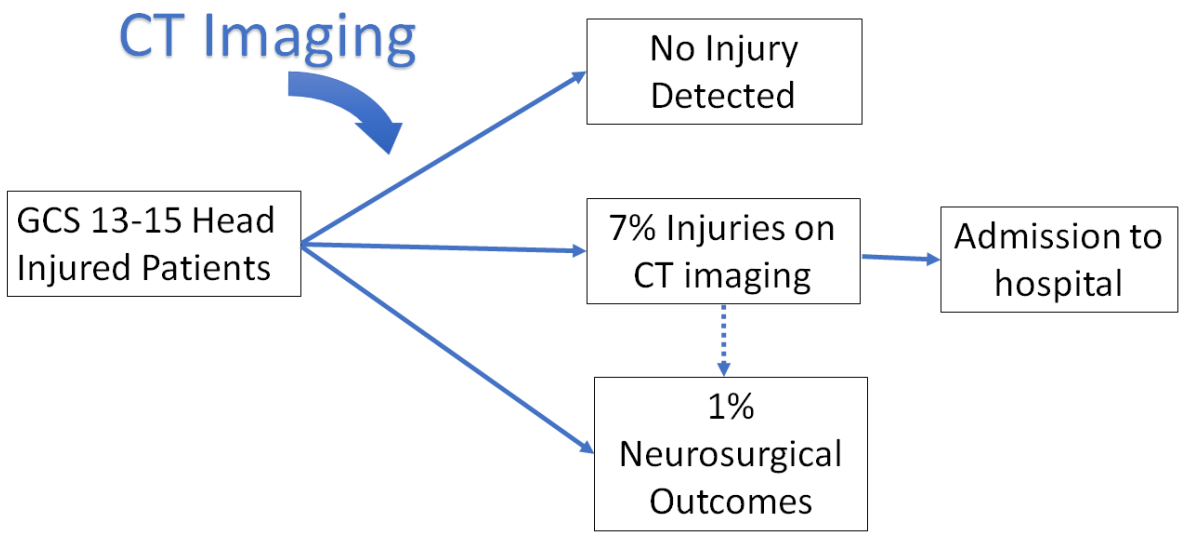

Figure 2