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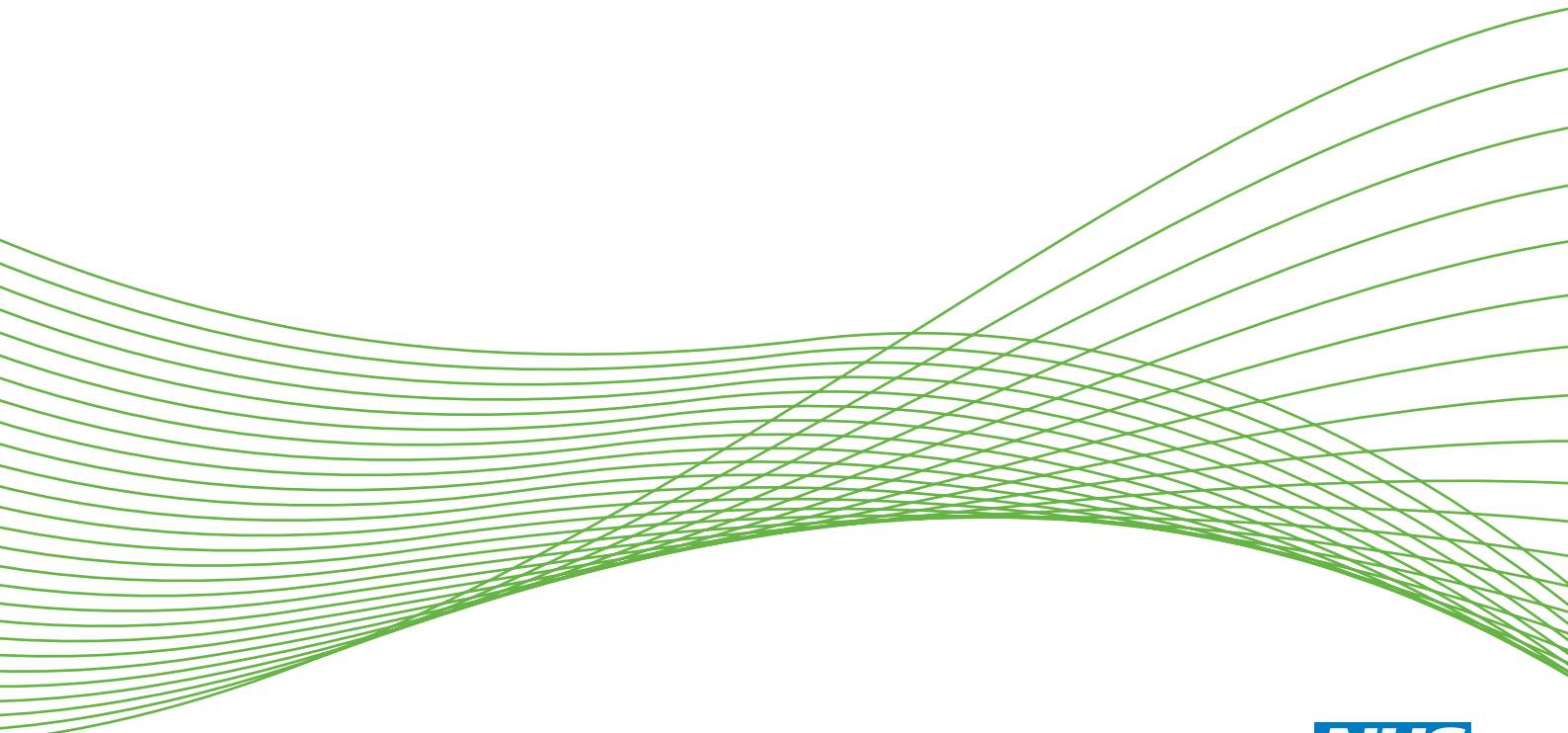
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Risk Adjustment In Neurocritical care (RAIN) – prospective validation of risk prediction models for adult patients with acute traumatic brain injury to use to evaluate the optimum location and comparative costs of neurocritical care: a cohort study

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KA Griggs, E Walmsley, M Smith, P Yeoman, FE Lecky, PJA Hutchinson,
DK Menon and KM Rowan*



***National Institute for
Health Research***

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Abstract

Risk Adjustment In Neurocritical care (RAIN) – prospective validation of risk prediction models for adult patients with acute traumatic brain injury to use to evaluate the optimum location and comparative costs of neurocritical care: a cohort study

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Objectives: To validate risk prediction models for acute traumatic brain injury (TBI) and to use the best model to evaluate the optimum location and comparative costs of neurocritical care in the NHS.

Design: Cohort study.

Setting: Sixty-seven adult critical care units.

Participants: Adult patients admitted to critical care following actual/suspected TBI with a Glasgow Coma Scale (GCS) score of < 15.

Interventions: Critical care delivered in a dedicated neurocritical care unit, a combined neuro/general critical care unit within a neuroscience centre or a general critical care unit outside a neuroscience centre.

Main outcome measures: Mortality, Glasgow Outcome Scale – Extended (GOSE) questionnaire and European Quality of Life-5 Dimensions, 3-level version (EQ-5D-3L) questionnaire at 6 months following TBI.

Results: The final Risk Adjustment In Neurocritical care (RAIN) study data set contained 3626 admissions. After exclusions, 3210 patients with acute TBI were included. Overall follow-up rate at 6 months was 81%. Of 3210 patients, 101 (3.1%) had no GCS score recorded and 134 (4.2%) had a last pre-sedation GCS score of 15, resulting in 2975 patients for analysis. The most common causes of TBI were road traffic accidents (RTAs) (33%), falls (47%) and assault (12%). Patients were predominantly young (mean age 45 years overall) and male (76% overall). Six-month mortality was 22% for RTAs, 32% for falls and 17% for assault. Of survivors at 6 months with a known GOSE category, 44% had severe disability, 30% moderate

disability and 26% made a good recovery. Overall, 61% of patients with known outcome had an unfavourable outcome (death or severe disability) at 6 months. Between 35% and 70% of survivors reported problems across the five domains of the EQ-5D-3L. Of the 10 risk models selected for validation, the best discrimination overall was from the International Mission for Prognosis and Analysis of Clinical Trials in TBI Lab model (IMPACT) (c-index 0.779 for mortality, 0.713 for unfavourable outcome). The model was well calibrated for 6-month mortality but substantially underpredicted the risk of unfavourable outcome at 6 months. Baseline patient characteristics were similar between dedicated neurocritical care units and combined neuro/general critical care units. In lifetime cost-effectiveness analysis, dedicated neurocritical care units had higher mean lifetime quality-adjusted life-years (QALYs) at small additional mean costs with an incremental cost-effectiveness ratio (ICER) of £14,000 per QALY and incremental net monetary benefit (INB) of £17,000. The cost-effectiveness acceptability curve suggested that the probability that dedicated compared with combined neurocritical care units are cost-effective is around 60%. There were substantial differences in case mix between the 'early' (within 18 hours of presentation) and 'no or late' (after 24 hours) transfer groups. After adjustment, the 'early' transfer group reported higher lifetime QALYs at an additional cost with an ICER of £11,000 and INB of £17,000.

Conclusions: The risk models demonstrated sufficient statistical performance to support their use in research but fell below the level required to guide individual patient decision-making. The results suggest that management in a dedicated neurocritical care unit may be cost-effective compared with a combined neuro/general critical care unit (although there is considerable statistical uncertainty) and support current recommendations that all patients with severe TBI would benefit from transfer to a neurosciences centre, regardless of the need for surgery. We recommend further research to improve risk prediction models; consider alternative approaches for handling unobserved confounding; better understand long-term outcomes and alternative pathways of care; and explore equity of access to postcritical care support for patients following acute TBI.

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List of abbreviations

AIC	Akaike information criterion	IMPACT	International Mission for Prognosis and Analysis of Clinical Trials in TBI
APACHE	Acute Physiology And Chronic Health Evaluation	INB	incremental net monetary benefit
BIC	Bayesian information criterion	IQR	interquartile range
CCMDS	Critical Care Minimum Data Set	ISS	injury severity score
CEA	cost-effectiveness analysis	LOS	length of stay
CEAC	cost-effectiveness acceptability curve	MICE	Multivariate Imputation by Chained Equations
CI	confidence interval	MRC	Medical Research Council
CMP	Case Mix Programme	MRIS	Medical Research Information Service
CRASH	Corticosteroid Randomisation After Significant Head injury	NCCNet	Neurocritical Care Network
CRN	Clinical Research Network	NICE	National Institute for Health and Care Excellence
CT	computerised tomography	NIGB	National Information Governance Board
DVR	data validation report	NIHR	National Institute for Health Research
EBIC	European Brain Injury Consortium	$PaCO_2$	partial pressure of carbon dioxide
ECC	Ethics and Confidentiality Committee	PaO_2	partial pressure of oxygen
EQ-5D-3L	European Quality of Life-5 Dimensions, 3-level version	QALY	quality-adjusted life-year
FiO_2	fraction of inspired oxygen	QOL	quality of life
GCS	Glasgow Coma Scale	R&D	research and development
GOS	Glasgow Outcome Scale	RAIN	Risk Adjustment In Neurocritical care
GOSE	Glasgow Outcome Scale – Extended	RCT	randomised controlled trial
GP	general practitioner	REC	Research Ethics Committee
HDU	high-dependency unit	ROC	receiver operating characteristic
HRG	Healthcare Resource Group	RTA	road traffic accident
ICER	incremental cost-effectiveness ratio	SAH	subarachnoid haemorrhage
ICNARC	Intensive Care National Audit and Research Centre	SF-36	Short Form questionnaire-36 items
ICU	intensive-care unit	SICSAG	Scottish Intensive Care Society Audit Group
IMD	Index of Multiple Deprivation		

LIST OF ABBREVIATIONS

SSI	site-specific information	TCDB	Trauma Coma Data Bank
TARN	Trauma Audit and Research Network	UKCCTF	UK Critical Care Trials Forum
TBI	traumatic brain injury	WBIC	Wolfson Brain Imaging Centre

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Background

Where adult patients with traumatic brain injury (TBI) should be optimally managed is an important question for the NHS, both in terms of outcomes and costs. Notwithstanding the lack of evidence, it has been recommended that patients with a severe TBI should be managed within a neuroscience centre. Currently, many (particularly those without surgically remedial lesions) are neither treated in, nor transferred to, one. A combination of geography, bed availability, local variation and clinical assessment of prognosis can often determine the location of definitive critical care for adult patients with TBI.

Recent research has suggested benefit from managing severe head injury in specialist centres; however, the results are inconclusive owing to lack of adjustment for all known confounders, no data on costs of care, only having follow-up data to hospital discharge, and not addressing whether provision should be in dedicated neurocritical care units or combined neurocritical/general critical care units within neuroscience centres.

Variation in the way services are organised and delivered can allow them to be compared using observational methods. This is only possible; however, if a valid, reliable, appropriate and accurate risk prediction model exists. A number of specific models for TBI exist but these models require further prospective validation, and potentially recalibration, before they can be applied with confidence for research and audit in neurocritical care in the NHS.

The primary aim of the Risk Adjustment In Neurocritical care (RAIN) study was to validate risk prediction models for acute TBI and to use the best model(s) to evaluate the optimum location and comparative costs of neurocritical care in the NHS.

Objectives

Specific, detailed objectives to achieve this aims were to:

1. identify existing risk prediction models for acute TBI
2. collect data for the selected risk prediction models
3. describe the case mix and outcomes, to 6 months, from TBI
4. validate the selected risk prediction models
5. compare the relative costs, consequences and cost-effectiveness of care for adult patients with TBI admitted to dedicated neurocritical care units within a neuroscience centre, combined neuro/general critical care units within a neuroscience centre, and general critical care units outside a neuroscience centre
6. make recommendations for policy, practice and future research in the NHS.

Methods

Selection of candidate risk prediction models for acute TBI was conducted through a systematic review of the literature, consultation with clinical experts and methodological assessment. A detailed data set was produced (based on publications of the selected risk prediction models plus location of care details) to describe and cost the patient journey; short-term outcomes; and contact details, to provide the information required for 6-month follow-up.

All neurocritical care units in the UK and adult general critical care units participating in the Case Mix Programme (CMP) were invited to participate. Data set familiarisation courses were held to explain the background, aims and rationale for the study and provide a detailed explanation of the data set.

All adult patients admitted to participating critical care units following an actual or suspected TBI, and with a Glasgow Coma Scale (GCS) score of < 15 following resuscitation were included. A sample size calculation indicated 3400 patients were required. Data were entered locally on to a dedicated, secure, web-based data entry system. To avoid duplication of data collection, the RAIN study was linked to two national clinical audits: the CMP for units in England and Wales and the Scottish Intensive Care Society Audit Group (SICSAG) for units in Scotland. Data validation was ongoing throughout and regular contact was maintained with all participating units.

Six-month patient follow-up was conducted centrally and was carefully conducted to prevent distress to either the patient or their carer(s). Surviving patients were sent, by post, an introductory letter, information sheet, consent form, questionnaires, freepost return envelope and pen. Carer(s) were asked to assist with completion of the consent form and, where relevant, questionnaires. Non-responders were followed up. Two questionnaires were included: one included the European Quality of life (EuroQol) 5-dimension, 3-level version (EQ-5D-3L) and the Glasgow Outcome Scale – Extended (GOSE) and the other included questions about use of health services following discharge from acute hospital.

Patients were included in the analysis if their last GCS score prior to sedation/admission to critical care was < 15. Case mix, length of stay (LOS) and outcomes were summarised overall and for subgroups defined by the cause of TBI – road traffic accident (RTA), fall or assault. GOSE responses were used to assign each patient to a GOSE category.

With respect to model validation, the case mix and outcomes of patients for each family of models was compared with those for patients in the RAIN study. Univariable analyses were conducted to assess the relationship between risk factors and outcomes. Each risk prediction model was then validated using measures of calibration, discrimination and overall fit. A nested, inter-rater reliability study was conducted on a sample of computerised tomography (CT) scans.

For the evaluation of alternative care locations, two distinct research objectives were identified that addressed separate decision problems, to compare the relative costs, consequences and cost-effectiveness of:

1. management in a dedicated neurocritical care unit compared with a combined neuro/general critical care unit; and
2. 'early' (within 18 hours of hospital presentation) transfer to a neuroscience centre compared with 'no or late' (after 24 hours) transfer, for patients who initially present at a non-neuroscience centre and do not require neurosurgery.

The evaluation was undertaken in two phases. In the first phase, risk-adjusted costs and consequences of alternative care locations at 6 months were compared. EQ-5D-3L profiles were combined with health-state preference values from the UK general population, to give an EQ-5D-3L utility index score and quality-adjusted life-years (QALYs) at 6 months were calculated by combining survival and utility score at 6 months. Each item of resource use was combined with the appropriate unit cost to report a cost per patient for each cost category (inpatient, outpatient, community and total costs) in 2010–11 prices. For research objective 2, subgroup analyses were undertaken by age, presence of major extracranial injury, and GCS score. In the second phase, estimates from the 6-month end points and the literature were used to project lifetime cost-effectiveness. Incremental net monetary benefits (INBs) were estimated by valuing incremental QALYs at a threshold of £20,000 per QALY and subtracting from this the incremental costs. The robustness of results to alternative assumptions was tested in extensive sensitivity analyses.

Missing data were addressed with multiple imputation.

Results

Ten risk prediction models, developed and validated in three studies – Hukkelhoven *et al.* (Hukkelhoven: Hukkelhoven CW, Steyerberg EW, Habbema JD, Farace E, Marmarou A, Murray GD, *et al.* Predicting outcome after traumatic brain injury: development and validation of a prognostic score based on admission characteristics. *J Neurotrauma* 2005;**22**:1025–39), the Medical Research Council (MRC) CRASH (Corticosteroid Randomisation After Significant Head injury) trial collaborators (CRASH: MRC CRASH trial collaborators. Predicting outcome after traumatic brain injury: practical prognostic models based on large cohort of international patients. *BMJ* 2008;**336**:425–9) and Steyerberg *et al.* [IMPACT (International Mission for Prognosis and Analysis of Clinical Trials in TBI): Steyerberg EW, Mushkudiani N, Perel P, Butcher I, Lu J, McHugh GS, *et al.* Predicting outcome after traumatic brain injury: development and international validation of prognostic scores based on admission characteristics. *PLoS Med* 2008;**5**:e165] were selected for external validation in the RAIN study. Four models were developed for predicting mortality at 6 months (one Hukkelhoven and three IMPACT) and six for predicting unfavourable outcome at 6 months (one Hukkelhoven, two CRASH and three IMPACT).

A total of 67 critical care units participated in the RAIN study: 31 within a neuroscience centre (13 dedicated neurocritical care units; 14 combined neurocritical/general critical units, and four additional critical care units admitting overflow patients from the neurocritical care unit); and 36 general critical care units outside a neuroscience centre.

The final RAIN study data set contained 3626 admissions; a highly representative sample of patients receiving critical care following acute TBI in the UK. After exclusions, 3210 patients remained. Of 2323 patients not reported by the Medical Research Information Service (MRIS) as having died, 1834 (79%) were successfully followed up [paper, $n = 1245$ (68%), or telephone, $n = 589$ (32%) questionnaire]. When combined with the 786 patients known to have died, this resulted in an overall follow-up rate of 82% (2620/3210).

Of 3210 patients, 101 (3.1%) had no GCS score recorded and 134 (4.2%) had a last pre-sedation GCS score of 15, which resulted in a data set of 2975 patients for analysis. The most common causes of TBI were RTA (33%), fall (47%) and assault (12%), with 3% other and 5% unknown cause. Major extracranial injury was present in 41% and intoxication confirmed/suspected in 45%. Patients were predominantly young (mean age 45 years) and male (76%).

A substantial burden of poor neurological outcomes and quality of life (QOL) 6 months after TBI was demonstrated. Mortality at discharge from acute hospital was 16% for assault, 21% for RTA and 30% for falls, rising to 17%, 22% and 32%, respectively, at 6 months. Of survivors at 6 months with a known GOSE category, 44% had severe disability, 30% had moderate disability, and only 26% had made a good recovery. When combined with the 26% mortality at 6 months, 61% of patients with known outcome had an unfavourable outcome (death or severe disability) at 6 months. Between 35% and 70% of survivors reported problems across the five domains of the EQ-5D-3L at 6 months.

Median total LOS in critical care was 7 days; this differed between survivors (median 8 days) and non-survivors (median 3 days). Median total LOS in acute hospital was 30 days for survivors compared with 5 days for non-survivors.

In terms of the statistical assessment of model performance, there was very little to choose between models of similar complexity from Hukkelhoven, CRASH and IMPACT. The best discrimination overall was from the IMPACT Lab model (c-index 0.779 for mortality and 0.713 for unfavourable outcome) – the only one of the models to include laboratory parameters – however, the improvement in performance over the

models of the next level of complexity (Hukkelhoven, CRASH CT, IMPACT Extended) was very small. There was a larger difference in performance between these models and the simplest models using core data only (CRASH Basic and IMPACT Core), suggesting that there is important prognostic information within the CT scan and the presence or absence of pre-hospital hypoxia/hypotension. The Hukkelhoven and IMPACT Lab models were well calibrated for mortality at 6 months but all models substantially underpredicted the risk of unfavourable outcome at 6 months. The substudy on inter-rater reliability of CT scan reporting suggested that the CT findings included in the models could be assessed with acceptable reliability.

For subsequent analyses, we therefore selected the IMPACT Lab model as the primary model for risk adjustment in the base-case analyses, with the CRASH CT model used for sensitivity analyses (chosen over the Hukkelhoven model as it included more substantially different predictor variables from the IMPACT Lab model).

In the evaluation of alternative locations of care, baseline patient characteristics were similar between dedicated neurocritical care units and combined neuro/general critical care units. At 6 months, mortality was similar between the groups (24% vs 25%) but the dedicated neurocritical care unit group had higher mean EQ-5D-3L utility index score for survivors (0.48 vs 0.43) and higher mean QALYs (0.18 vs 0.16), although none of these differences was statistically significant after case mix adjustment. Critical care length of stay was longer for the dedicated neurocritical care unit group (mean 13 vs 11 days) resulting in higher mean total costs at 6 months (incremental cost £3694 after case mix adjustment).

There were substantial differences in case mix between patients in the 'early' and the 'no or late' transfer groups; patients in the 'early' transfer group were on average younger and with less severe case mix (median predicted risk of death at 6 months 18.3% vs 24.6%). At 6 months, patients in the 'early' transfer group had substantially lower mortality (19% vs 41%), higher mean EQ-5D-3L utility index score for survivors (0.55 vs 0.44) and higher mean QALYs (0.22 vs 0.13). These differences were reduced but remained significant after case mix adjustment. All categories of resource use in the 'early' transfer group were approximately double that of the 'no or late' transfer group, resulting in substantially higher mean total costs at 6 months (incremental cost £15,001 after case mix adjustment).

In the lifetime cost-effectiveness analysis (CEA), dedicated neurocritical care units had higher mean lifetime QALYs at small additional mean costs, with an incremental cost-effectiveness ratio (ICER) of £14,000 per QALY and INB of £1300. The cost-effectiveness acceptability curve (CEAC) suggested that the probability that dedicated compared with combined neurocritical care units are cost-effective is around 60%.

After adjusting for differences in baseline characteristics, the 'early' transfer group reported higher lifetime QALYs, at an additional cost, with an ICER of £11,000 per QALY and INB of £17,000. The CEAC suggested that the probability that 'early' transfer was cost-effective is close to 100%. The results for the subgroup analyses suggested that 'early' transfer has a very low probability of being cost-effective for patients aged >70 years, around 60% probability of being cost-effective for patients without major extracranial injury, and 60–80% probability of being cost-effective for patients with mild to moderate TBI (GCS score of 9–14). The results in the alternative subgroup were close to 100% in each case.

The results of the lifetime CEA were robust to alternative assumptions.

Conclusions

The risk prediction models evaluated in the RAIN study demonstrated sufficient statistical performance to support their use in research studies but fell below the level that would be required to recommend their use to guide individual patient decision-making.

Although the results of the RAIN study suggest that, within a neuroscience centre, management in a dedicated neurocritical care unit may be cost-effective compared with management in a combined neuro/general critical care unit, there was considerable statistical uncertainty in this finding. The results of the RAIN study support current recommendations that all patients with severe TBI (GCS score of 3–8) would benefit from transfer to a neuroscience centre, regardless of their need for neurosurgery. However, caution should be exercised with regard to the risk of residual confounding. Benefit was also found for patients with mild or moderate TBI (GCS score of 9–14) requiring critical care. The only exception was in patients aged of >70 years, for whom transfer was associated with increased risk of death, and the most cost-effective strategy was management within the hospital at which they presented.

We recommend further research to:

1. explore the potential to improve on the current risk prediction models for acute TBI
2. consider alternative approaches for handling the potential impact of unobserved confounders on the RAIN study results
3. continue to follow up the RAIN study cohort to obtain data on long-term mortality, functional outcomes and QOL
4. better understand the alternative pathways of care for patients following acute TBI and the impact of these on costs and outcomes, and
5. explore equity of access to post-critical care support for patients following acute TBI.

The RAIN study should inform future research studies in the neurocritical care of adult patients following acute TBI through provision of reliable data for sample size calculations and exploratory analyses, and informing the choice of risk adjustment methods and data set design.

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Chapter 1 Introduction

Risk prediction models have been in established use in adult general critical care units for >30 years, since the publication of the original Acute Physiology And Chronic Health Evaluation (APACHE) model in 1981.¹ In the UK, the first large-scale validation of a risk prediction model was the Intensive Care Society's APACHE II study in Britain and Ireland (1987–9).^{2,3} This study produced recalibrated coefficients for the APACHE II model, and led, in 1994, to the formation of the Intensive Care National Audit and Research Centre (ICNARC) and the Case Mix Programme (CMP), the national clinical audit of adult general critical care units in England, Wales and Northern Ireland. ICNARC has continued to pioneer developments in risk prediction in the CMP, most recently through the validation and recalibration of a number of general risk prediction models⁴ and subsequent development of a new model – the ICNARC model.⁵

Unlike adult general critical care, no data are routinely collected in the NHS for risk-adjusted comparison of outcomes from neurocritical care. Consequently, a number of dedicated neurocritical care units currently participate in the CMP. However, there are significant limitations to using models developed and validated for general critical care for patients receiving neurocritical care. Using a spectrum of measures for calibration and discrimination, risk prediction models – successfully developed and validated for adult admissions to general critical care units – showed significant departure from perfect calibration in admissions with head injuries to adult general and dedicated neurocritical care units.⁶ The inclusion and handling within general risk models of variables of specific prognostic importance in acute traumatic brain injury (TBI) is often poor.⁶ For example, the APACHE II model assumes that any patient who is sedated for the entire first 24 hours in the critical care unit is deemed neurologically normal, which is unlikely to be correct for TBI patients and has led to that the use of pre-sedation values of the Glasgow Coma Scale (GCS) for such patients.⁷ The only general model to take any account of changes detected on computerised tomography (CT) scan is the Mortality Prediction Model (MPM) II, and the inclusion of CT information in this model is limited to the presence of an intracranial mass effect. Furthermore, all risk prediction models for adult general critical care use an outcome of mortality at discharge from acute hospital, which is not considered adequate for neurocritical care when longer-term (e.g. 6-month) mortality and, importantly, functional outcome are more valid.⁸

Although a large number of risk prediction models for TBI exist, a systematic review found that most models are limited by being based on small samples of patients, having poor methodology, and rarely being validated on external populations.⁹ Despite the more recent development of models based on larger, more representative data sources,¹⁰ these models require further prospective validation, and potentially recalibration, before they can be applied with confidence for research and audit in neurocritical care in the NHS.

In the NHS, adult patients with TBI are rarely managed by a single service. They are usually managed by a succession of services from first contact to definitive critical care and the latter is not always within a dedicated neurocritical care unit within a neuroscience centre. Despite guidelines recommending that all patients with severe TBI be treated within a neuroscience centre,¹¹ many (particularly those without surgically remedial lesions) are currently neither treated in nor transferred to one. A combination of geography, bed availability, local variation and clinical assessment of prognosis can often determine the location of definitive critical care for an adult patient with TBI. The Neurocritical Care Stakeholder Group, established to offer expert advice to Department of Health and Commissioners, indicated in its audit report that, within the NHS, only 67% of beds that are ring-fenced for neurocritical care were in dedicated neurocritical care units and that neurocritical care unit occupancy rates exceeded 90% (especially for Level 3 beds).¹² Most neurocritical care for adult patients with TBI was delivered either in dedicated neurocritical care units (42%) or in combined neuro/general critical care units within a neuroscience centre (35%). However, despite clear guidelines and the progressive regionalisation of neurosurgical care since 1948, 23% of patients with TBI were treated in general critical care units outside a neuroscience centre.

Local critical care consultant opinion indicated that at least 83% of these patients required transfer to a neuroscience centre. No data were available, or are routinely collected even in 2012, within the NHS for risk-adjusted comparisons.

Where adult patients with TBI should be optimally managed is an important question for the NHS, in terms of both outcomes and costs. Belief and limited evidence has underpinned the establishment, and continuing expansion, of dedicated, neurocritical care facilities in the UK^{13,14} but no formal evaluation has been undertaken. Increased centralisation has been hypothesised to improve outcomes through concentration of knowledge and expertise, higher volumes of patients and greater adherence to evidence-based protocols. Recent research has suggested benefit from managing severe head injury in specialist centres;^{15,16} however, the results are inconclusive owing to lack of adjustment for all known confounders, no data on costs of care, and having follow-up data only to hospital discharge. The existing research also does not address the issue of dedicated compared with combined critical care units within neuroscience centres. A key issue for policy-makers is whether the additional initial costs of more specialised care are justified by subsequent reductions in morbidity costs and/or improvements in patient outcomes. Although conventional randomised controlled trial (RCT) methodology may be impractical in this setting, the presence of variation in the way services are organised and delivered can allow them to be compared using observational methods. This is possible only if a valid, reliable, appropriate and accurate risk prediction model exists.

The Risk Adjustment In Neurocritical care (RAIN) study was originally conceived in 2001. At its inaugural meeting in February 2007, the newly formed Neurocritical Care Network (NCCNet), a network of units and staff providing neurocritical care to patients in both dedicated and general units, identified establishing a risk prediction model to investigate and evaluate the location and outcomes of care for adult patients with TBI as their first, and top, priority. It was recognised that this aim could only be achieved through validation of an accurate risk prediction model for adult patients with TBI and the RAIN study was therefore adopted by NCCNet.

The primary aims of the RAIN study were to validate risk prediction models for acute TBI in the setting of neurocritical care in the NHS, and to use these models to evaluate the optimum location and comparative costs of neurocritical care in the NHS. Specific, detailed objectives to achieve these aims were to:

1. identify, from the literature, the existing risk prediction models for acute TBI most likely to be applicable to a neurocritical care setting, and identify a full list of variables required in order to be able to calculate these models (see *Chapter 2*)
2. collect complete, valid and reliable data for the variables identified above for consecutive adult admissions with TBI to dedicated neurocritical care units within a neuroscience centre, combined neuro/general critical care units within a neuroscience centre and general critical care units outside a neuroscience centre within the NHS (see *Chapter 3*)
3. describe the case mix of these patients and their survival, neurological outcome and quality of life (QOL) at 6 months following the TBI (see *Chapter 4*)
4. undertake a prospective, external validation of existing models for adult patients with TBI admitted to critical care, to identify the strengths and weaknesses of each model, and, if possible, to identify the best model to use for risk adjustment in this setting (see *Chapter 5*)
5. describe and compare adjusted outcomes and cost-effectiveness of care for adult admissions with TBI between dedicated neurocritical care units within a neuroscience centre, combined neuro/general critical care units within a neuroscience centre and general critical care units outside a neuroscience centre within the NHS (see *Chapter 6*)
6. make recommendations for policy and practice within the NHS (see *Chapter 7*).

Chapter 2 Selection of risk prediction models for critically ill patients with acute traumatic brain injury

Introduction

This chapter reports the process that was undertaken to select the most appropriate risk prediction models for external validation in the RAIN study. The aim was to identify the models most likely to be applicable in a neurocritical care setting in the NHS.

Methods

Selection of candidate risk prediction models was conducted in two phases. First, a systematic review of the literature was conducted to identify existing risk prediction models for acute TBI that are most likely to be applicable to a critical care setting and to identify the variables required to be able to calculate these models. Second, eligible models identified by the systematic review were reviewed by the RAIN Study Steering Group (see *Acknowledgements*) to determine if there were any relevant models that had been missed and to select the most appropriate models for external validation in the RAIN study.

Perel *et al.*⁹ previously conducted a systematic review to identify and assess existing risk prediction models for TBI.⁹ The first stage of the systematic review therefore was to update the existing review to identify relevant risk prediction models that had been published since 2006. The second stage was to assess the eligibility of studies previously identified by Perel *et al.*⁹ and by the updated searches for the RAIN study.

Search strategy

The electronic search strategy was based on that used by Perel *et al.*⁹ (see *Appendix 1*) and was performed using EMBASE (incorporating MEDLINE) to identify eligible studies, published in English, from 2006 to 2008, which (1) gave an overall prognostic estimation by combining the predictive information from at least two variables – studies could develop new prognostic models (derivation studies) or evaluate previous ones (validation studies); (2) used variables collected before hospital discharge, which were therefore considered as predictors; (3) included patients of any age; (4) included patients with any type or severity of TBI; and (5) predicted any outcome, such as neurological impairment, disability, survival, etc. There was no time restriction for the evaluation of outcomes. Three search themes were combined: ‘traumatic brain injury’; ‘brain/coma/consciousness/craino/skull’; and ‘prognosis/predicts’. One reviewer (GPr) examined titles, abstracts and keywords of records identified by the electronic database searches for eligibility. The full text of all potentially eligible papers was obtained and independently assessed by two reviewers (GPr and DAH) for eligibility using the pre-defined inclusion criteria described above. Disagreement was resolved by a third reviewer (KMR). The reference lists of all full-text papers reviewed were checked for any additional potentially eligible studies.

The studies previously identified by Perel *et al.*⁹ and by the updated searches were then independently assessed by two reviewers (GPr and DAH) for eligibility for the RAIN study. Studies were eligible for inclusion if they (1) were based on adult (> 16 years) populations; (2) had a sample size of greater than 500 patients in either the development or validation data set; (3) aimed to evaluate outcome regardless of care received during the hospital stay; and (4) were UK based or multicentre. Disagreement was resolved by a third reviewer (KMR).

Assessment of methodological quality

There is no gold standard tool for quality assessment of either RCTs or observational studies. Assessment of the methodological quality of studies eligible for the RAIN study was conducted using the same approach as Perel *et al.*⁹ considering two domains: (1) internal validity, which refers to systematic error and is related to the study design and (2) external validity, which refers to the generalisability of the study and whether the results can be extrapolated to other populations and settings. Eighteen questions related to internal and external validity were considered for each of the studies, as follows:

Internal validity

- Did the study have adequate follow-up?
- Was a discussion included about the rationale to include predictors?
- Were the predictive variables clearly defined?
- Were the outcomes predicted valid?
- Were missing data adequately managed?
- Was an adequate strategy performed to build the multivariable model?
- Were interactions between the variables examined?
- Were the continuous variables handled appropriately?
- Were there > 10 events per variable included?

External validity

- Was a description of the sample population reported?
- Was there a clear explanation on how to estimate the prognosis provided?
- Were measures of discrimination reported?
- Were measures of calibration reported?
- Were confidence intervals (CIs) reported?
- Was the model validated?
- Was the model internally validated?
- Was the model externally validated?
- Was the effect of the model established?

Expert review

All studies eligible for the RAIN study were then reviewed by the RAIN Study Steering Group to identify any additional studies, either published or ongoing, of relevance, and to select the most appropriate models for validation in a UK critical care setting.

Results

The electronic database searches identified a total of 1832 citations. After screening of titles and abstracts, 23 potentially eligible papers were identified for full-text review.^{17–39} In addition, the electronic database searches identified seven review articles,^{40–46} the references lists of which did not identify any further potentially eligible papers. Of the 23 full-text papers reviewed, 13 were excluded because either they were not studies that had developed or evaluated prognostic models for TBI or they were prognostic models that included predictors measured after discharge from hospital (*Figure 1*).

A total of 53 studies reporting 102 models were identified by Perel *et al.*⁹ However, of these, the authors considered the models developed by Signorini *et al.*⁴⁷ and Hukkelhoven *et al.*⁴⁸ to be the most clinically useful for patients from high-income countries with moderate and severe TBI, as they fulfilled the majority of the methodological requirements and showed acceptable performance in the external validation. They were also considered to be available in a user-friendly way. A total of 12 potentially eligible studies were therefore identified from Perel *et al.*⁹ and from the updated searches (see *Figure 1*).

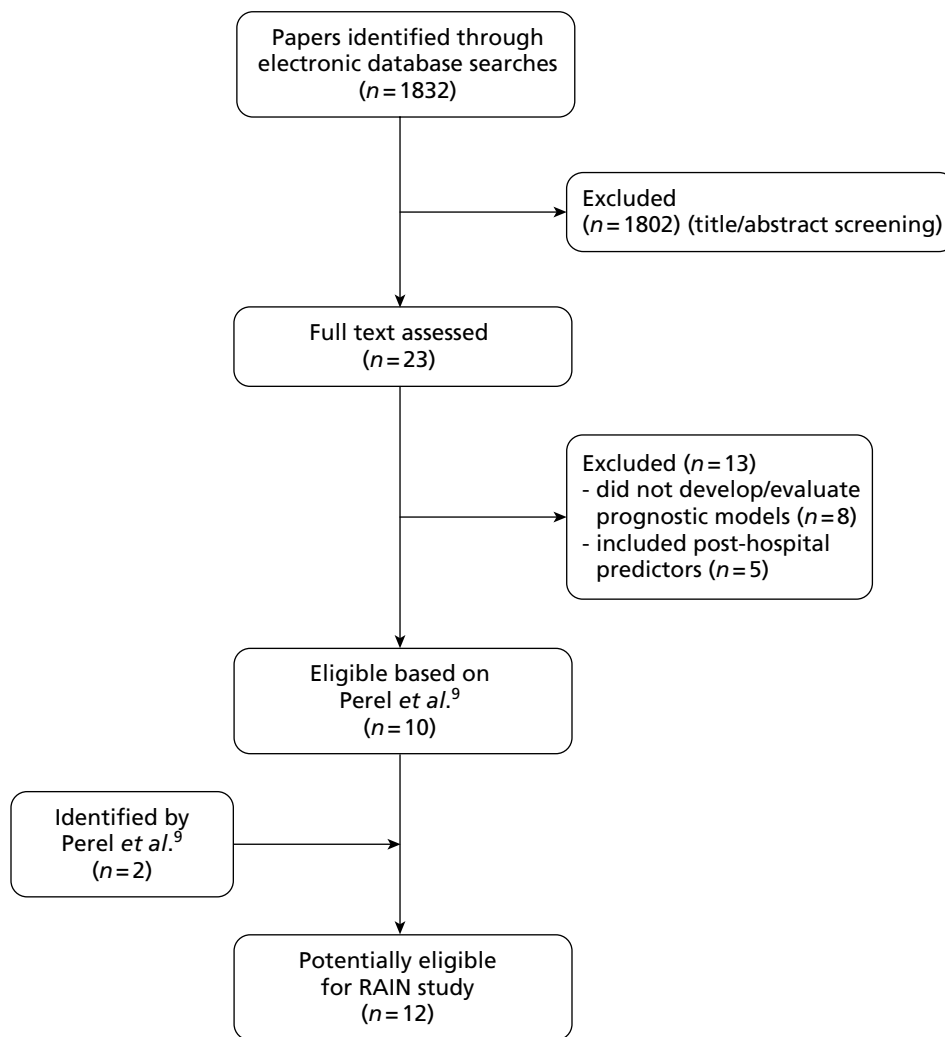


FIGURE 1 Stage 1 of the selection process: update of Perel *et al.*⁹ systematic review.

Of the 12 potentially eligible studies, eight did not fulfil the RAIN study eligibility criteria because the models had been developed in paediatric populations, were based on samples of fewer than 500 patients, adjusted for care received within hospital or had been conducted in a single-centre, non-UK setting (*Figure 2*). This resulted in four eligible studies for review by the RAIN Study Steering Group.

Description of eligible studies

Four studies,^{30,35,47,48} reporting a total of 17 risk prediction models, met the RAIN study eligibility criteria. A brief description of each is given below and a summary is provided in *Table 1*.

Signorini *et al.*

Signorini *et al.*⁴⁷ developed a risk prediction model in a cohort of consecutive patients admitted to a regional trauma centre with moderate or severe head injury ($n = 372$) between January 1989 and July 1991. The criteria for enrolment into the study were (1) age ≥ 14 years and (2) admission or last known GCS score of < 12 , or of 13–15 with concomitant systemic injuries giving an injury severity score (ISS) of ≥ 16 . The outcome assessed was mortality at 1 year. The variables included in the model are detailed in *Table 1*. The model was externally validated in a similar cohort of patients in the same centre accrued as part of an almost identical study between July 1991 and April 1996 ($n = 520$).

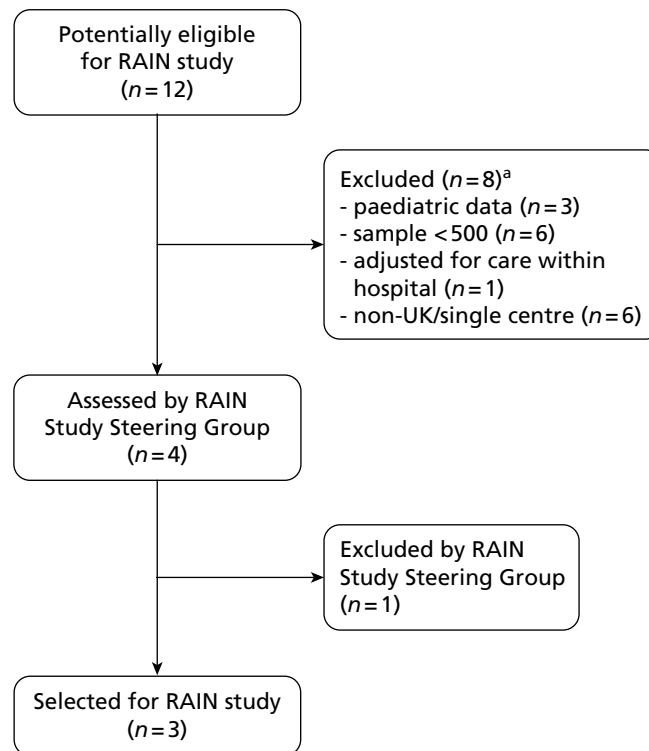


FIGURE 2 Stage 2 of the selection process: selection of models for external validation in the RAIN study. (a) Studies were excluded for more than one reason.

Hukkelhoven *et al.*

Hukkelhoven *et al.*⁴⁸ developed two risk prediction models using data from two multicentre RCTs: (1) the International Tirilazad trial ($n = 1120$) conducted in 40 centres in Europe, Israel and Australia from 1992 to 1994⁴⁹ and (2) the North America Tirilazad trial ($n = 1149$) conducted in 36 centres in the USA and Canada from 1991 to 1994.⁵⁰ Patients were included who (1) were aged ≤ 65 years; (2) had a total GCS score of < 9 or a total GCS score of $9-12$ and an abnormal CT scan; (3) had a GCS motor score available; (4) had a CT scan available; and (5) had been admitted to hospital within 4 hours of the TBI. The outcomes assessed were mortality at 6 months and unfavourable outcome (death, vegetative state or severe disability) at 6 months, defined using the Glasgow Outcome Scale (GOS). The variables included in the models are detailed in *Table 1*. The model for mortality at 6 months was externally validated in two populations of patients: the core data survey conducted by the European Brain Injury Consortium (EBIC), which included 796 patients with severe or moderate TBI consecutively collected between February and April 1995 from 55 European centres in which the 6-month outcome assessment was routinely performed,⁵¹ and the Traumatic Coma Data Bank (TCDB), which contained data collected on 746 patients with non-penetrating severe TBI admitted to four centres in the USA between 1984 and 1988.⁵² The model for unfavourable outcome at 6 months was externally validated in the EBIC data set only.

Medical Research Council CRASH trial collaborators

The Medical Research Council (MRC) Corticosteroid Randomisation After Significant Head injury (CRASH) trial collaborators³⁰ developed eight risk prediction models using data from the MRC CRASH trial, a large international RCT which enrolled 10,008 patients between 1999 and 2004.^{53,54} Risk models were developed for death at 14 days and unfavourable outcome at 6 months in patients with TBI in low-/middle- and high-income countries. The risk models that were eligible for the RAIN study were those developed using data from high-income countries ($n = 2482$). The outcome of interest for the RAIN study was unfavourable outcome at 6 months. Two models were developed: (1) the Basic model, which included only clinical and demographic variables, and (2) the CT model, which also included CT scan results. Patients were included who (1) were aged ≥ 16 years; (2) had a total GCS score of < 15 ; and

(3) were within 8 hours of the TBI. The variables included in the model are detailed in *Table 1*. The models, with some modifications, were externally validated in a cohort of 8509 patients with moderate to severe TBI from the International Mission for Prognosis and Analysis of Clinical Trials in TBI [IMPACT (International Mission for Prognosis and Analysis of Clinical Trials in TBI)] database (described below). For validation of the Basic model, the 'variable major extracranial injury' was excluded, and for validation of the CT model, the 'variable petechial haemorrhages' was excluded, as these variables were not available in the validation sample.

Steyerberg *et al.*

Steyerberg *et al.*³⁵ developed three risk models using data from the IMPACT database,⁵⁵ which includes data from eight RCTs and three observational studies conducted between 1984 and 1997. Patients were included who had a GCS score of <13. The outcomes assessed were mortality and unfavourable outcome at 6 months. Three models were developed for each outcome: a Core model, an Extended model and a Laboratory model. The variables included in each of the models are detailed in *Table 1*. The Core model and a variant of the Extended model were validated using data from the CRASH trial (described above). For validation of the Extended model, the variables 'hypoxia', 'hypotension' and 'extradural haemorrhage' were excluded, as these were not available in the validation sample. It was not possible to externally validate the Laboratory model, as laboratory values were not recorded in the CRASH trial.

Assessment of methodological quality

The quality assessment of the four studies,^{30,35,47,48} using the criteria of Perel *et al.*,⁹ is summarised in *Table 2*. Neither the MRC CRASH trial collaborators³⁰ nor Steyerberg *et al.*³⁵ reported completeness of follow-up in their respective papers reporting development of the CRASH and IMPACT models. However, for the CRASH trial, a separate paper reporting the trial results indicated overall follow-up of 95% for GOS at 6 months,⁵⁴ and a paper reporting the design of the IMPACT database indicated overall follow-up of 95% for GOS at 6 months (including last observation carried forward imputation of 18% of values from 3 months).⁵⁵

All of the studies^{30,35,47,48} provided some justification for the predictors included in the models, reflecting a combination of an existing established relationship with outcome and ease of collection and use. However, none of the investigators reported clear definitions for the predictors. All of the studies^{30,35,47,48} used valid outcomes (mortality and/or GOS) in the models. Handling of missing data varied. In two studies,^{30,47} complete case analyses were used. The final number of patients included in the model of Signorini *et al.*⁴⁷ was not reported; however, 20% of patients were missing CT assessment alone and, therefore, a maximum of 80% of the original sample of 365 patients can have been used in fitting the final model. The MRC CRASH trial collaborators³⁰ cited low levels of missing data as justification for their complete case approach; however, this approach resulted in only 88% of the original sample being included in the Basic model for high-risk countries and 79% in the CT model. In contrast, for the remaining two studies,^{35,48} statistical imputation methods were used, resulting in all patients being included in the final models. Hukkelhoven *et al.*⁴⁸ used regression imputation to impute the 4.8% of missing values, acknowledging that such an approach would slightly underestimate the true variability and Steyerberg *et al.*³⁵ used the gold standard method of multiple imputation.

In all four studies,^{30,35,47,48} risk prediction models were developed using logistic regression, although the approach to variable selection varied. Signorini *et al.*⁴⁷ used a form of forward stepwise selection but with the order of variables being added to the model based on a combination of data completeness and clinical criteria rather than statistical significance alone. Hukkelhoven *et al.*⁴⁸ fitted a full model and used backward stepwise selection to remove variables with $p > 0.2$. The MRC CRASH trial collaborators³⁰ included variables in the final models if they were significant at the 5% level in a full multivariable model. Finally, Steyerberg *et al.*³⁵ based inclusion in their final models on partial Nagelkerke R^2 -values from a previous multivariable analysis of the same database.⁵⁷ The only authors who reported evaluating interactions between predictors were Steyerberg *et al.*;³⁵ however, it was unclear which, or how many, potential interactions were examined. All of the studies^{30,35,47,48} used continuous modelling for continuous variables, and all either

TABLE 1 Description of models meeting RAIN study eligibility criteria

Model	Variables in model	Derivation sample	External validation	Outcome	Discrimination c-index (95% CI) ^a	Calibration, <i>p</i> -value from Hosmer–Lemeshow test
Signorini et al. (1999)⁴⁷						
	GCS score Pupil reactivity ISS Haematoma	Single-centre observational study (n = 372)	Single-centre observational study (n = 520)	Mortality at 1 year	0.835	<0.001
Hukklehoven et al. (2005)⁴⁸						
Model	Age GCS motor score Pupil reactivity Hypoxia Hypotension CT classification ^b SAH	Two multicentre RCTs (n = 2,269)	EBIC (n = 796) TCDB (n = 746) EBIC (n = 796)	Mortality at 6 months Mortality at 6 months Unfavourable outcome at 6 months	0.87 (0.84 to 0.89) 0.89 (0.87 to 0.91) 0.83 (0.80 to 0.86)	0.42 <0.001 0.05
MRC CRASH trial collaborators (2008)³⁰ – CRASH models						
Basic model	Age GCS score Pupil reactivity Major extracranial injury ^c	One multicentre RCT (n = 2185)	IMPACT database (n = 8509)	Unfavourable outcome at 6 months	0.81	0.70
CT model	As above for Basic model/ <i>plus</i> : Petechial haemorrhages ^c Obliteration of the third ventricle or basal cisterns SAH Midline shift Non-evacuated haematoma	One multicentre RCT (n = 1955)	IMPACT database (n = 8509)	Unfavourable outcome at 6 months	0.83	0.63

Model	Variables in model	Derivation sample	External validation	Outcome	Discrimination c-index (95% CI) ^a	Calibration, <i>p</i> -value from Hosmer–Lemeshow test	
Steyerberg et al. (2008)³⁵ – IMPACT models							
Core model	Age	IMPACT database (n = 8509)	CRASH trial (n = 6272)	Mortality at 6 months	0.78	–	
	GCS motor score Pupil reactivity			Unfavourable outcome at 6 months	0.78	–	
Extended model	As above for core model plus:	IMPACT database (n = 6999)	CRASH trial (n = 6272)	Mortality at 6 months	0.80	–	
	Hypoxia ^c			Unfavourable outcome at 6 months	0.80	–	
	Hypotension ^c						
	CT classification ^b						
Laboratory model	SAH	IMPACT database (n = 3554)	Not externally validated	Mortality at 6 months	–	–	
	Extradural haemorrhage ^c			Unfavourable outcome at 6 months	–	–	
	As above for Core and Extended models plus: Glucose Haemoglobin						

SAH, subarachnoid haemorrhage.

^a Where reported.

^b Based on Marshall classification.⁵⁶

^c Variables were excluded from model for external validation as these were not available in the validation sample.

included or considered some degree of non-linearity. The criterion of at least 10 events per predictor variable included in the modelling process was met by three of the four studies.^{30,35,48} Signorini *et al.*⁴⁷ reported approximately eight events per predictor variable included in the model.

A description of the sample population, including important case mix variables, was reported for all four studies.^{30,35,47,48} In addition, simple methods for calculating predictions, including a nomogram, simple clinical scores, web calculators and a spreadsheet calculator, were provided. Measures of discrimination were reported in all papers, although only Hukkelhoven *et al.*⁴⁸ included a CI on the c-index [area under the receiver operating characteristic (ROC) curve]. In all papers, calibration was summarised graphically and tested for perfect calibration with the Hosmer–Lemeshow test, with CIs reported on model estimates.

All models were validated either internally and/or externally as described above and summarised in *Table 1*. None of the models was evaluated for its effect in clinical practice.

Internal validation was performed by Hukkelhoven *et al.*⁴⁸ and the MRC CRASH trial collaborators³⁰ using bootstrap methods, and by Steyerberg *et al.*³⁵ using cross-validation across the 11 separate study data sets comprising the IMPACT database. The model of Signorini *et al.*⁴⁷ was externally validated using data from a further 520 patients admitted to the same single centre. The models of Hukkelhoven *et al.*⁴⁸ were externally validated using data from approximately 1500 patients from observational registries. Modified versions of the CRASH models were validated using the IMPACT database.³⁰ The IMPACT Core models and modified versions of the IMPACT Extended models were validated in the CRASH trial data set; however, it was not possible to externally validate the IMPACT Lab models, as the CRASH trial did not record the required laboratory values.³⁵

Expert review

The RAIN Study Steering Group did not identify any further studies (either published or ongoing) that would be potentially eligible for the RAIN study. The four studies identified by the systematic review reported development and validation of 17 risk prediction models. Of these, 11 were potentially eligible for validation in the RAIN study; the models developed by the MRC CRASH trial collaborators³⁰ for low-income countries and predicting mortality at 14 days were excluded. Following review by the RAIN Study Steering Group, 10 risk prediction models were selected for external validation in the RAIN study. The model developed by Signorini *et al.*⁴⁷ was excluded because the model was developed using data from a relatively small single-centre study with mortality at 1 year as the outcome. The remaining three studies were large multicentre studies, which considered functional outcome as well as mortality at 6 months. There was also concern about the data burden associated with the ISS included in the Signorini *et al.* model.⁴⁷

Discussion

Principal findings

The systematic review of the literature identified four studies^{30,35,47,48} reporting development and validation of 17 risk prediction models for TBI. Of the 17 models, 11 were eligible for the RAIN study. Following assessment of their methodological quality and review by the RAIN Study Steering Group, 10 models, developed and validated in three studies,^{30,35,48} were selected for external validation in the RAIN study. Four models were developed for mortality at 6 months^{35,48} and six models were developed for unfavourable outcome, using the GOS, at 6 months.^{30,35,48}

The variables included across the 10 selected models were age, GCS score, GCS motor score, pupil reactivity, presence of major extracranial injury, hypoxia, hypotension, glucose, haemoglobin, Marshall CT classification,⁵⁶ presence of traumatic subarachnoid haemorrhage (SAH), presence of extradural haematoma, presence of petechial haemorrhages, obliteration of the third ventricle or basal cisterns, midline shift and non-evacuation of haematoma. The outcomes assessed were mortality and unfavourable outcome, using the GOS, at 6 months.

TABLE 2 Quality assessment of studies meeting RAIN study eligibility criteria

Quality criteria, Perel <i>et al.</i> (2006) ⁹	Signorini <i>et al.</i> (1999) ⁴⁷	Hukkelhoven <i>et al.</i> (2005) ⁴⁸	MRC CRASH trial collaborators (2008) ³⁰	Steyerberg <i>et al.</i> (2008) ³⁵	
Internal validity – study					
1	Did the study have adequate follow-up?	Yes (>90%)	Yes (>90%)	Yes (>90%)	Yes (>90%)
Internal validity – variables					
2	Was a discussion included about rationale to include the predictors?	Yes	Yes	Yes	Yes
3	Were the predictive variables clearly defined?	No	No	No	No
4	Were the outcomes predicted valid?	Yes (mortality)	Yes (mortality/GOS)	Yes (GOS)	Yes (mortality/GOS)
5	Were missing data adequately managed?	No (complete case analysis)	Yes (regression imputation)	No (complete case analysis)	Yes (multiple imputation)
Internal validity – analysis					
6	Was an adequate strategy performed to build the multivariable model?	Forward selection based on clinical criteria and completeness	Backward stepwise selection ($p < 0.2$)	$p < 0.05$ in full model	Partial R^2 from previous analysis of same database
7	Were interactions between the variables examined?	Not reported	No	No ^a	Yes
8	Were continuous variables handled appropriately?	Yes	Yes	Yes	Yes
9	Were > 10 events per variable included?	No	No	Yes	Yes
External validity					
10	Was the description of the sample reported?	Yes	Yes	Yes	Yes
11	Was it clearly explained how to estimate the prognosis?	Yes (nomogram)	Yes (simple score)	Yes (web calculator)	Yes (simple score, web calculator and spreadsheet)
12	Were measures of discrimination reported?	Yes (with CI)	Yes	Yes	Yes
13	Were measures of calibration reported?	Yes	Yes	Yes	Yes
14	Were CIs presented?	Yes	Yes	Yes	Yes
15	Was the model validated?	Yes	Yes	Yes	Yes
16	Was the model internally validated?	No	Yes (bootstrap)	Yes (bootstrap)	Yes (cross-validation)
17	Was the model externally validated?	Yes	Yes	Yes ^b	Yes/no ^c
18	Was the effect of using the model established?	No	No	No	No

a Except for interactions with high- vs low-/middle-income countries.

b Modified versions of models for unfavourable outcome at 6 months validated.

c Core models and modified version of extended models validated; laboratory models not validated.

Strengths and weaknesses

A major strength of this systematic review was being built on a previous, rigorous systematic review.⁹ One of the strengths of the Perel *et al.*⁹ review is that there was no restriction on the types of patients, i.e. any age and any severity of TBI, or on the setting. Interestingly, although the burden of trauma is much greater in low-income countries, only 2% of the models identified included patients from these countries. The MRC CRASH trial collaborators³⁰ identified significant interactions between the country's income level and several predictors and so developed separate models for low-/middle-income countries and for high-income countries. Given that the RAIN study was seeking to validate prognostic models for use in a UK NHS setting, models developed for low-/middle-income countries were excluded.

There are some limitations to the systematic review. The original literature search by Perel *et al.*⁹ was restricted to 1990 onwards. However, this was on the basis that changes in management and diagnostic technology in recent years means that prognostic models developed before 1990 are unlikely to be relevant for the current medical care of patients with TBI. In addition, only studies that explicitly combined at least two predictors were included, which means that studies that used multivariable analysis to investigate individual predictors but did not report an overall estimation were excluded. Similarly, studies that assessed clinical prediction rules considering more than one variable were excluded if they did not combine them.

Methodological quality of the risk prediction models

The original systematic review by Perel *et al.*⁹ and the recent update reveal that a large number of prognostic models for TBI have been published. However, their methodological quality is relatively poor. Limitations include, small sample sizes (fewer than 10 events per variable), loss to follow-up rates in excess of 10%, inappropriate handling of missing data (i.e. not using statistical imputation methods), and rarely being validated in external populations. Perel *et al.*⁹ reported that of the 102 models (in 53 studies) identified, they considered only the three models developed by Signorini *et al.*⁴⁷ and Hukkelhoven *et al.*⁴⁸ to be clinically useful for patients from high-income countries. All three models fulfilled the eligibility criteria for inclusion in the RAIN study. The updated search identified an additional eight models (from two studies^{30,35}) that were also eligible. In general, the methodological quality of these 11 models was good. However, eight models^{35,48} were developed using data from multiple sources and may therefore be limited by differences between data sets in eligibility criteria, definitions of variables and timings of measurements. Although all of the studies included discussion about the rationale for including specific predictors, none reported clear definitions for predictive variables. In addition, there was variation in how missing data were handled: two of the four studies used regression or multiple imputation and two used complete case analysis on the basis that there were few missing data; however, this meant that for at least one of the models, only 79% of the original sample was included.³⁰

Of the 11 eligible models, 10 risk prediction models were selected by the RAIN Study Steering Group for validation in the RAIN study.^{30,35,48} All were developed using some or all data from RCTs, which may limit their external validity. Even in large pragmatic RCTs, such as the CRASH trial,³⁰ external validity may be affected by self-selection of centres and patients to participate in the trial, as well as the potential for patients enrolled in a trial (in both the active and control arms) to receive better standard of care than in usual clinical practice.^{58,59} To assess whether a model is generalisable to other populations, it is important to conduct external validation. Of the 10 models, all except two were validated on patients from different centres. However, for four of the remaining eight models, a limitation was that some variables had to be excluded from the models for validation as they were not available in the validation sample. Therefore, only four of the 10 models – those by Hukkelhoven *et al.*⁴⁸ and the Core models from Steyerberg *et al.*³⁵ – have been externally validated without undergoing any modifications.

Summary

In summary, three families of risk prediction models including 10 individual models were identified that are most likely to be applicable to a UK critical care setting.^{30,35,48} These models require further prospective validation, and potentially recalibration, before they can be applied with confidence in neurocritical care in the NHS.

Chapter 3 The Risk Adjustment In Neurocritical care study

Introduction

The systematic review of the literature identified three families of risk prediction models for acute TBI that were likely to be applicable to a neurocritical care setting. In order to externally validate these models and to use them to evaluate the optimum location and comparative costs of neurocritical care in the NHS, a prospective cohort study was undertaken in dedicated neurocritical care units, combined neuro/general critical care units within a neuroscience centre and general critical care units outside a neuroscience centre. Data were collected on consecutive adult patients admitted to critical care with suspected acute TBI. This chapter reports the RAIN study set-up from research governance, through design and development of the data set, recruitment of sites and patients, data management, and 6-month follow-up of neurological outcomes and QOL.

Methods

Research governance

The RAIN study was sponsored by ICNARC. The contract for the study was signed in December 2008 and, once the study co-ordinator was appointed, the process of completing research governance approvals commenced. Owing to the inclusion of adults with incapacity, two separate applications were made to the NHS Research Ethics Committee (REC) for Wales, covering sites in England and Wales under the Mental Capacity Act 2005, and to the Scotland A REC, covering sites in Scotland under the Adults with Incapacity (Scotland) Act 2000. Favourable opinions were received on 13 March 2009 (ref. 09/MRE09/10) and 30 March 2009 (ref. 09/MRE00/15), respectively.

In response to the unique problems faced by patients with acute TBI in critical care, we delayed the request for consent until 6 months after the TBI at the point of follow-up. At hospital/critical care unit admission these patients are often unconscious and their level of consciousness continues to vary during their stay in the critical care unit. Generally, treatment needs to be started urgently, so there is little time for health-care staff to adequately explain research studies to patients or their families. This is, of course, a stressful and emotional time for families. In view of these difficulties in gaining informed consent, an application was made to the National Information Governance Board (NIGB) Ethics and Confidentiality Committee (ECC) for support under Section 251 of the NHS Act 2006 for permission to hold sufficient patient identifiable data, prior to patient consent, in order for us to contact the patient at 6 months post TBI and gain their consent. Section 251 support, covering sites in England and Wales, was obtained on 4 August 2009 [ref. ECC 2–06(d)/2009]. For the two sites in Scotland, falling outside the remit of the NHS Act 2006, approval was sought from the Caldicott Guardian and was granted on 10 November 2009 and 25 March 2010.

Central Research and Development (R&D) approval was gained on 4 August 2009. Site-specific information (SSI) forms were submitted for each for each NHS Trust, with the last form submitted on 3 November 2009 and the final approval gained on 28 January 2010.

The National Institute for Health Research (NIHR) Clinical Research Network (CRN) Portfolio details high-quality clinical research studies that are eligible for support from the NIHR CRN in England. The RAIN study was adopted on to the NIHR CRN Portfolio on 27 August 2009 (ref. 7349).

Changes to protocol

The initial RAIN study protocol submitted for approvals was Version 1.3 (21 January 2009). Amendments to the RAIN study follow-up documentation, not requiring changes to the study protocol, were submitted in March 2009, May 2009, July 2009 and November 2009, and approved by the RECs. A final non-substantial amendment to the Study Protocol (Version 1.4, 1 February 2011; see *Appendix 2*) was submitted in February 2011, clarifying explicitly that participating critical care units would be required to submit anonymised CT scans to the Wolfson Brain Imaging Centre (WBIC) at Addenbrooke's Hospital (University of Cambridge/Cambridge University Hospitals NHS Foundation Trust) for the purpose of the substudy on inter-rater reliability of CT scan reporting.

Design and development of data set

The initial RAIN study data set was developed and produced by the RAIN study team from the original model publications. Definitions for some of the fields were refined through discussion and consultation with the clinical experts on the RAIN Study Steering Group. There were five elements to the data set: (1) characteristics of the patients and their injury; (2) risk factors for the selected risk prediction models; (3) location of care details, to describe and cost the patient journey in order to investigate the effect of location of neurocritical care; (4) short-term outcomes at discharge from critical care and acute hospital; and (5) contact details, to provide the information required for the 6-month follow-up.

To avoid duplication of data collection, the RAIN study was piggybacked on to the CMP in England and Wales and linked with data provided by the Scottish Intensive Care Society Audit Group (SICSAG) in Scotland. Both the CMP and SICSAG databases have been independently assessed to be of high quality against 10 criteria for coverage and accuracy by the Directory of Clinical Databases at docdat.ic.nhs.uk. Critical care units in England and Wales that were not participating in the CMP recorded all required fields within the RAIN study data set.

The publications reporting each risk prediction model, other associated publications and, where available, original study documentation relating to the data sources were examined for definitions for each field to be included in the data set. The definitions and, in particular, the time points for data collection were often not clearly defined and/or varied both between risk models and between different data sources used for the development of the same risk model. Clinical experts from the RAIN Study Steering Group also identified a small number of additional fields that they felt to be important predictors of outcome following TBI that were not included in any of the risk prediction models, the collection of which was considered valuable for informing future work in this area.

The full RAIN study data set and definitions are provided in *Appendix 3*. A brief summary is given below.

Characteristics

Patients were characterised by their age, sex, residential postcode (permitting linkage to small area deprivation statistics), residence prior to hospital admission and prior dependency. The injury was characterised by timing, cause, intoxication at the time of injury and presence, and site(s) of major extracranial injury.

Risk factors

Pupil reactivity and GCS score data were collected both pre-hospital (prior to attendance at first hospital) and at admission to the first hospital (within 12 hours of attendance at the first hospital). GCS score was collected additionally as the last value prior to sedation, and pupil reactivity at the point of admission to the critical care unit. CT scan data were evaluated based on the first CT scan performed after the TBI.

Location of care details

The patient journey prior to admission to the critical care unit was recorded using the immediate prior location and, for patients who were admitted from a more transient location (e.g. theatre, imaging, emergency department), their location prior to this. Data for resource use was based on the total numbers

of calendar days of both organ support and levels of care as defined for the Department of Health Critical Care Minimum Data Set (CCMDS).

Short-term outcomes

Survival status at discharge from the critical care unit was recorded in the RAIN study for all admissions. For survivors, subsequent information on location following discharge (including critical care transfers), and outcomes at final discharge from critical care and acute hospital were also collected.

Contact details

The patient's full name, address and any telephone number(s) were included to permit the follow-up of patients by postal (or telephone) questionnaire at 6 months following the TBI. The patient's NHS number was included to ensure accurate linkage to national death registration using the 'list cleaning' service of the Medical Research Information Service (MRIS) at the NHS Information Centre for Health and Social Care. Name and contact details for the patient's general practitioner (GP) were included to confirm from the GP that the patient was still alive prior to sending the questionnaire.

Sample size calculation

We performed a simulation study to assess the power to detect a difference in the c-index (area under the ROC curve) between two different risk prediction models applied to the same population. Simulations were based on the following assumptions: the rate of unfavourable outcome (death or severe disability) at 6 months in the population will be 40% (based on the observed rate of unfavourable outcomes in high-income countries in the CRASH trial³⁰ and consistent with the results of a regional audit in East Anglia⁶⁰); statistical tests will be based on a two-sided p -value of $p = 0.05$; and the ability to detect, with 80% power, a 10% relative difference in c-index from the value of 0.83 observed for the CRASH model in the development sample.³⁰ A total of 17,500 data sets were simulated at different sample sizes using a binormal model⁶¹ and the empirical power was assessed at each sample size as the proportion of data sets in which a statistically significant difference was detected (see *Appendix 2*).

Based on these simulations, a sample size of 3100 patients was required for model validation. To allow for 8% loss to follow-up [based on the observed follow-up rates from the CRASH⁶² and Randomised Evaluation of Surgery with Craniectomy for Uncontrollable Evaluation of Intra-Cranial Pressure (RESCUEicp) RCTs⁶³], we aimed to recruit 3400 patients.

Using data from the CMP database, we anticipated the rate of admission of adult patients following acute TBI to be approximately eight per unit per month for dedicated neurocritical care units, six per unit per month for combined neuro/general critical care units, and 0.5 per unit per month for general critical care units outside a neuroscience centre. We therefore aimed to recruit at least 12 dedicated neurocritical care units, 13 combined neuro/general critical care units and 30 general critical care units outside neuroscience centres to complete recruitment within 18 months.

Recruitment of sites and patients

Recruitment of sites

All neurocritical care units in the UK and adult general critical care units participating in the CMP were invited to participate in the RAIN study. Standalone high-dependency units (HDUs) were not eligible for participation in the study. The RAIN study was publicised to critical care units via the CMP, NCCNet, the Intensive Care Society and the UK Critical Care Trials Forum (UKCCTF).

Maintenance and motivation of sites

Regular contact was maintained with all participating critical care units during the course of the RAIN study. Newsletters were sent on a monthly to quarterly basis, depending on the stage of the study, to maintain motivation and encourage involvement by keeping data collectors informed of study progress. Newsletters were also used as an opportunity to clarify any data issues and remind local collaborators to

enrol all eligible patients. The study co-ordinator maintained close contact with all sites by telephone and e-mail throughout the study and was available to answer queries.

Updates on study progress were also given at meetings of the CMP, NCCNet, the Neuroanaesthesia Society of Great Britain and Ireland and the UKCCTF in order to maintain the profile of the RAIN study in the critical care community. Regular updates on study progress were also provided to the NIHR Comprehensive CRN Critical Care Specialty Group. Members of the RAIN Study Steering Group also publicised the study at relevant conferences.

Recruitment of patients

All adult patients (defined as aged ≥ 16 years) admitted to participating adult critical care units following an actual or suspected TBI, and with a GCS score of < 15 , following resuscitation, were identified.

Data management

Start-up meetings/data set familiarisation courses

The start-up meetings/data set familiarisation courses were 1-day events, at which the background, aims and rationale for the RAIN study were discussed with the collaborating clinicians, research nurses and data clerks. This was followed by a detailed explanation of the definition for each field in the data set with opportunities for questions and examples. At least one member of staff from each site was required to attend a RAIN study start-up meeting/data set familiarisation course to ensure that they understood the aims of the RAIN study and the precise rules and definitions of the data set. Each delegate was given a RAIN study Data Collection Manual to take back with them to their site for reference purposes.

The Data Collection Manual contained precise, standardised definitions for each field (see *Appendix 3*), along with data collection forms and flows (see *Appendix 4*), to guide them through the data collection process. The Data Collection Manual was regularly reviewed and new versions released to ensure clarity and to answer common queries.

Data entry and monitoring of recruitment

From the data collection forms, data were entered by members of the research team at participating sites on to a dedicated, secure, web-based data entry system ('web portal') developed and hosted by ICNARC. A guide to using the web portal was produced and sent to research staff to assist in data entry. Data Collection Manuals, flows and forms, definitions and error checking were also available from the web portal, either for download or built into the design.

Data management was an ongoing process. Data were monitored throughout the data collection period in order to ensure that the database was as complete as possible and the rate of recruitment was as expected to minimise the time between the end of data collection and the start of data analysis. For each site, the number of patients entered on to the web portal and the date the last patient was entered was monitored. Neurocritical care units were contacted if no patients had been admitted in one calendar month. General critical care units outside a neuroscience centre received monthly e-mails to remind them to monitor for eligible patients. Quarterly CMP data submissions were reviewed to identify any admissions recorded in the CMP with a reason for admission to that critical care unit that potentially indicated a TBI that had not been entered on to the RAIN web portal.

Every patient initially thought to have TBI was entered on to the RAIN web portal to ensure completeness of recruitment. However, any patient that was subsequently found to have a different cause for their neurological impairment (e.g. cerebrovascular accident) was excluded from analyses.

Data validation reports

Two data validation reports (DVRs) were sent regularly to participating critical care units. The purpose of the first DVR was to ensure complete data entry of the fields required for patient follow-up. This DVR was

sent on a weekly to fortnightly basis and checked all patients reaching 4 weeks post TBI to ensure that complete identifiers and contact details (full name and postal address, contact telephone number, NHS number, date of birth and GP details) were available. Data collectors were asked to enter data, where missing, or confirm with the RAIN study team that data were unavailable.

The second DVR checked data accuracy. These checks identified any incomplete data (missing values) and inconsistent data (unusual, although not impossible, data that must be confirmed as correct by the data collectors) both within individual fields and across fields. Following receipt of a DVR, data collectors either updated/corrected the data on the web portal or responded to the RAIN study team to confirm the data were correct in order to clear queries.

Data linkage with the Case Mix Programme

RAIN study data were linked with the corresponding CMP data using the CMP admission number and checked using date of birth, sex, NHS number, date and time of admission to the critical care unit and status on discharge from the critical care unit. Any discrepancies between the two databases were resolved with the respective data collectors. Data linkage between the RAIN study database and CMP database was performed regularly, to ensure outcome data required for the 6-month follow-up of patients were available.

Data linkage with the Scottish Intensive Care Society Audit Group

RAIN study data were linked with the corresponding SICSAG data using the SICSAG Key (unique identifier) and checked using the age in years, sex, and date and time of admission to the critical care unit. Data linkage between the RAIN study database and SICSAG database was performed once at the end of the study.

External validation against the Trauma Audit and Research Network database

The Trauma Audit and Research Network (TARN; www.tarn.ac.uk) is the trauma registry for England and Wales with coverage of approximately 70% of trauma-receiving hospitals. For hospital sites in TARN with a critical care unit participating in the RAIN study, TARN provided data on the number of admissions to critical care associated with TBI as an external data source to verify the completeness of recruitment to the RAIN study.

Data linkage with death registration

The follow-up of patients was carefully monitored to prevent any potential distress to those who care for the patient from receiving a letter addressed to a deceased relative or partner. In order to obtain an outcome for patients at 6 months after acute TBI, the follow-up process started at 4.5 months to allow for the administrative processes. On a weekly basis, the status of any patient that had reached 4.5 months post TBI was checked on the web portal. A list of patients who were not indicated as 'dead' was then sent to the MRIS to confirm the mortality status of patients. Patients indicated as having died were logged and the follow-up process ended; all other patients started the 6-month follow-up process to ascertain their neurological outcome and QOL. At the end of the study, a final file was sent to the MRIS to confirm the final survival status of all patients in the RAIN study.

Six-month follow-up of neurological outcome and quality of life

Patients identified as not having died at 4.5 months using data from the critical care unit and from MRIS followed the process shown in *Figure 3*.

Patient outcomes were collected centrally by the RAIN study team at ICNARC, using methods based on those undertaken in previous research studies, including the CRASH⁶² and RESCUEicp RCTs.⁶³ For patients registered with a general practice, their GP was sent a letter explaining the RAIN study and a form to complete to confirm that the patient had not died and to verify the patient's address. GPs could confirm the patient's status and address in a variety of ways: by returning the form by post or fax, completing a secure on-line response form or telephoning the RAIN study team. If no response was received, a follow-up

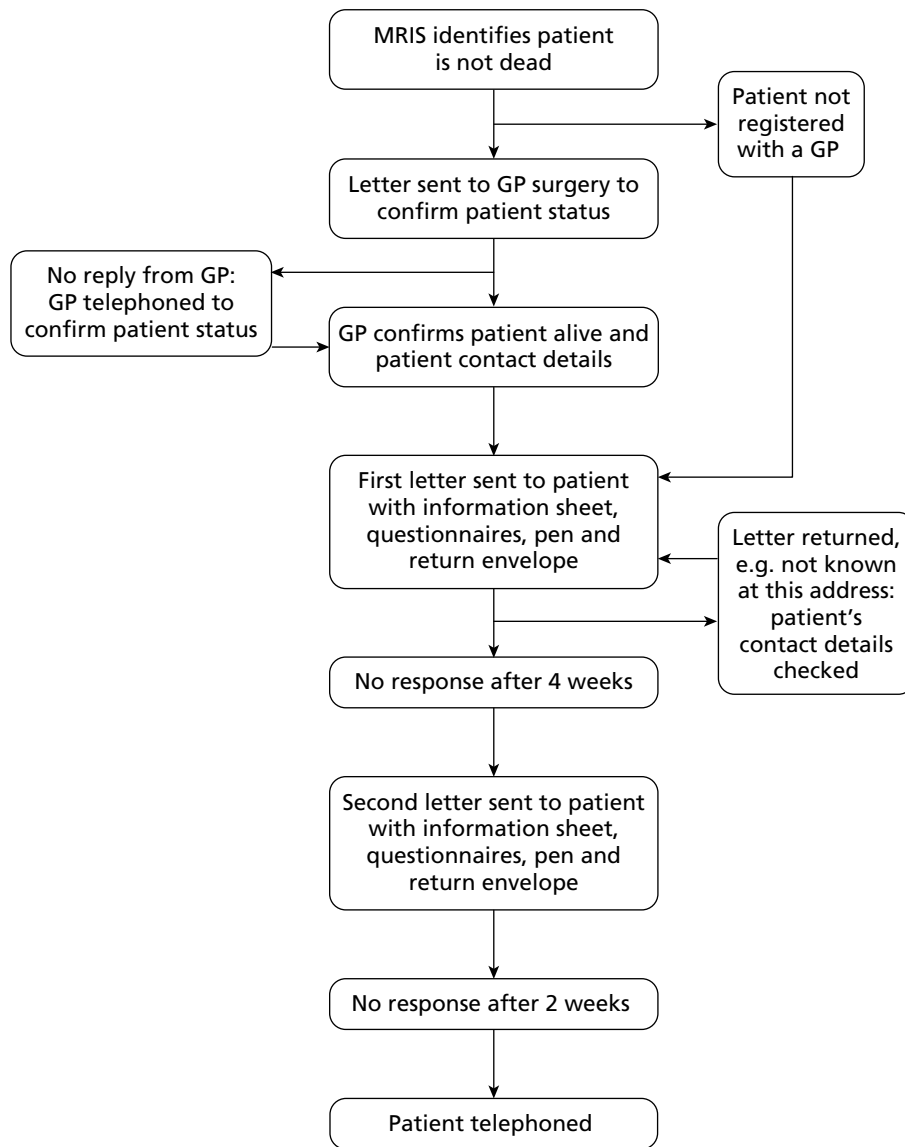


FIGURE 3 Patient follow-up process.

telephone call was made to ensure the original information had been received. In cases where patients were not registered with a GP, REC approval allowed for them to be contacted directly. When informed that a patient was no longer registered with the GP contacted, attempts were made to ascertain the patient’s current GP.

Patients were then sent, by post, an introductory letter, information sheet, consent form, questionnaires, freepost return envelope and pen (see *Appendix 5*), following best evidence-based practice to maximise response.⁶⁴ In instances where the patient was unable to consent, a boxed section on the letter addressing their carer asked them to offer what they feel would be the presumed will of the patient. Two questionnaires were included: the Your Health Questionnaire and the Health Services Questionnaire. The Your Health Questionnaire included the required questions to evaluate the European Quality of life (EuroQol) 5-dimension, 3-level version (EQ-5D-3L)⁶⁵ and the Glasgow Outcome Scale – Extended (GOSE)⁶⁶ measures. The EQ-5D-3L was included to enable the calculation of quality-adjusted life-years (QALYs) as the best available global measure of health outcome.⁶⁷ The GOSE questionnaire is the most widely used measure of functional outcome following acute TBI,⁶⁸ and has been used in most of the large, recent and ongoing RCTs.^{54,63} Use of a postal questionnaire to collect the GOSE questionnaire responses has been

found to have high reliability.⁶⁹ The Health Services Questionnaire included questions about the patients use of health services following discharge from acute hospital and was used to cost subsequent use of health services (see *Chapter 6*). Patients were asked to complete the consent form and questionnaires if they wished to take part in the RAIN study, or to return the questionnaires blank to indicate that they did not wish to take part. Non-responders were followed up with a second letter after 4 weeks, including the same enclosures as the original.

If no postal response was received after a further 2 weeks following the second letter, then patients were telephoned if contact details were available. A telephone interview template was used to explain the RAIN study and to ask for informed consent. In order not to overburden the interviewee, the telephone interview included only the GOSE questionnaire as the primary outcome for the RAIN study. Telephone calls were made at various times from Monday to Saturday between 0900 and 2030 hours to maximise the chances of contacting the patient.

Follow-up ended when a postal questionnaire was returned, either complete or blank, or when a telephone interview was completed or refusal obtained. When post was returned (e.g. not known at this address, no longer at this address, address inaccessible, etc.) the critical care unit and GP were contacted to check the address details and to elicit any updates to the patient information.

When patients were identified either as discharged to or subsequently moved to a care home, rehabilitation centre or another hospital, these institutions were contacted to establish the status of the patient and the most appropriate way to proceed with follow-up. If a patient had capacity to consent but required assistance in reading and/or completing the questionnaire then health-care professionals would often assist the patient. For those unable to consent, institutions advised on the most appropriate person to contact to gain consent. In cases in which a patient did not have the capacity to consent and either there was no next-of-kin or the next-of-kin was also unable to consent, where possible, an Independent Mental Capacity Advocate was identified.

If patients were identified as having no fixed abode but were registered with a GP or had regular contact with a homeless shelter then letters were sent to be passed (when appropriate) to them at their next appointment or visit. The usual process was then followed and if telephone contact details were available then this approach would also be attempted.

When attempts to make contact by telephone were repeatedly unsuccessful, for example where telephone numbers would ring through to an answering service or a mobile telephone was continually switched off, and attempts had been made on various days and at various times of day over at least a month, and no alternative contact information was available, if an answering service was available, a message with information to contact the RAIN study team was left and if the call was not returned then the patient was considered lost to follow-up.

Data management of 6-month follow-up data

Two databases were set up for central data entry of questionnaire responses: one for the Your Health Questionnaire and one for the Health Services Questionnaire. Ambiguous responses (e.g. two boxes ticked, responses written instead of ticked, alterations made to questions, etc.) were initially left blank for subsequent review. Following data entry, all GOSE questionnaires with blank responses (except for those where responses were unnecessary for scoring, e.g. return to work for patients who were retired prior to the injury) were identified and manually reviewed to determine whether (1) the response was clearly indicated by the information available on the questionnaire (e.g. the word 'yes' or 'very' written next to a box rather than the box being ticked); (2) the response could be imputed with reasonable confidence from the other information on the questionnaire; or (3) there was insufficient information to assume a response. Changes to data owing to situations (1) or (2) were identified separately on the database, such that the data could be reanalysed with imputed GOSE responses excluded.

Glasgow Outcome Scale–Extended responses were used to assign each patient to a GOSE category based on their worst response using an algorithm supplied by the original developers of the postal questionnaire. Following guidelines for the application of the questionnaire,^{69,70} all of those assigned to the categories of upper or lower severe disability were reviewed if other responses appeared to contradict this categorisation (e.g. return to the same work as prior to the injury). In addition, all questionnaires for patients assigned to the category of pre-existing severe disability or severe disability not due to the injury were reviewed to confirm whether the questionnaire responses were consistent with this categorisation. When questionnaires were reviewed, the entire response to all questions, including the EQ-5D-3L when available, was used to assign the patient to the most appropriate GOSE category.

For a few patients, two separate responses were received (either two paper questionnaires or one paper questionnaire and one telephone interview). These were reviewed to determine the most appropriate questionnaire to use for the analysis, taking into account the respondent (patient preferred over family member preferred over carer), timing of the response (favouring responses closer to/after 6 months) and completeness of questionnaire (favouring more complete responses).

All questionnaire reviews were performed by two investigators with any areas of ambiguity or disagreement reviewed and discussed with a third.

Results

Recruitment of sites

Recruitment of sites took place between December 2008 and December 2009. In total, 74 critical care units expressed an interest in taking part in the study and were sent an SSI form to complete. Of these, one neurocritical care unit was unable to take part owing to a conflicting, ongoing research study and a further four general critical care units outside a neuroscience centre did not reach the R&D submission stage. Local R&D approval was sought and gained for 69 critical care units. R&D approvals took a median of 68 days [interquartile range (IQR) 32 to 237] from submission of SSI form. R&D approval to start of RAIN study data collection took a median of 27 days (IQR 13 to 119). Two neurocritical care units withdrew, as they were unable to meet the study start date giving a total of 67 critical care units. This exceeded the recruitment targets with 13 dedicated neurocritical care units, 14 combined neuro/general critical units, four additional critical care units within a neuroscience centre (admitting overflow patients from the neurocritical care unit) and 36 general critical care units outside a neuroscience centre participating in the RAIN study (*Table 3*). One neurocritical care unit (and an additional critical care unit within the same neuroscience centre) withdrew from the study in August 2010 owing to research staffing shortages. All other critical care units collected data until March 2011 (*Figure 4*).

Each critical care unit was represented at a start-up meeting/data set familiarisation course. In total, seven start-up meetings/data set familiarisation courses were held between May 2009 and March 2010.

Recruitment of patients

The first patient was recruited to the RAIN study on 19 August 2009 and patient recruitment continued until 31 March 2011. The final RAIN study data set contained a total of 3626 critical care unit admissions. After excluding multiple admissions of the same patient and patients who did not prove finally to have a TBI, 3210 patients remained (*Figure 5*). Of these, 28 patients were homeless, 61 were non-UK residents and for 12 patients (military) the address details were withheld, resulting in a cohort of 3109 patients (97%) that were followed up for 6-month survival by data linkage with death registrations.

As a result of the regular feedback to critical care units participating in the CMP, four instances of a missed admission for TBI were identified after recruitment of patients had closed and these were, therefore, unable to be included in the study. There were also six admissions for which the research team at the unit was unable to confirm whether or not the patient had a TBI. Validation against figures from TARN

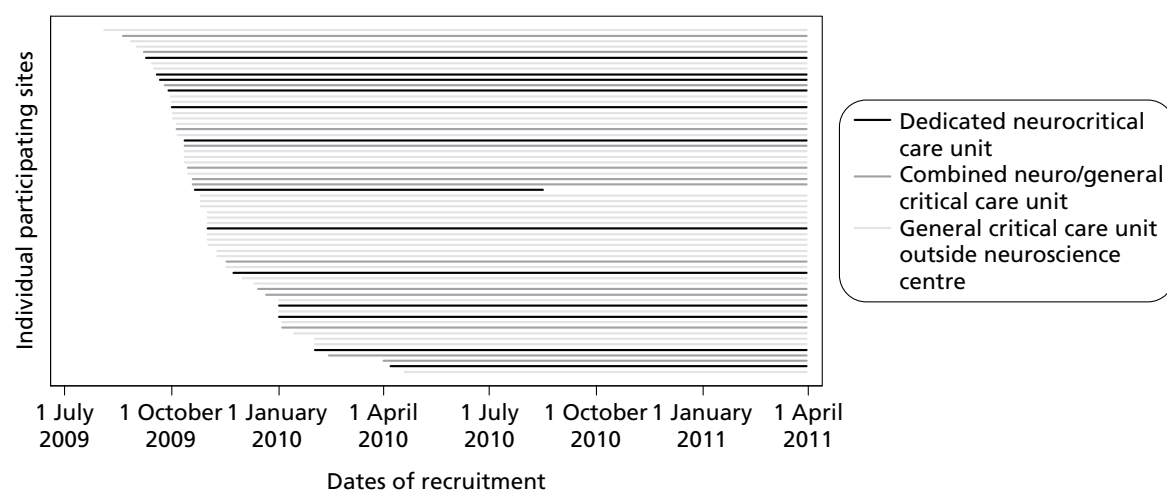
TABLE 3 Distribution and representativeness of critical care units across UK by neuroscience vs non-neuroscience centres

Geographical region	Neuroscience centres ^a		Non-neuroscience centres	
	Number (%) in RAIN ^b	Total number in region	Number (%) in RAIN	Total number in region
UK	27 (84)	32	36 (16)	223
<i>England</i>	23 (92)	25	34 (19)	180
East Midlands SHA	1 (100)	1	4 (33)	12
East of England SHA	1 (100)	1	7 (41)	17
London SHA	6 (86)	7	3 (11)	28
North East SHA	2 (100)	2	2 (13)	15
North West SHA	2 (67)	3	6 (24)	25
South Central SHA	2 (100)	2	1 (9)	11
South East Coast SHA	1 (100)	1	2 (11)	18
South West SHA	2 (100)	2	3 (18)	17
West Midlands SHA	3 (100)	3	3 (16)	19
Yorkshire and the Humber SHA	3 (100)	3	3 (17)	18
<i>Wales</i>	2 (100)	2	2 (14)	14
<i>Northern Ireland</i>	0 (0)	1	0 (0)	9
<i>Scotland</i>	2 (50)	4	0 (0)	20

SHA, Strategic Health Authority.

a Including those with dedicated neurocritical care units and with combined neuro/general critical care units.

b Four additional critical care units admitting overflow patients not counted within these figures.

**FIGURE 4** Recruitment timeline.

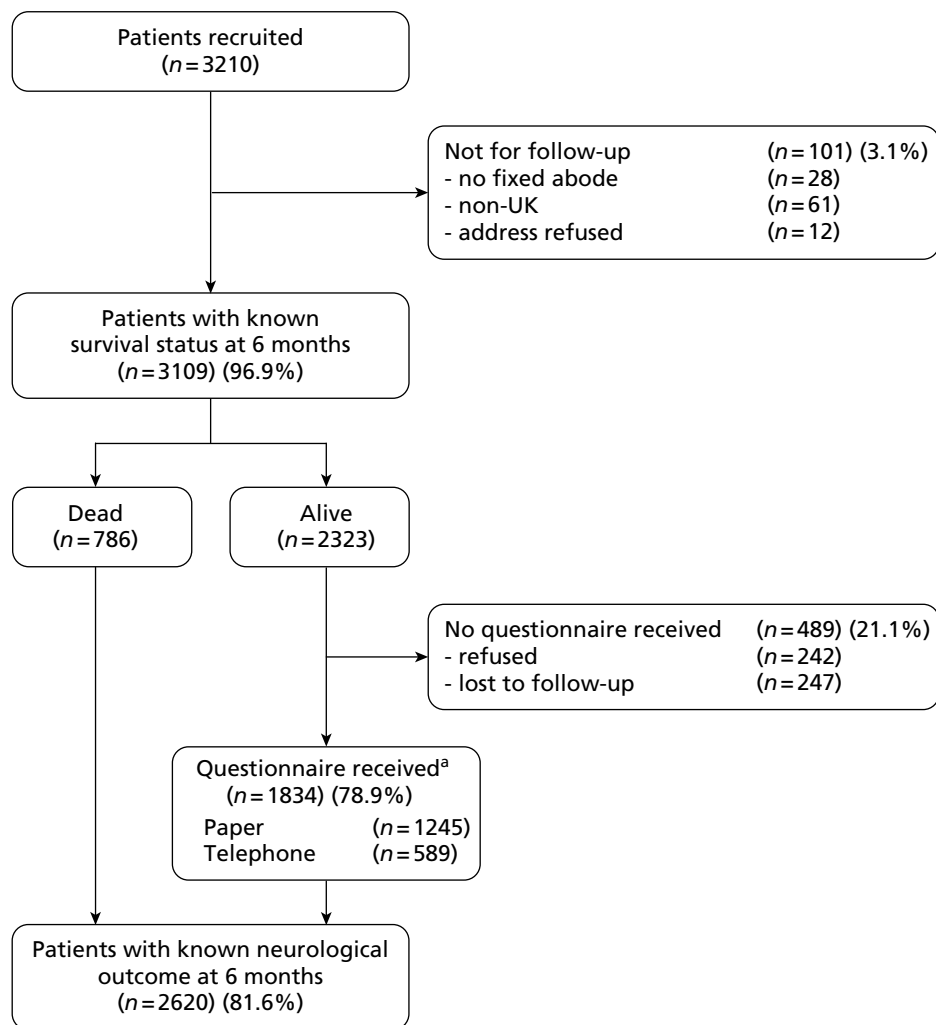


FIGURE 5 Patient flow. a, Paper questionnaire included full Your Health Questionnaire (GOSE and EQ-5D-3L) and Health Services Questionnaire; telephone questionnaire included GOSE only.

indicated similar numbers of patients recruited to the RAIN study as reported through TARN. In some sites, the number of patients in the RAIN study exceeded the number reported to TARN by a small amount and, in other sites, the reverse was true, reflecting different definitions for TBI in the two projects.

Six-month follow-up of neurological outcome and quality of life

Of 2323 patients not reported as dead by MRIS, 242 (10%) refused follow-up and 247 (11%) were lost to follow-up (the first patient was recruited to the RAIN study on 19 August 2009 and patient recruitment continued until 31 March 2011).

A breakdown of the 242 patients for whom outcome data were refused is shown in *Table 4*. The majority of refusals (177, 73%) were by return of a blank questionnaire (from which no further information was available).

A breakdown of the 247 patients lost to follow-up is shown in *Table 5*. The largest number of patients lost to follow-up (122, 49%) were those with whom we were unable to make any contact, despite exhausting all options available to us. On four occasions, contact to a patient was blocked by their GP because the patient had not consented in advance, despite NIGB and REC approval for the follow-up process used in the study. Eight requests were received from GPs not to contact the patient or family, either on compassionate grounds or because the GP had spoken to the patient or family and they did not wish to be

TABLE 4 Breakdown of refusals to participate in 6-month follow-up

Method of/reason for refusal	Number of patients
Return of blank questionnaire	177
During telephone follow-up	65
By patient	29
Patient refused before study could be explained	2
Patient refused without giving reason	23
Patient found questionnaire distressing or confusing	4
By family member or carer	36
Family member could not determine whether relative was able to consent	7
Family member did not wish to answer on behalf of relative who was unable to consent	9
Family member or friend blocked access to a patient who would have had capacity to consent	5
Family member or carer informed us that patient did not wish to take part	10
Carer informed us that family member did not wish the patient to take part	5

TABLE 5 Breakdown of patients lost to follow-up

Reason for loss to follow-up	Number of patients
Follow-up stopped by health-care professional	20
GP blocked access to patient because the patient had not consented in advance	4
GP requested we should not contact the patient or family	8
Health-care professional informed us patient was unable to consent and no next-of-kin available	8
Other reasons	222
Patient died after 6 months while attempts to make contact were ongoing	21
Family member informed us that patient had capacity to consent but did not want us to contact them	6
Patient or family member informed us that a postal questionnaire had been returned but this was never received	26
Patient or family member informed us that they had received a postal questionnaire but wished to consider the study and did not want to complete the questionnaire by telephone or be contacted again	39
Adequate communication prevented by poor understanding of English	4
Unable to contact the patient – prisoner	4
Unable to contact the patient or family despite repeated attempts	122
Processing errors	5
Incorrect data entry on web portal – patient reported to have died	5

contacted, and on six occasions family members did not want us to contact their relative. All such requests were respected.

Questionnaires were completed a median of 199 days (IQR 166 to 239 days) after the TBI (*Figure 6*). Two questionnaires were received very early, owing to data entry errors in the date of TBI that were not

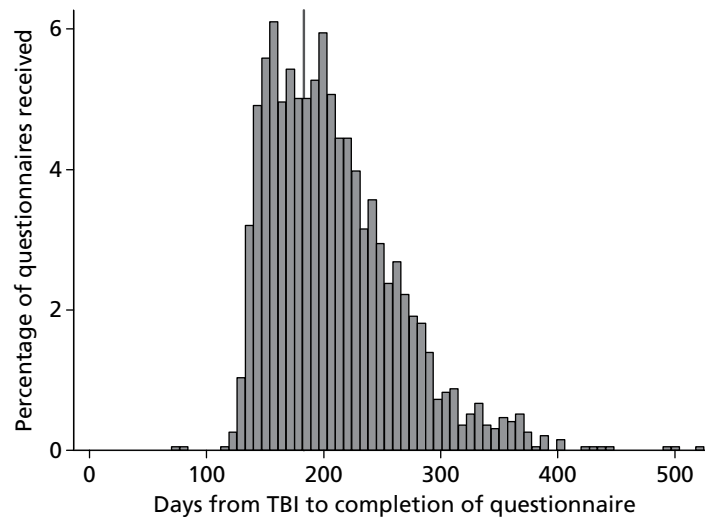


FIGURE 6 Distribution of days from TBI to completion of questionnaire. Vertical line indicates 6 months post TBI.

identified until follow-up had commenced. There was an initial peak at around 160 days corresponding to postal questionnaires returned following the initial posting, a second peak at around 200 days corresponding to postal questionnaires returned following the second posting, and a subsequent heavy tail of the patients followed up by telephone that were often difficult to contact. A total of 30 patients were eventually contacted for the 6-month follow-up more than 1 year after their TBI.

Discussion

Principal findings

The RAIN study has provided case mix data from the time of injury and presentation at hospital and outcomes data at 6 months following injury on a highly representative sample of patients receiving critical care following acute TBI in the UK.

Challenges in conducting the study

Patients with TBI present a challenging population for obtaining reliable, longer-term outcome data. The reasons for this are wide ranging and must be considered when discussing those who were lost to follow-up. Identifying the current location of the patient is not straightforward because of the frequent movement between hospitals and health-care institutions, entry into rehabilitation programmes and moving back to live with family and friends after TBI, as well as a relatively high proportion of homeless patients and those from overseas. Other challenges include ascertaining whether a patient has the capacity to consent and to accurately answer the questions. For example, in some instances, we were informed by health-care professionals or family that while the patient had the capacity to consent following the TBI they had tendencies to confabulate and that answers provided may not have been accurate.

Throughout the follow-up process, every effort was taken to avoid causing unnecessary distress to patients or their families. Following MRIS confirmation, for those registered with a GP, it was necessary to send a letter to confirm the patient's status. There were a small number of cases where the GP blocked contact with the patient or refused to provide the information because prior patient consent had not been obtained. This was despite GPs being fully informed, by letter and telephone, about the study and the governance and ethics approvals. There were also instances where the GP contacted the patient and the patient requested not to be contacted by the Study Team. This raises possible questions whether such patients were fully informed about the study. However, the benefits of contacting GPs do appear to outweigh these possible missed follow-ups. In 28 cases, patients were not reported as having died by MRIS but, on contacting the GP, were found to have died. Despite this being a relatively small number

in comparison with the resources and time required to collect GP responses, the prevention of distress to these families by this intervention cannot be ignored. In cases where GPs requested that we did not contact the patient or family for compassionate reasons, this was respected. Despite the dual safeguards of checking for reported deaths both with MRIS and GPs, there were seven cases in which, on making contact with the family, we were informed the patient had recently died. It is inevitable, when following up a high-risk population, that such situations will occur, but it is the responsibility of the researcher to do everything possible to keep these to a minimum.

The use of postal questionnaires may have been a factor in our response rate. Twenty-six patient questionnaires were reported to have been posted by the patient or family but were never received and, once it appeared that undelivered mail could potentially be influencing response rates and fluctuations in the returns were noticed, Royal Mail was contacted. The registered freepost envelope presented a possible issue. Considering this, and research indicating that stamped addressed envelopes may improve response rates over reply-paid envelopes,⁶⁴ we switched to using stamps during the course of the study. Additionally, when patients indicated during telephone follow-up that they had already returned a questionnaire by post, we requested that they also complete a telephone interview so that in the event the postal questionnaire was not received an outcome would still be available.

Chapter 4 Case mix and outcomes at 6 months for critically ill patients with acute traumatic brain injury

Introduction

This chapter describes the case mix of patients in the RAIN study admitted to critical care units following acute TBI and their survival, neurological outcome and QOL at 6 months following TBI.

Methods

Selection of patients

Despite a GCS score of < 15 being an inclusion criterion for the RAIN study, some patients with suspected TBI were recruited with no GCS score recorded, and others who had an initial GCS score of < 15, either pre-hospital or on presentation at hospital, subsequently improved prior to sedation. Patients from the RAIN study database were included in the analysis if their last GCS score prior to sedation/admission to critical care was < 15.

Statistical methods

Case mix, length of stay (LOS) and outcomes were summarised overall and for subgroups defined by the cause of TBI – road traffic accident (RTA), fall or assault. Patients with other or unknown causes of injury were included in the overall group but excluded from the subgroups. All analyses were descriptive and no statistical testing was undertaken.

Case mix

For presentation, case mix variables are categorised by causal factors; pre-injury status; date/time of TBI; hospital source of admission to critical care; age/sex; neurological dysfunction; and physiology.

Causal factors include the cause of TBI, categorised as above, with RTA details, height of fall (where relevant), presence and site(s) of major extracranial injury (defined as an injury that would require hospital admission in its own right) and presence of confirmed or suspected intoxication (with alcohol, drugs, etc.) at the time of injury.

Pre-injury status includes residence prior to admission to acute hospital, dependency prior to admission to acute hospital and deprivation status. Deprivation was assessed using the English Index of Multiple Deprivation (IMD) 2010⁷¹ and the Welsh IMD 2008⁷² for patients with a valid residential postcode. IMD quintiles of deprivation within Wales were assumed similar to the quintiles in England. Patients resident outside England and Wales were excluded from the assessment of deprivation, as sufficiently equivalent measures of deprivation were not available.

Date/time of TBI was categorised by the day of the week and hour of the day. Hospital source of admission to critical care was described by the location immediately prior to admission to the critical care unit. Age and sex were summarised both separately and by describing the overall age/sex distribution.

Neurological dysfunction includes the total GCS score, motor score component of the GCS score, pupil reactivity, Marshall CT classification⁵⁶ and presence of traumatic SAH. GCS score, motor score and pupil reactivity were summarised for each time point at which they were recorded for all patients with an assessment available at that time point. Marshall CT classification and presence of traumatic SAH were assessed from the first CT scan following the injury.

Physiology includes the first recorded-at-hospital values of core physiology, arterial blood gases and laboratory parameters. Core physiological parameters recorded were temperature, systolic blood pressure, heart rate and oxygen saturation. Arterial blood gas parameters were partial pressure of oxygen (PaO_2), fraction of inspired oxygen (FiO_2), partial pressure of carbon dioxide ($PaCO_2$) and pH. Laboratory parameters were serum glucose, haemoglobin and platelet count.

Length of stay

Length of stay in critical care was summarised by the median and IQR of the total stay in critical care, including transfers between critical care units, and stratified by the survival status at final discharge from critical care. Similarly, LOS in acute hospital was summarised by the median and IQR of the total stay in acute hospital, including transfers between acute hospitals, and stratified by the survival status at final discharge from acute hospital.

Outcomes

The outcomes reported were mortality, neurological outcome and QOL. Mortality was reported at final discharge from critical care, final discharge from acute hospital, and at 6 months following the TBI. Survival over time to 6 months following the TBI was displayed using Kaplan–Meier plots. Neurological outcome was summarised by the GOSE category at 6 months, and dichotomised as favourable (GOSE category of good recovery or moderate disability) or unfavourable (GOSE category of death or severe disability; note that the questionnaire used for collection of GOSE responses did not distinguish vegetative state from lower severe disability). Quality of life at 6 months was described by the responses to the five domains of the EQ-5D-3L and by the patients' self-rated current health on a visual analogue scale from 0 (worst imaginable) to 100 (best imaginable).

Results

Selection of patients

Of the 3210 patients in the RAIN study data set, 101 (3.1%) had no GCS score recorded, and 134 (4.2%) had a last pre-sedation GCS score of 15, resulting in a data set for analysis of 2975 patients.

Case mix

Causal factors

The most common causes of TBI were RTA (33%), fall (47%) and assault (12%), with 3% from other causes and 5% of unknown cause (*Figure 7*). RTA details are shown in *Figure 8* and fall height in *Figure 9*.

A major extracranial injury, sufficient to require hospital admission in its own right, was present in 41% and was particularly common for RTAs (70% compared with 28% for falls and 22% for assaults). Among assaults, major extracranial injuries were predominantly of the head and neck, whereas for falls and particularly for RTAs the sites of major extracranial injury were more widespread (*Figure 10*). Intoxication was either confirmed or suspected in almost half (45%), and varied by cause of TBI (26% for RTAs, 49% for falls and 74% for assaults; *Figure 11*).

Pre-injury status

Table 6 reports the pre-injury status of patients, overall and by cause of TBI. The vast majority of patients were living independently prior to the TBI, indicated by 96% with a prior residence of 'home' and 95% able to live without assistance in activities of daily living. *Figure 12* shows the distribution of deprivation by quintiles of IMD. There was a marked socioeconomic gradient that was strongest for assault (38% in the most deprived quintile vs 9% in the least deprived) and weakest for RTA (22% vs 19%).

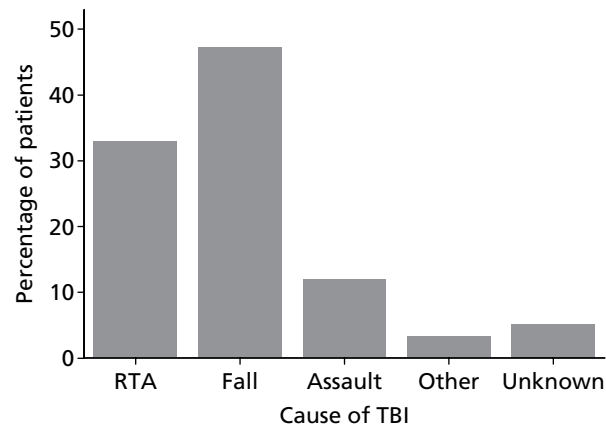


FIGURE 7 Cause of TBI.

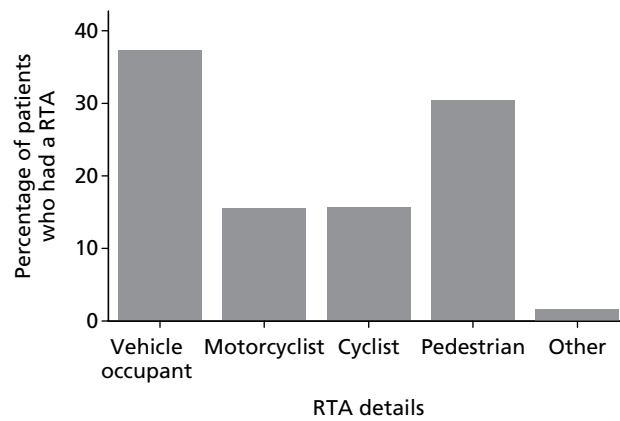


FIGURE 8 Road traffic accident details.

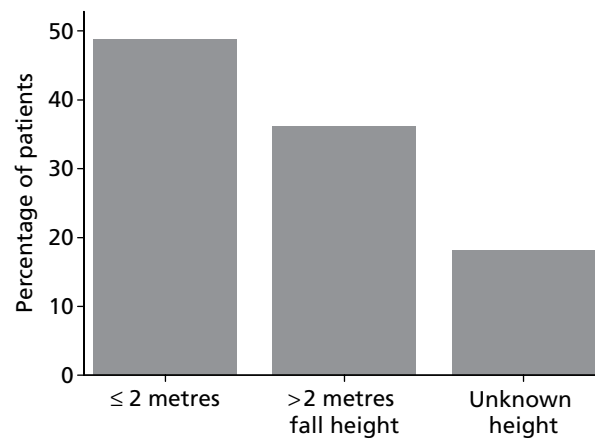


FIGURE 9 Height of fall.

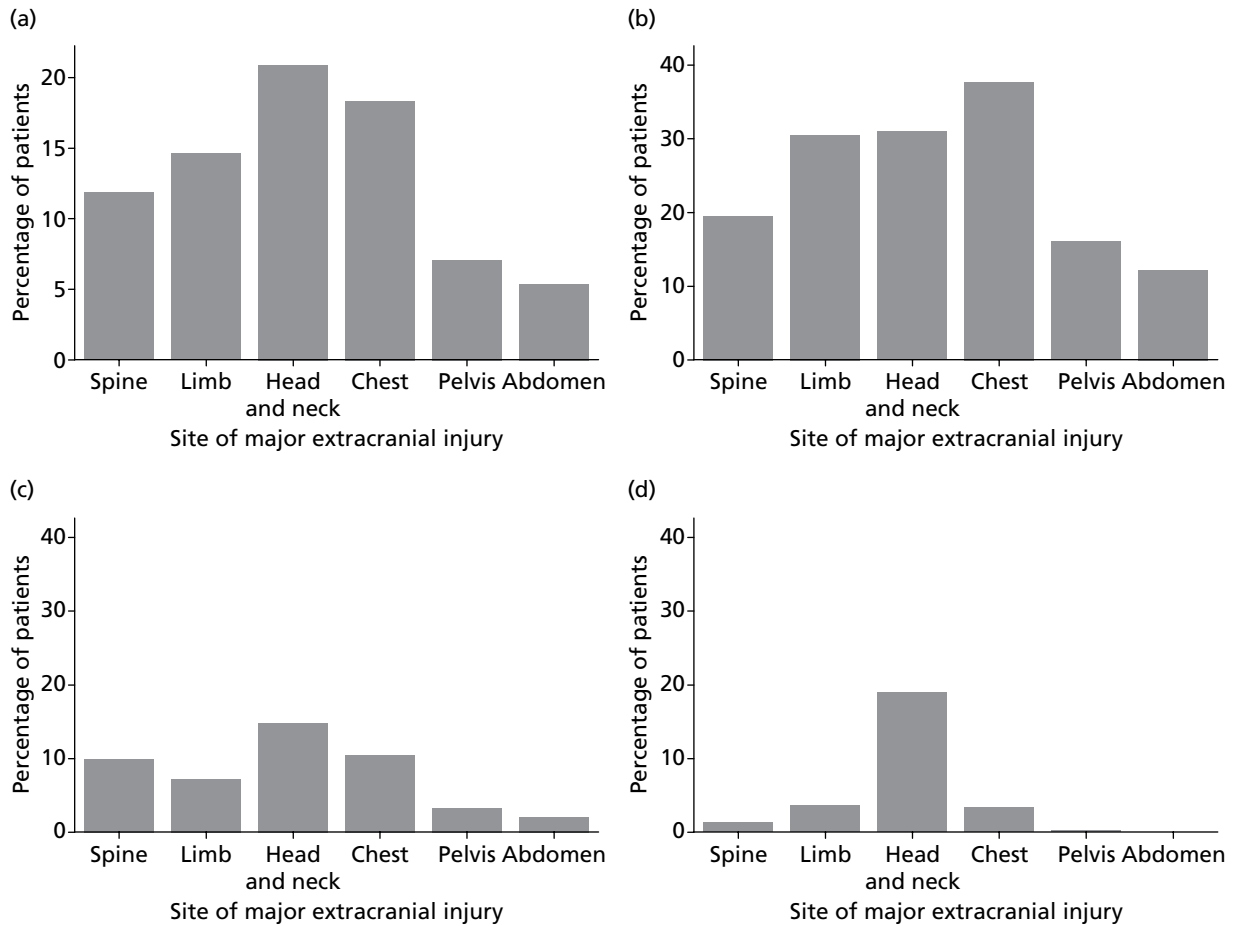


FIGURE 10 Major extracranial injury by site, overall and by cause of TBI. (a) Overall; (b) RTA; (c) fall; (d) assault.

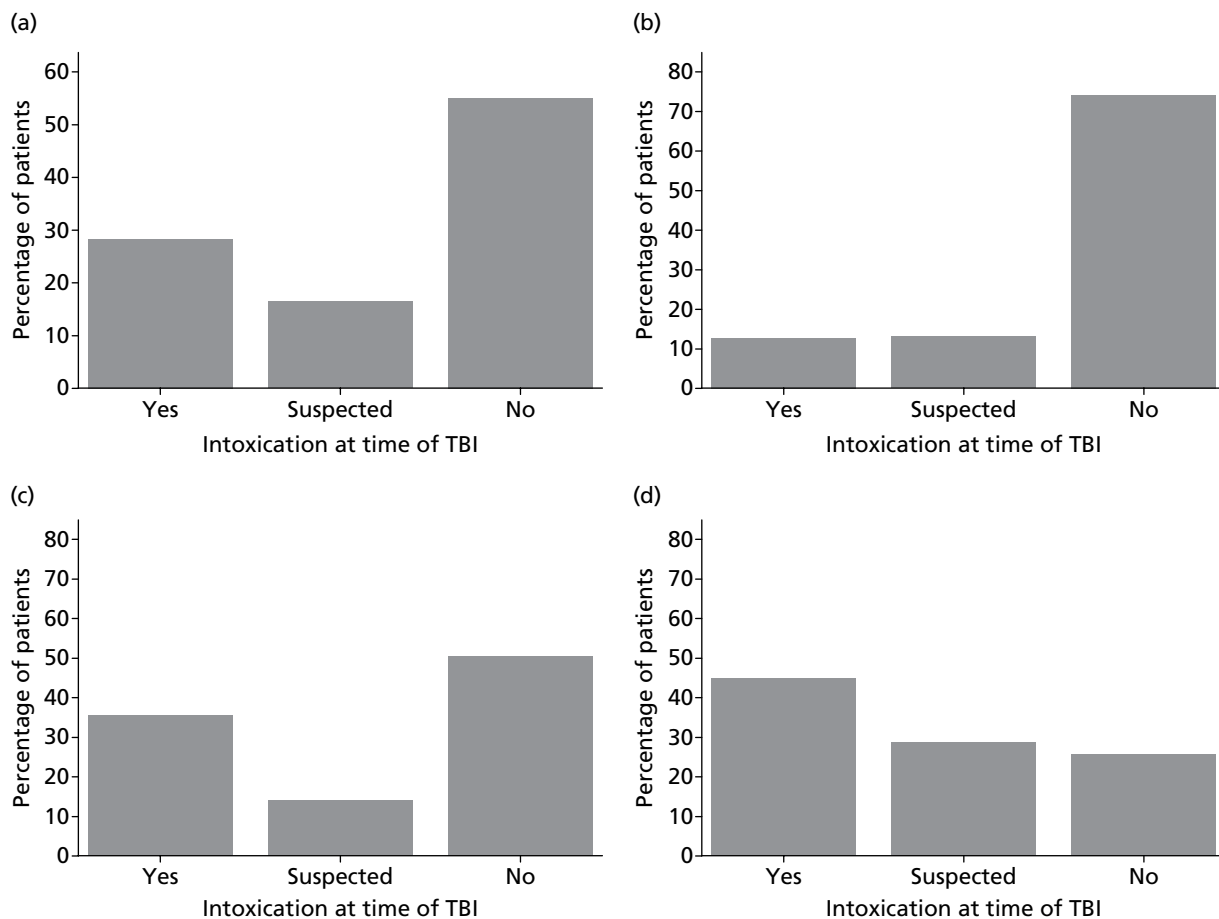


FIGURE 11 Confirmed or suspected intoxication at time of TBI, overall and by cause of TBI. (a) Overall; (b) RTA; (c) fall; (d) assault.

TABLE 6 Pre-injury status, overall and by TBI cause

Case mix factors	Overall (<i>n</i> = 2975 ^a)	RTA (<i>n</i> = 976)	Fall (<i>n</i> = 1399)	Assault (<i>n</i> = 353)
Residence prior to admission, <i>n</i> (%) [<i>N</i>]	[2971]	[975]	[1398]	[351]
Home	2846 (95.8)	948 (97.2)	1345 (96.2)	330 (94.0)
No fixed abode or temporary abode	57 (1.9)	15 (1.5)	20 (1.4)	13 (3.7)
Residential place of work/education	27 (0.9)	8 (0.8)	3 (0.2)	4 (1.1)
Nursing home or equivalent	18 (0.6)	1 (0.1)	16 (1.1)	0 (0)
Health-related institution	13 (0.4)	2 (0.2)	10 (0.7)	0 (0)
Non-health-related institution	10 (0.3)	1 (0.1)	4 (0.3)	4 (1.1)
Prior dependency, <i>n</i> (%) [<i>N</i>]	[2895]	[944]	[1376]	[337]
Able to live without assistance in daily activities	2742 (94.7)	921 (97.6)	1258 (91.4)	333 (98.8)
Minor assistance with some daily activities	132 (4.6)	19 (2.0)	102 (7.4)	3 (0.9)
Major assistance with majority of/all daily activities	19 (0.7)	4 (0.4)	15 (1.1)	0 (0)
Total assistance with all daily activities	2 (0.1)	0 (0)	1 (0.1)	1 (0.3)

^a Includes 95 patients with other causes of TBI and 152 with unknown cause.

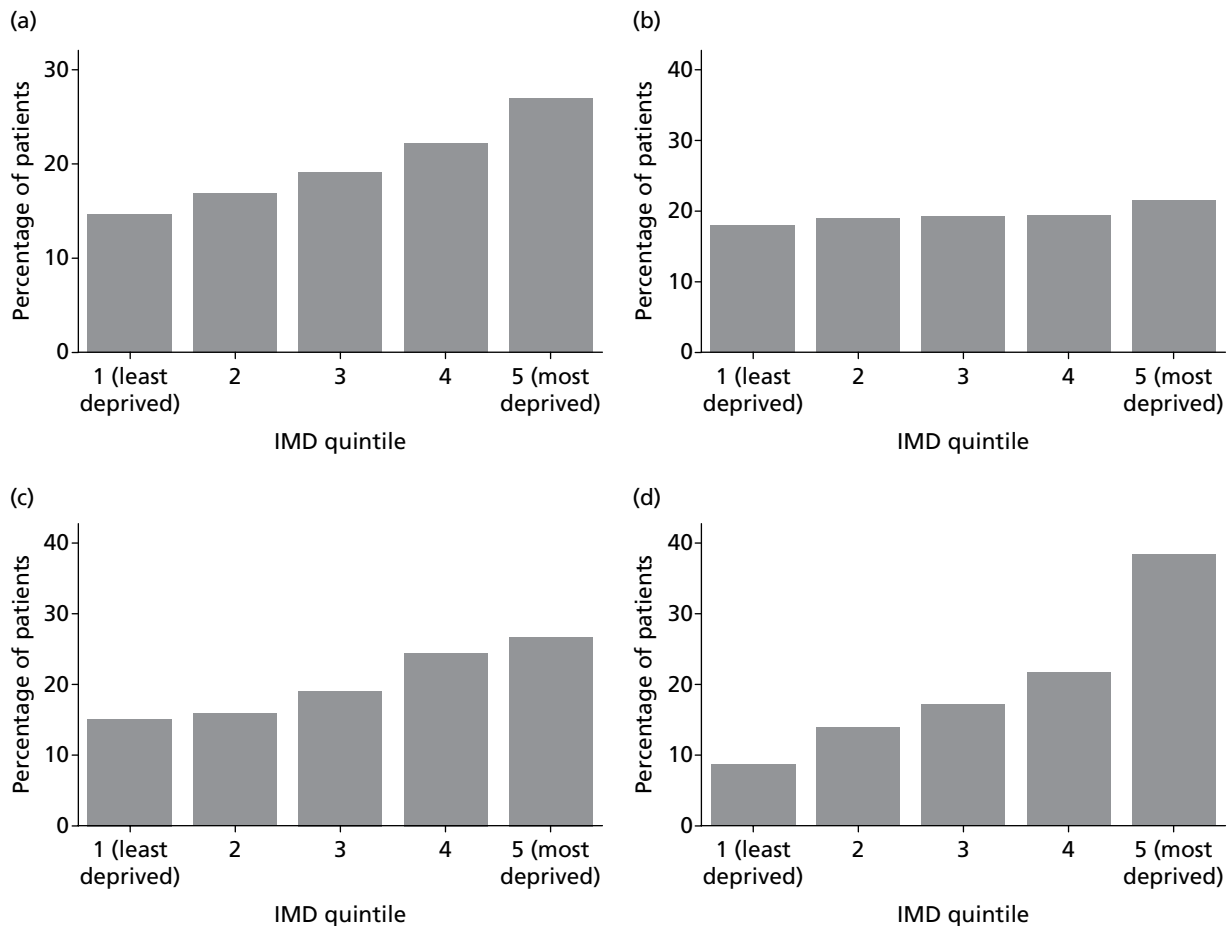


FIGURE 12 Deprivation, overall and by cause of TBI. (a) Overall; (b) RTA; (c) fall; (d) assault.

Date/time of traumatic brain injury

Figure 13 shows the day of TBI, overall and by cause. TBI was more common at the weekend (37% overall), particularly for assaults (50%). TBI occurred throughout the day with a distribution that varied considerably by cause of TBI (Figure 14). For RTA, there were peaks corresponding to the morning and evening rush hours and a further peak in the late evening. Falls occurred throughout the day, particularly during waking hours. Assaults were much more common in the late evening and early hours of the morning, with almost half of all assaults occurring between 2300 and 0300 hours.

Hospital source of admission to critical care

The majority of patients in the RAIN study were admitted to the critical care unit either from an emergency department (56%) or from theatre and recovery (27%; Table 7). The distribution of source of admission was similar by cause of TBI, although more patients were admitted from theatre following a fall or assault than following an RTA. Overall, 9% of patients were transferred to the critical care unit directly from another critical care area; two-thirds of these were from a level 3 bed in another critical care unit (not participating in the RAIN study).

Age and sex

Patients were predominantly young (mean age 45 years overall) and male (76% overall; Table 8). The overall distribution of age was bimodal with peaks in the twenties and forties (Figure 15). This was, however, very much driven by different distributions by cause of TBI. For RTA, age of admissions peaked for males in their late teens and twenties, for falls the peak was among males in their forties, and for assaults, which were almost exclusively (95%) male, the peak was in the twenties.

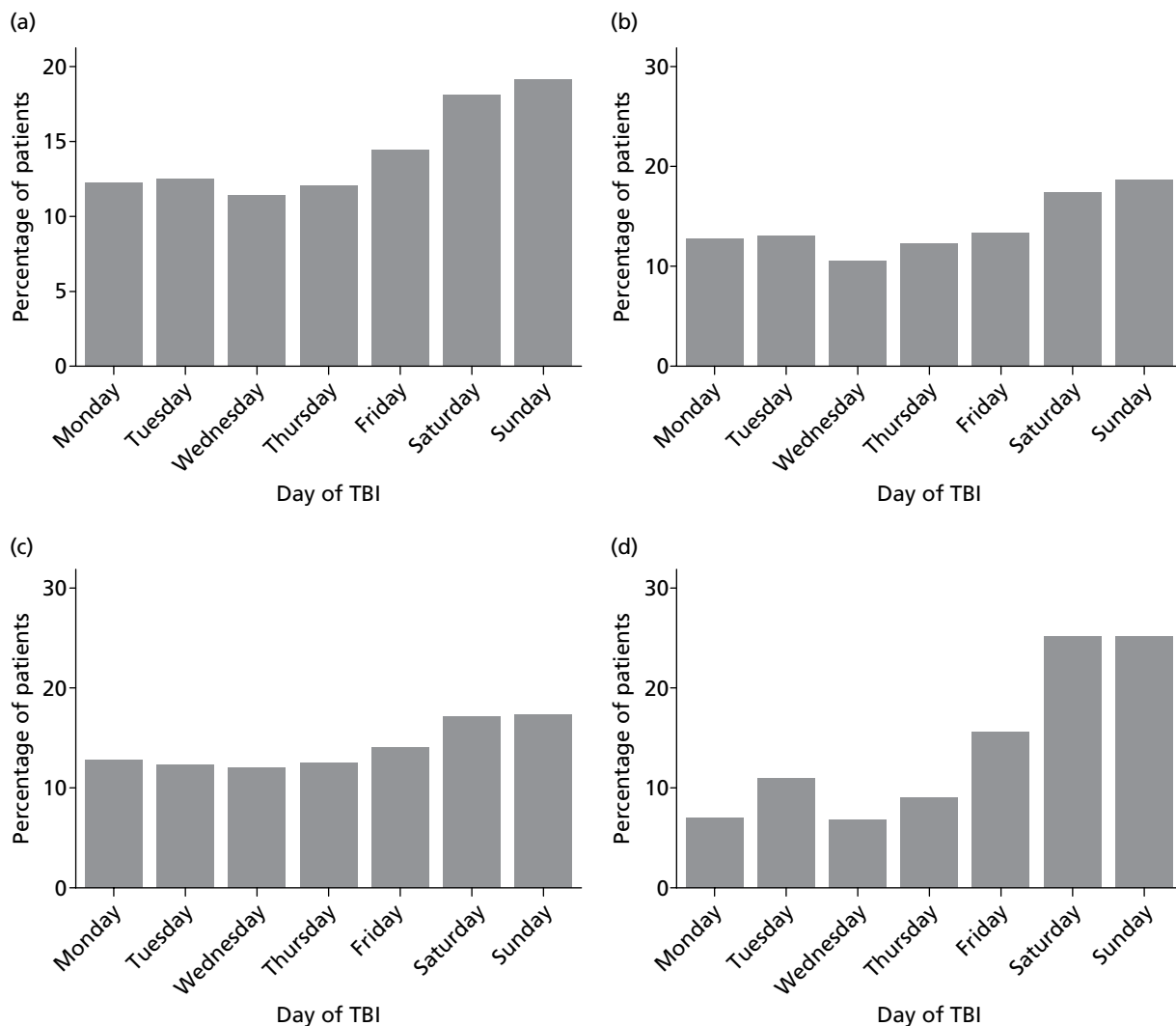


FIGURE 13 Day of TBI, overall and by cause. (a) Overall; (b) RTA; (c) fall; (d) assault.

Neurological dysfunction

Glasgow Coma Scale score was assessed and recorded pre-hospital for 2252 (76%) patients, including 9% with a pre-hospital GCS score of 15 that subsequently deteriorated such that the last pre-sedation GCS score was <15. For 576 patients (19%), the pre-hospital GCS score was their last pre-sedation GCS score. The remaining 2399 patients all had a first at hospital GCS score recorded (within 12 hours following initial presentation at hospital), including 7% with a first recorded-at-hospital GCS score of 15 that subsequently deteriorated such that the last pre-sedation GCS score was <15. For 1275 patients (43%), the first recorded-at-hospital GCS score was their last pre-sedation GCS score and the remaining 1124 (38%) patients had a subsequent last pre-sedation GCS score documented. The severity of TBI, as assessed by the GCS score, was generally worst for RTA, followed by assault and then fall (*Figure 16*). The motor score component of GCS score showed a U-shaped distribution with the highest proportions observed at the most extreme (low and high) values (*Figure 17*). Pupil reactivity was assessed pre-hospital, within 12 hours of initial presentation at hospital and on admission to the critical care unit for 52%, 90% and 97% of patients, respectively. For 20 (0.7%), 11 (0.4%) and 8 (0.3%) patients at each time point, respectively, neither pupil was able to be assessed, whereas the majority of missing data were not documented. Patients admitted following an RTA were more likely to have unreactive pupils than those admitted following either a fall or an assault (*Figure 18*).

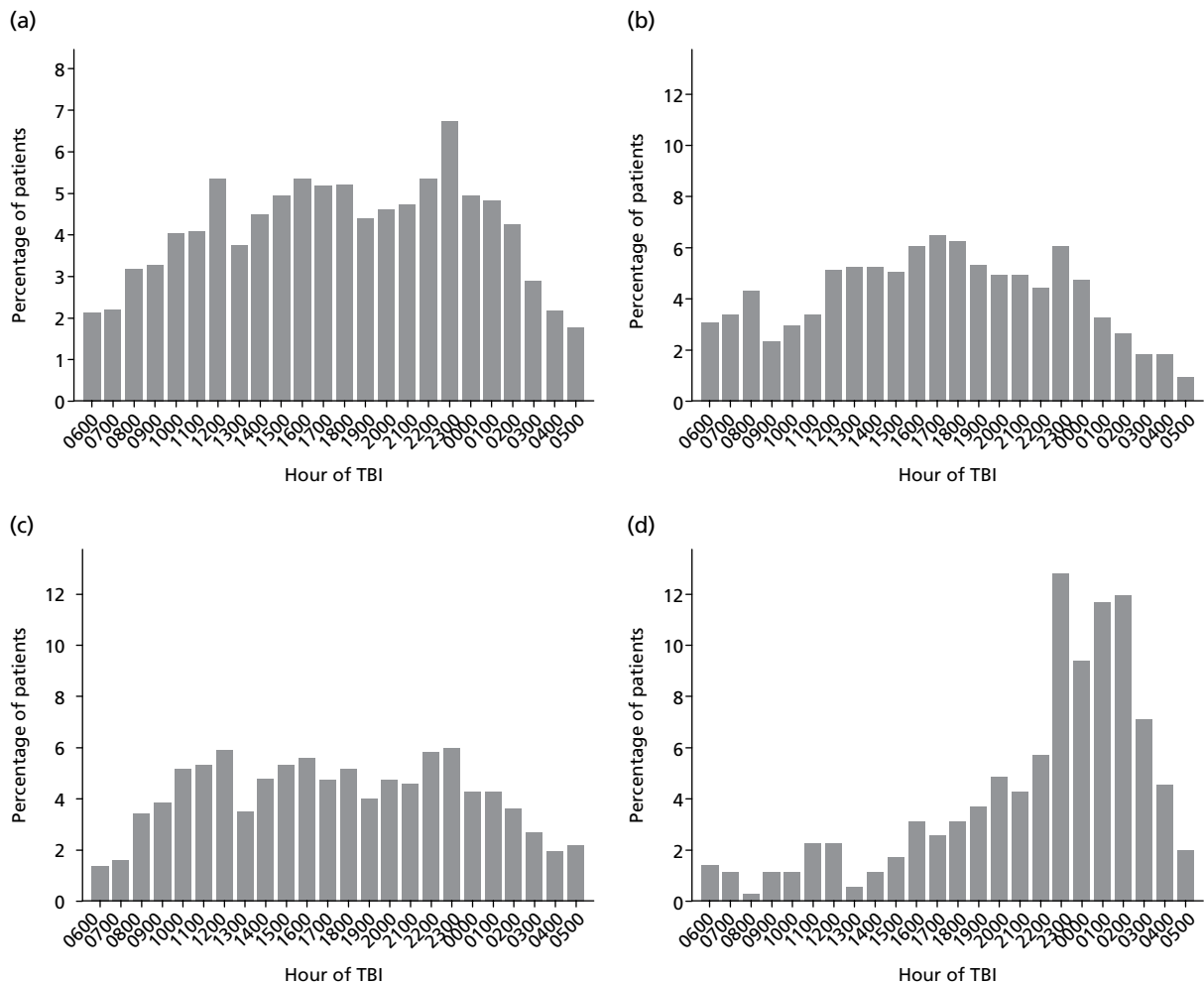


FIGURE 14 Time of TBI, overall and by cause. (a) Overall; (b) RTA; (c) fall; (d) assault.

A first CT scan was available for 2817 (95%) patients and, of these, sufficient data were available to assign a Marshall CT classification for 2773 (98%; *Figure 19*). Very few patients (<5%) had no abnormalities on the CT scan. The most common Marshall categories, each accounting for about one-third of patients, were diffuse injury II (basal cisterns present, midline shift 0–5 mm, no high- or mixed-density lesion >25 ml) and evacuated mass lesion. Evacuation of a mass lesion was approximately twice as common among patients admitted following a fall (43%) or an assault (40%) than an RTA (20%). Overall, 56% of patients with a CT scan available had a traumatic SAH, and this was similar across the different causes of TBI (RTA 54%, fall 58%, assault 55%).

TABLE 7 Hospital source of admission to the critical care unit, overall and by cause of TBI

Case mix factors	Overall (n = 2975 ^a)	RTA (n = 976)	Fall (n = 1399)	Assault (n = 353)
Hospital source of admission, n (%) [N]	[2972]	[975]	[1397]	[353]
Emergency department	1676 (56.4)	605 (62.1)	734 (52.5)	215 (60.9)
Theatre and recovery	805 (27.1)	222 (22.8)	408 (29.2)	100 (28.3)
Recovery only ^b	37 (1.2)	9 (0.9)	23 (1.7)	4 (1.1)
Level 3 bed in other ICU or ICU/HDU	193 (6.5)	74 (7.6)	80 (5.7)	17 (4.8)
Level 2 bed in other ICU or ICU/HDU	14 (0.5)	3 (0.3)	9 (0.6)	0 (0)
Paediatric ICU/HDU	2 (0.1)	1 (0.1)	1 (0.1)	0 (0)
Adult HDU	13 (0.4)	0 (0)	12 (0.9)	0 (0)
Intermediate care area	53 (1.8)	23 (2.4)	16 (1.2)	5 (1.4)
Ward	110 (3.7)	13 (1.3)	76 (5.4)	8 (2.3)
Imaging	59 (2.0)	20 (2.1)	35 (2.5)	3 (0.9)
Specialist treatment area	9 (0.3)	5 (0.5)	3 (0.2)	0 (0)
Not in hospital	1 (<0.1)	0 (0)	0 (0)	1 (0.3)

ICU, intensive-care unit.

a Includes 95 patients with other causes of TBI and 152 with unknown cause.

b Recovery used as a temporary critical care area.

TABLE 8 Age and sex, overall and by TBI cause

Case mix factors	Overall (n = 2975 ^a)	RTA (n = 976)	Fall (n = 1399)	Assault (n = 353)
Age [N]	[2975]	[976]	[1399]	[353]
Mean (SD)	44.7 (18.9)	36.3 (17.6)	53.4 (17.5)	33.9 (12.6)
Median (IQR)	44 (28 to 59)	31 (22 to 47)	54 (42 to 67)	30 (24 to 42)
Sex, n (%) [N]	[2975]	[976]	[1399]	[353]
Male	2263 (76.1)	727 (74.5)	985 (70.4)	334 (94.6)
Female	712 (23.9)	249 (25.5)	414 (29.6)	19 (5.4)

SD, standard deviation.

a Includes 95 patients with other causes of TBI and 152 with unknown cause.

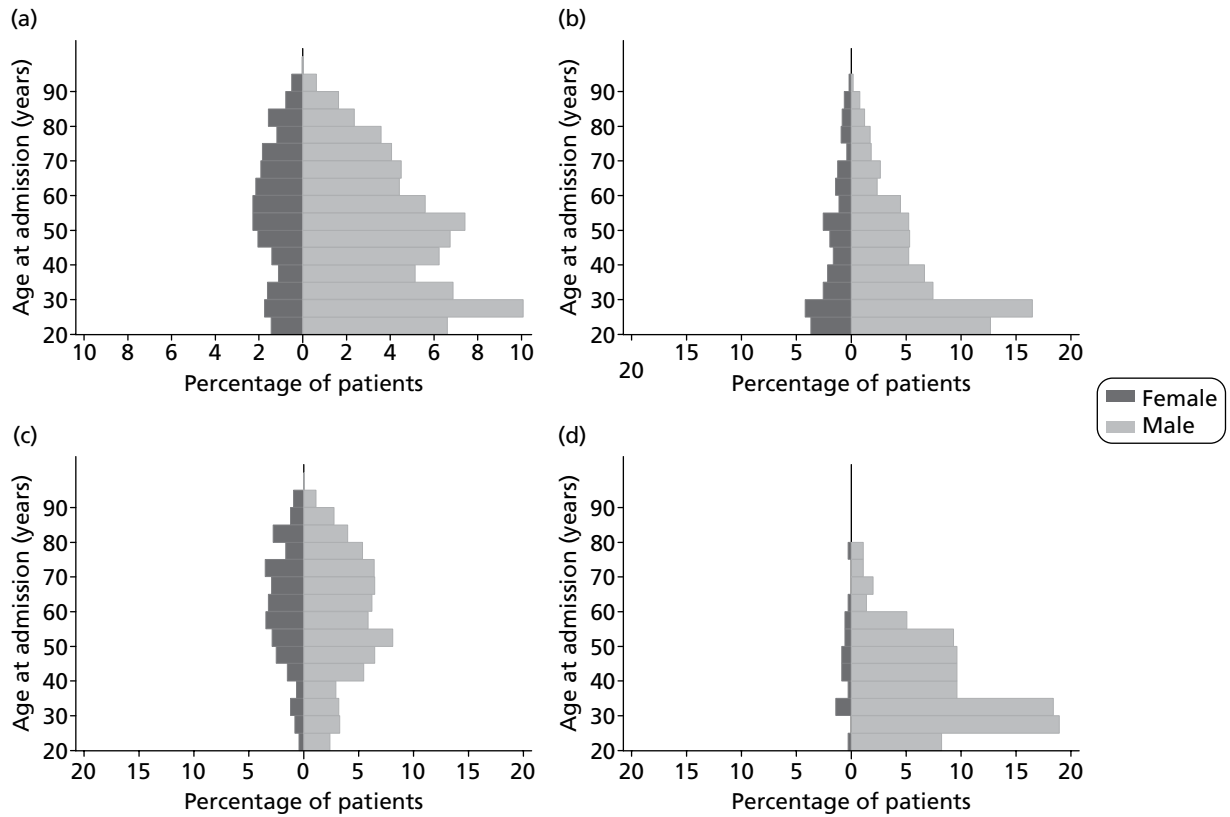


FIGURE 15 Age and sex distribution, overall and by cause of TBI. (a) Overall; (b) RTA; (c) fall; (d) assault.

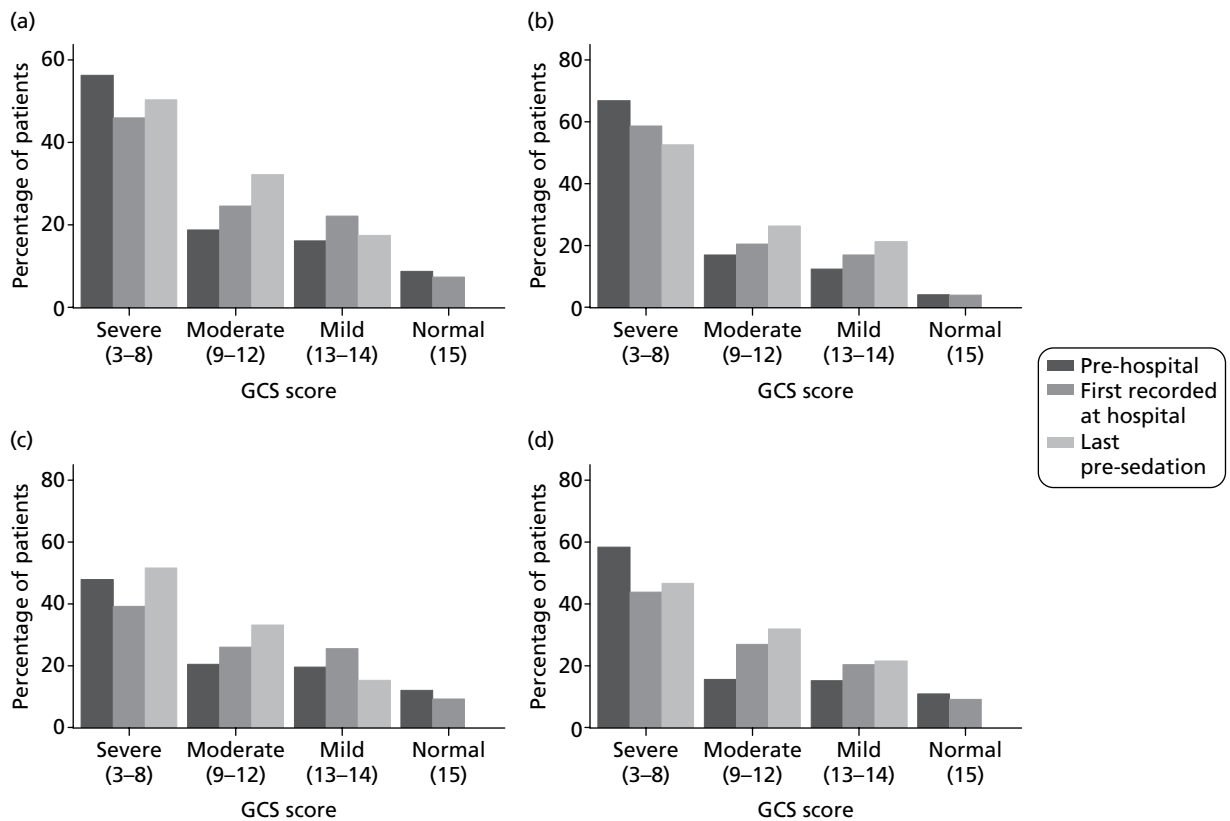


FIGURE 16 Glasgow Coma Scale score, overall and by cause of TBI. (a) Overall; (b) RTA; (c) fall; (d) assault.

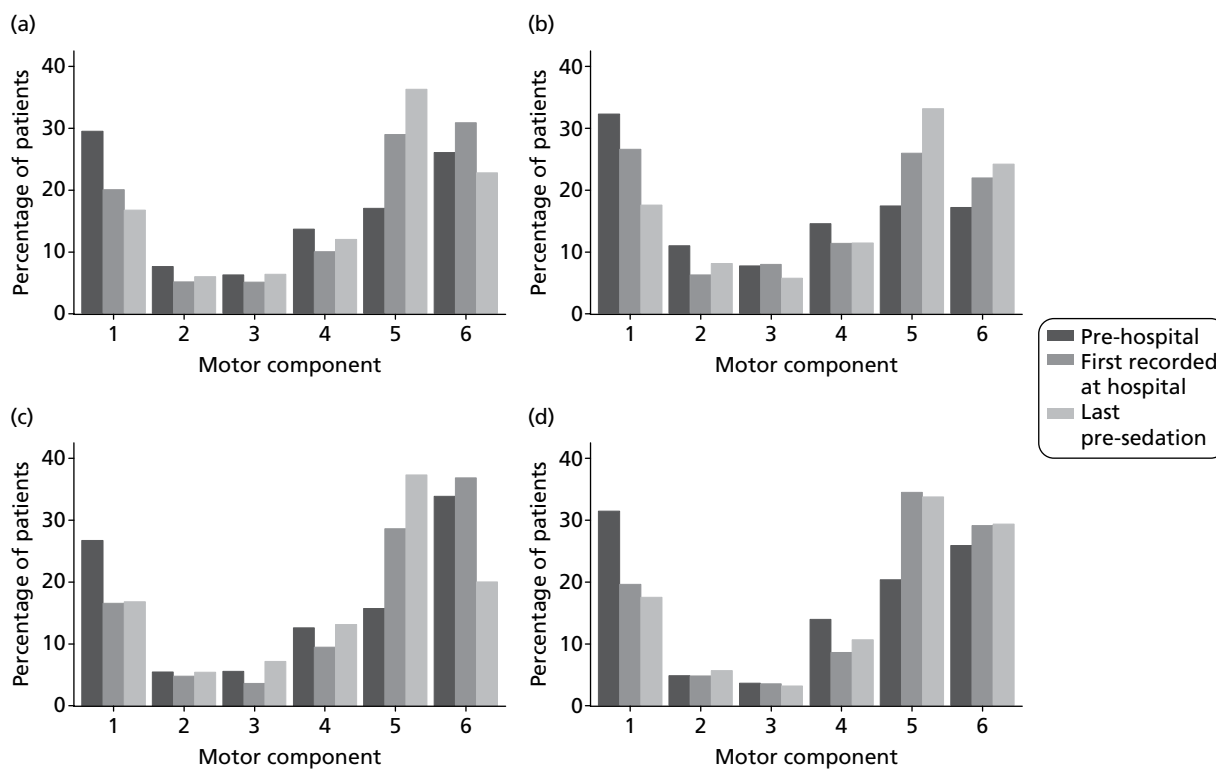


FIGURE 17 Glasgow Coma Scale motor score component, overall and by cause of TBI. (a) Overall; (b) RTA; (c) fall; (d) assault.

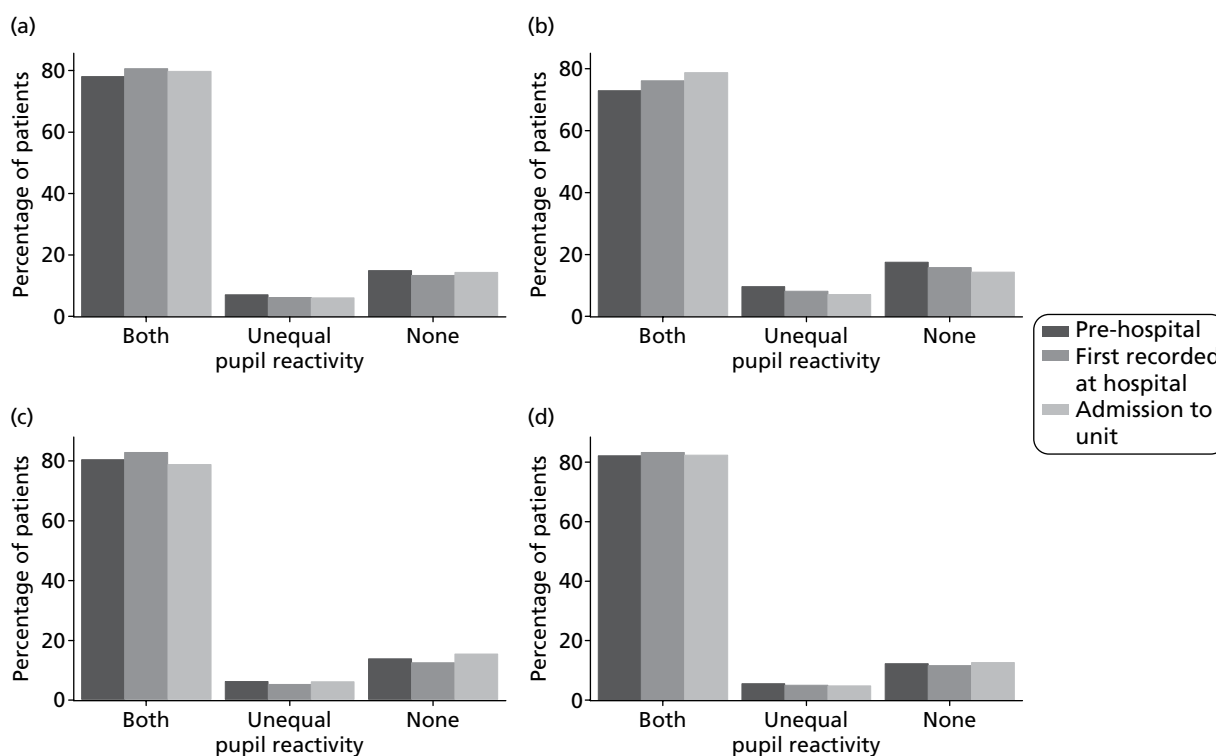


FIGURE 18 Pupil reactivity, overall and by cause of TBI. (a) Overall; (b) RTA; (c) fall; (d) assault.

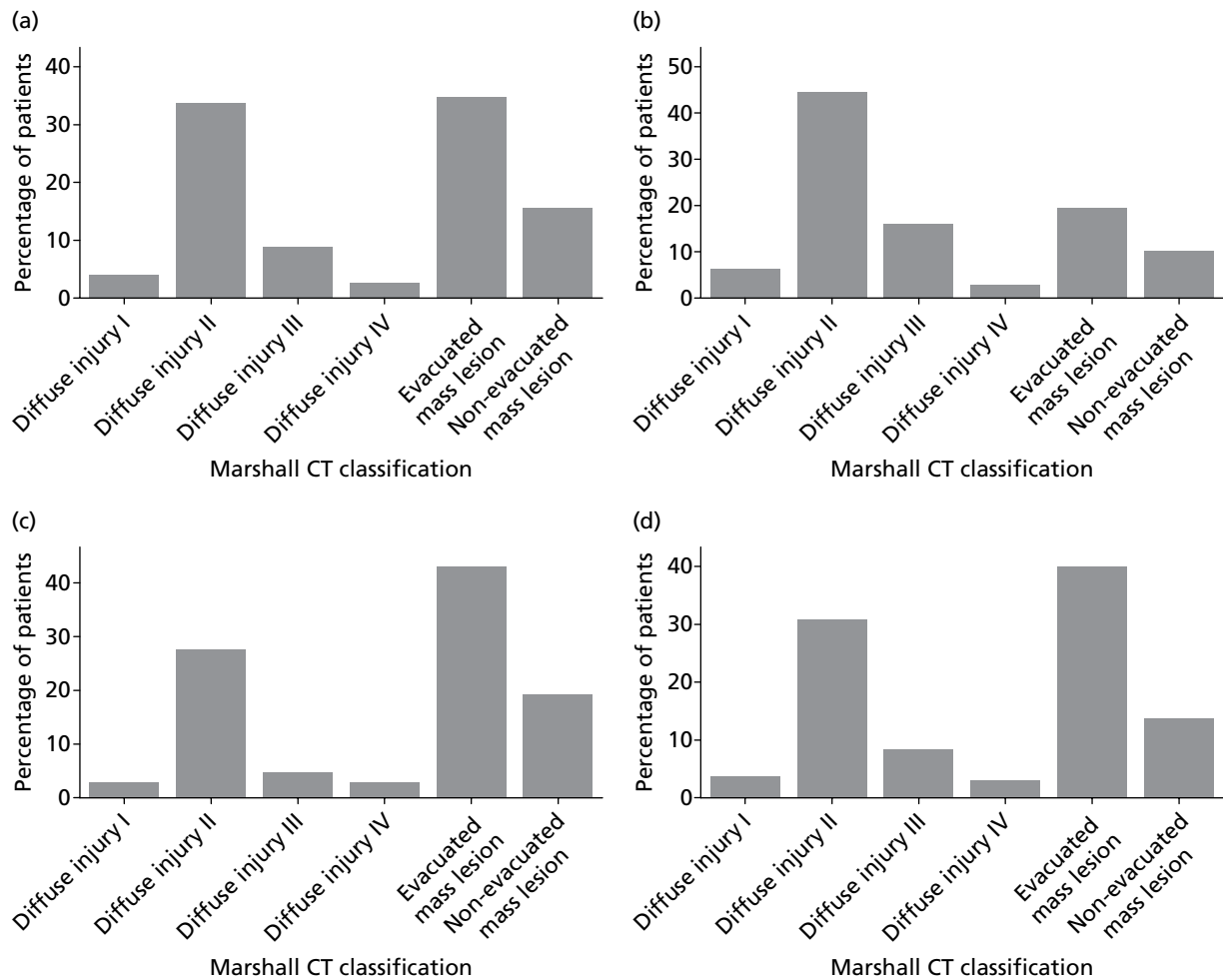


FIGURE 19 Marshall CT classification, overall and by cause of TBI. (a) Overall; (b) RTA; (c) fall; (d) assault.

Physiology

Table 9 summarises the first recorded physiological parameters following presentation at hospital. Core physiological parameters were available for between 87% and 95% of patients, arterial blood gas parameters were available for between 72% and 80% of patients, and laboratory parameters were available for between 84% and 90% of patients. There was little difference in the degree of physiological derangement by cause of TBI.

Length of stay

Table 10 reports the LOS overall and by cause of TBI. The median total LOS in critical care was 7 days but this differed substantially between survivors (median 8 days) and non-survivors (median 3 days) of critical care. The critical care LOS distribution was similar for non-survivors across different causes of TBI, but for survivors was longer for patients admitted following an RTA (median 11 days) than for a fall or assault (median 7 and 6 days, respectively). The median total LOS in acute hospital was 30 days for survivors compared with 5 days for non-survivors. The LOS in acute hospital for survivors again varied substantially by cause of TBI, with the longest stay for patients admitted following an RTA (median 37 days), followed by for a fall (median 30 days), and for an assault (median 20 days).

Mortality

Mortality at final discharge from critical care was 18% and was highest for falls (21%) followed by RTAs (18%) and assaults (14%) (Table 11). At final discharge from acute hospital, mortality had increased

TABLE 9 First recorded-at-hospital physiology, overall and by cause of TBI

Case mix factors	Overall (n = 2975 ^a)	RTA (n = 976)	Fall (n = 1399)	Assault (n = 353)
Core physiology, median (IQR) [N]				
Temperature (°C)	36.0 (35.2 to 36.7) [2590]	35.9 (35.0 to 36.5) [829]	36.0 (35.3 to 36.8) [1235]	36.0 (35.3 to 36.5) [311]
Systolic blood pressure (mmHg)	139 (121 to 157) [2829]	136 (120 to 153) [933]	142 (123 to 161) [1333]	133 (120 to 149) [335]
Heart rate (beats per minute)	87 (72 to 105) [2830]	93 (76 to 114) [934]	85 (70 to 102) [1334]	84 (70 to 100) [334]
Oxygen saturation (%)	99 (97 to 100) [2797]	99 (97 to 100) [920]	98 (96 to 100) [1322]	99 (97 to 100) [333]
Arterial blood gas parameters, median (IQR) [N]				
PaO ₂ (kPa)	28.7 (15.0 to 45.5) [2375]	31.7 (15.3 to 50.5) [811]	26.8 (14.2 to 41.4) [1106]	31.7 (16.6 to 49.6) [271]
FiO ₂	0.8 (0.5 to 1.0) [2131]	1.0 (0.5 to 1.0) [729]	0.7 (0.5 to 1.0) [992]	0.6 (0.5 to 1.0) [245]
PaCO ₂ (kPa)	5.2 (4.5 to 6.1) [2378]	5.3 (4.6 to 6.2) [812]	5.2 (4.4 to 6.0) [1108]	5.2 (4.6 to 6.0) [271]
pH	7.4 (7.3 to 7.4) [2360]	7.4 (7.3 to 7.4) [806]	7.4 (7.3 to 7.4) [1099]	7.4 (7.3 to 7.4) [271]
Laboratory parameters, median (IQR) [N]				
Serum glucose (mmol/l)	7.6 (6.3 to 9.5) [2496]	7.7 (6.4 to 9.7) [817]	7.6 (6.4 to 9.4) [1180]	7.2 (6.1 to 8.8) [303]
Haemoglobin (g/dl)	13.4 (11.9 to 14.6) [2683]	13.4 (11.7 to 14.6) [896]	13.2 (11.8 to 14.5) [1259]	14.0 (12.8 to 14.9) [315]
Platelet count (× 10 ⁹ /l)	219 (169 to 273) [2608]	224 (178 to 274) [878]	213 (157 to 271) [1216]	222 (180 to 274) [307]

a Includes 95 patients with other causes of TBI and 152 with unknown cause.

TABLE 10 Length of stay, overall and by cause of TBI

Length of stay	Overall (n = 2975 ^a)	RTA (n = 976)	Fall (n = 1,399)	Assault (n = 353)
LOS (days), median (IQR) [N]				
Total LOS in critical care				
Survivors	8 (3 to 17) [2416]	11 (4 to 20) [801]	7 (2 to 16) [1099]	6 (2 to 13) [304]
Non-survivors	3 (1 to 6) [540]	3 (1 to 7) [169]	2 (1 to 6) [291]	3 (1 to 5) [49]
All	7 (2 to 15) [2956]	9 (3 to 18) [970]	6 (2 to 14) [1390]	4 (1 to 12) [353]
Total LOS in acute hospital				
Survivors	30 (14 to 59) [2163]	37 (17 to 68) [741]	30 (14 to 58) [941]	20 (9 to 44) [290]
Non-survivors	5 (2 to 12) [696]	5 (1 to 11) [195]	5 (2 to 12) [403]	3 (1 to 7) [55]
All	22 (8 to 50) [2859]	28 (9 to 60) [936]	20 (7 to 46) [1344]	16 (6 to 39) [345]

a Includes 95 patients with other causes of TBI and 152 with unknown cause.

to 24%, with the differential outcomes by cause of TBI maintained. Of the patients who survived to discharge from acute hospital, very few died before 6 months following the TBI, with 6-month mortality of 26%. The Kaplan–Meier survival curve (Figure 20) indicates that the majority of deaths occurred within

TABLE 11 Mortality at discharge from critical care and acute hospital and mortality and unfavourable outcome at 6 months following TBI, overall and by TBI cause

Outcomes	Overall (n = 2975 ^a)	RTA (n = 976)	Fall (n = 1399)	Assault (n = 353)
Mortality, deaths (%) [N]				
At final discharge from critical care	546 (18.4) [2962]	171 (17.6) [972]	295 (21.2) [1394]	49 (13.9) [353]
At final discharge from acute hospital	705 (24.5) [2883]	197 (20.9) [944]	410 (30.2) [1358]	55 (15.9) [346]
At 6 months	748 (26.0) [2881]	204 (21.5) [948]	439 (32.0) [1370]	56 (16.8) [333]
Unfavourable outcome at 6 months, ^b n (%) [N]	1481 (61.2) [2422]	466 (57.3) [813]	776 (66.7) [1164]	137 (51.7) [265]

a Includes 95 patients with other causes of TBI and 152 with unknown cause.

b Denominator includes 24 patients who could not be assigned to a specific GOSE category, but where the questionnaire responses, although incomplete, were sufficient to indicate the patient did not have an unfavourable outcome.

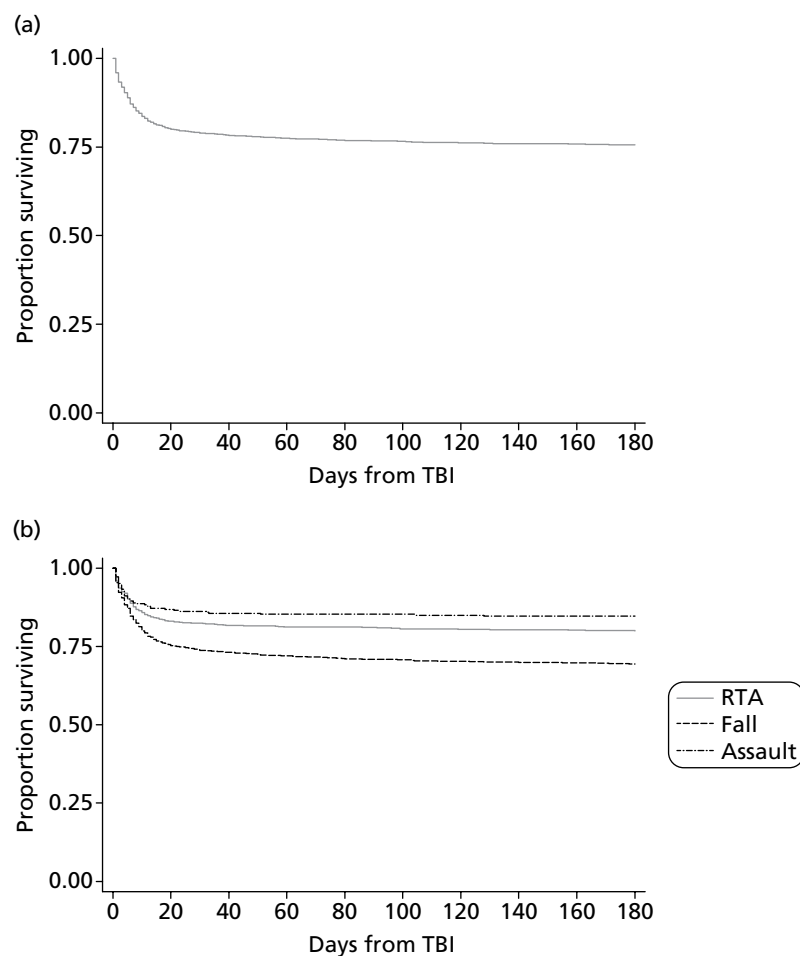


FIGURE 20 Kaplan–Meier survival curves to 6 months following TBI. (a) Overall; (b) by cause of TBI.

the first 30 days following the TBI, with a slow decline in survival thereafter. The same was true across each cause of TBI, with the differential mortality by cause established by 30 days and maintained to 6 months.

Neurological outcome at 6 months

There was a substantial burden of disability at 6 months, with only 26% of surviving patients with a known GOS-E category reporting a good recovery compared with 44% reporting severe disability (Figure 21). In addition to the 26% of patients who had died by 6 months, a similar proportion was known to have severe disability (Figure 22). When presented as a percentage of those with a known GOS-E category, this corresponds to a rate of unfavourable outcome (death or severe disability) at 6 months of 61% (see Table 11). Outcomes were worst for falls, then for RTAs and assaults, with unfavourable outcome rates of 67%, 57% and 52%, respectively. The GOS-E categories were reported for all patients with known survival status at 6 months ($n = 2881$) to avoid biasing the proportions towards deaths. Unfavourable outcome at 6 months is reported only for those with a known GOS-E category ($n = 2422$) and, therefore, the reported rate of 61% is likely to represent an overestimate of the actual percentage with unfavourable outcome at 6 months because deaths will be over-represented owing to more complete follow-up. This is addressed in the following chapter using multiple imputation.

Quality of life at 6 months

European Quality of Life-5 Dimensions (3-level version) responses were available for 1132 patients (53% of those known to be alive at 6 months). Figure 23 summarises the EQ-5D-3L responses for each of the five domains. The EQ-5D-3L responses indicated substantial issues with QOL at 6 months, including 70% of

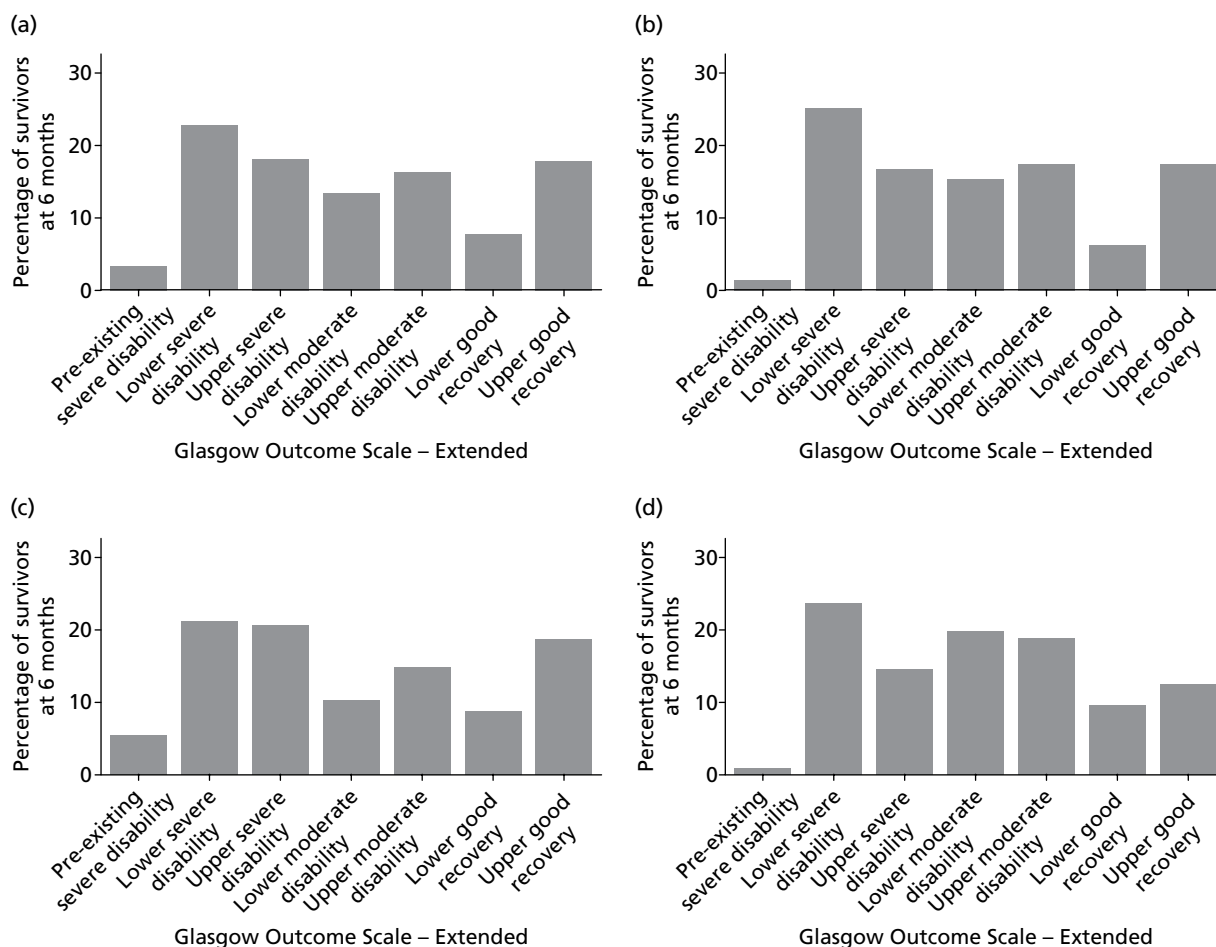


FIGURE 21 Glasgow Outcome Scale – Extended at 6 months following TBI as a percentage of survivors with known GOS-E category, overall and by cause of TBI. (a) Overall; (b) RTA; (c) fall; (d) assault.

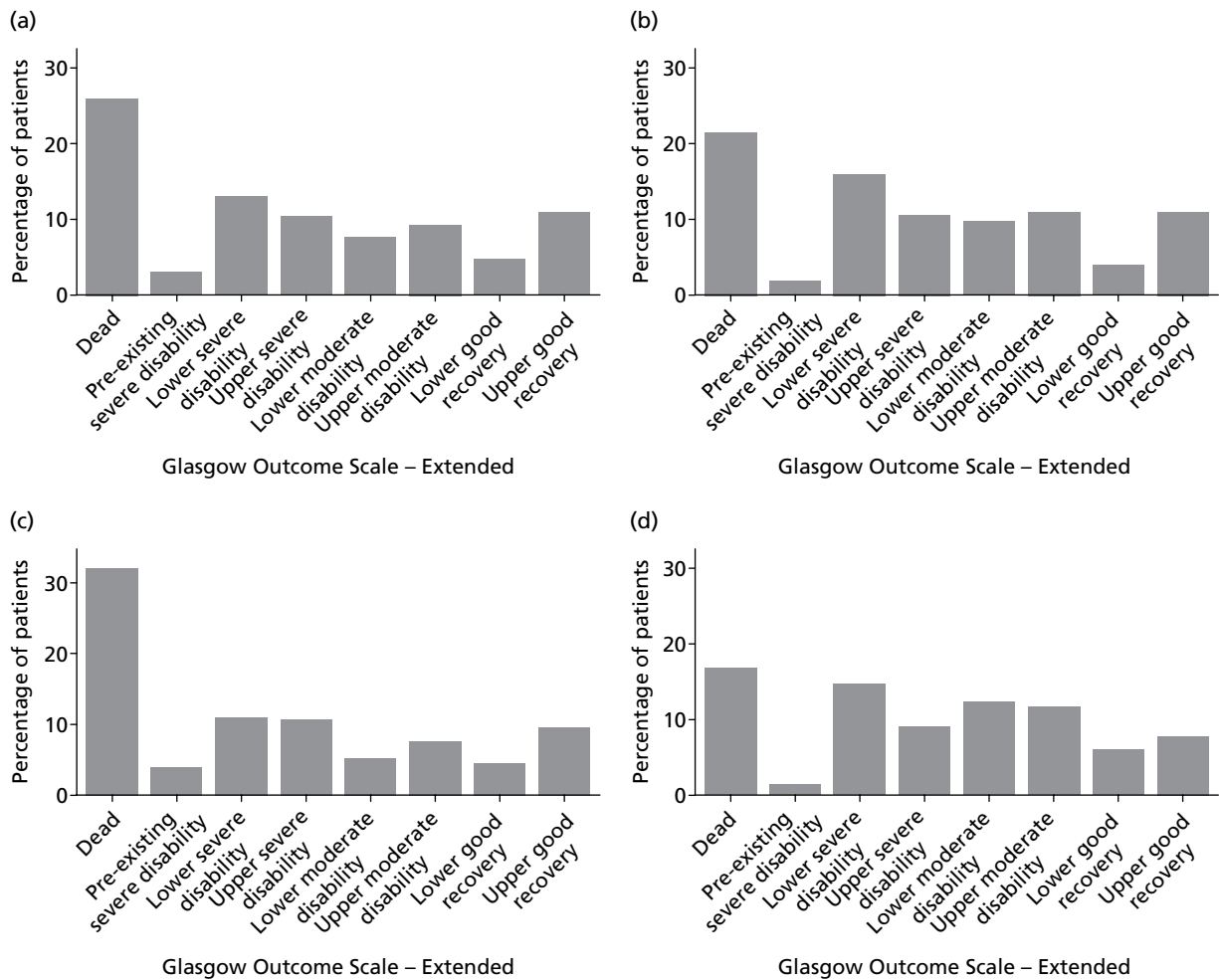


FIGURE 22 Glasgow Outcome Scale – Extended at 6 months following TBI as a percentage of all patients with known survival status, overall and by cause of TBI. Denominator includes 483 (17%) patients who were alive at 6 months following TBI but with unknown GOSE category. (a) Overall; (b) RTA; (c) fall; (d) assault.

patients reporting problems with performing usual activities, around 60% reporting problems with pain or discomfort and anxiety or depression, around 50% reporting problems with mobility and around 35% reporting problems with self care. There was little difference across the EQ-5D-3L domains by cause of TBI, although those admitted following an RTA reported slightly higher proportions in the worst categories for physical functioning (mobility, self care and usual activities), whereas patients admitted following assault reported slightly higher proportions in the worst categories for pain or discomfort, and anxiety or depression.

Figure 24 summarises the self-rated health from the visual analogue scale for the 1078 patients who completed this section of the questionnaire, overall and by cause of TBI. The overall median self-rated health was 70 (IQR 50 to 85). Self-rated health was lower for patients following assault (median 60, IQR 45 to 80) than for either RTA or fall (both 70, 50 to 85).

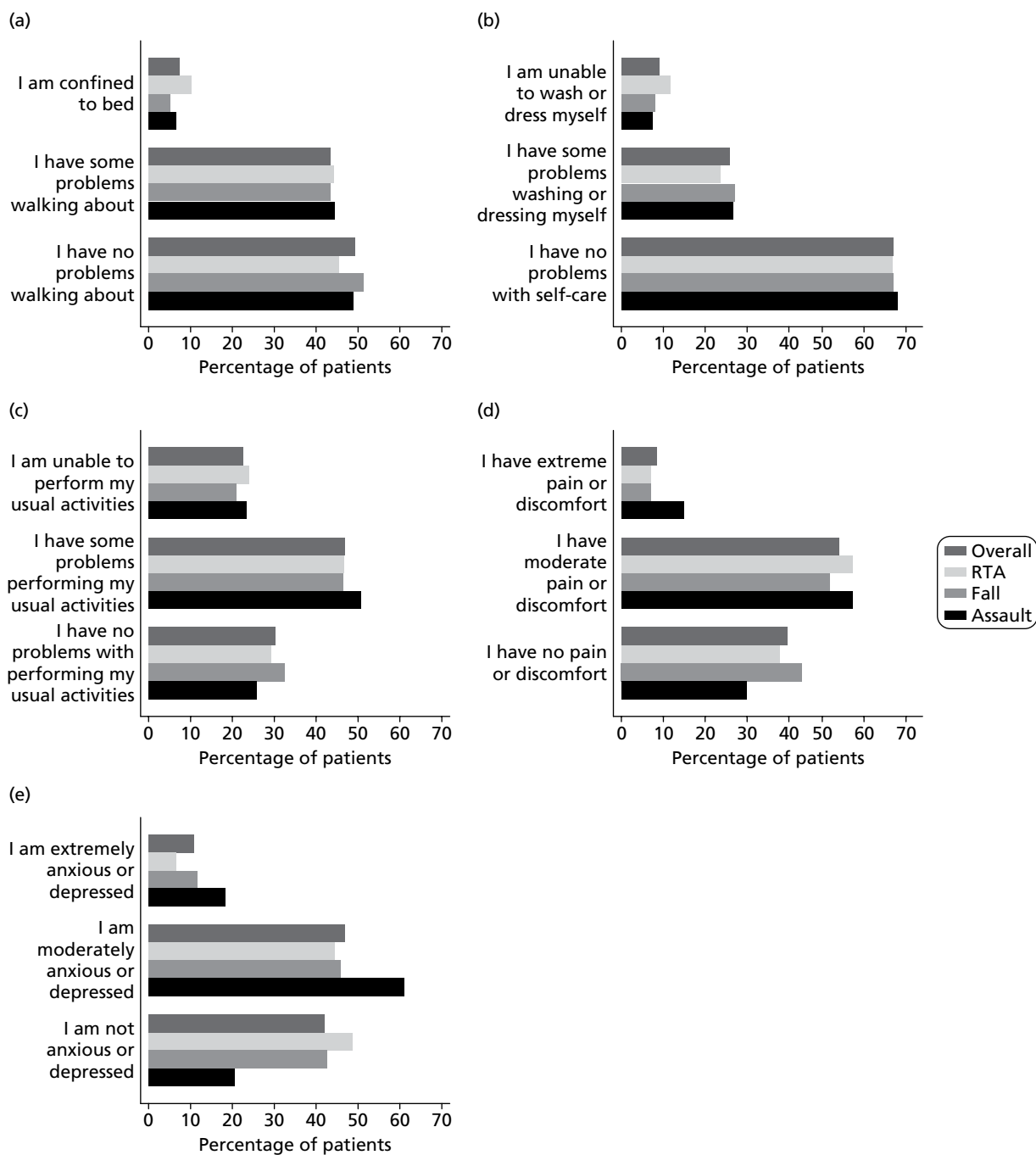


FIGURE 23 European Quality of Life-5 Dimensions (3-level version) responses by domain, overall and by TBI cause. (a) Mobility; (b) self-care; (c) usual activities; (d) pain/discomfort; (e) anxiety/depression.

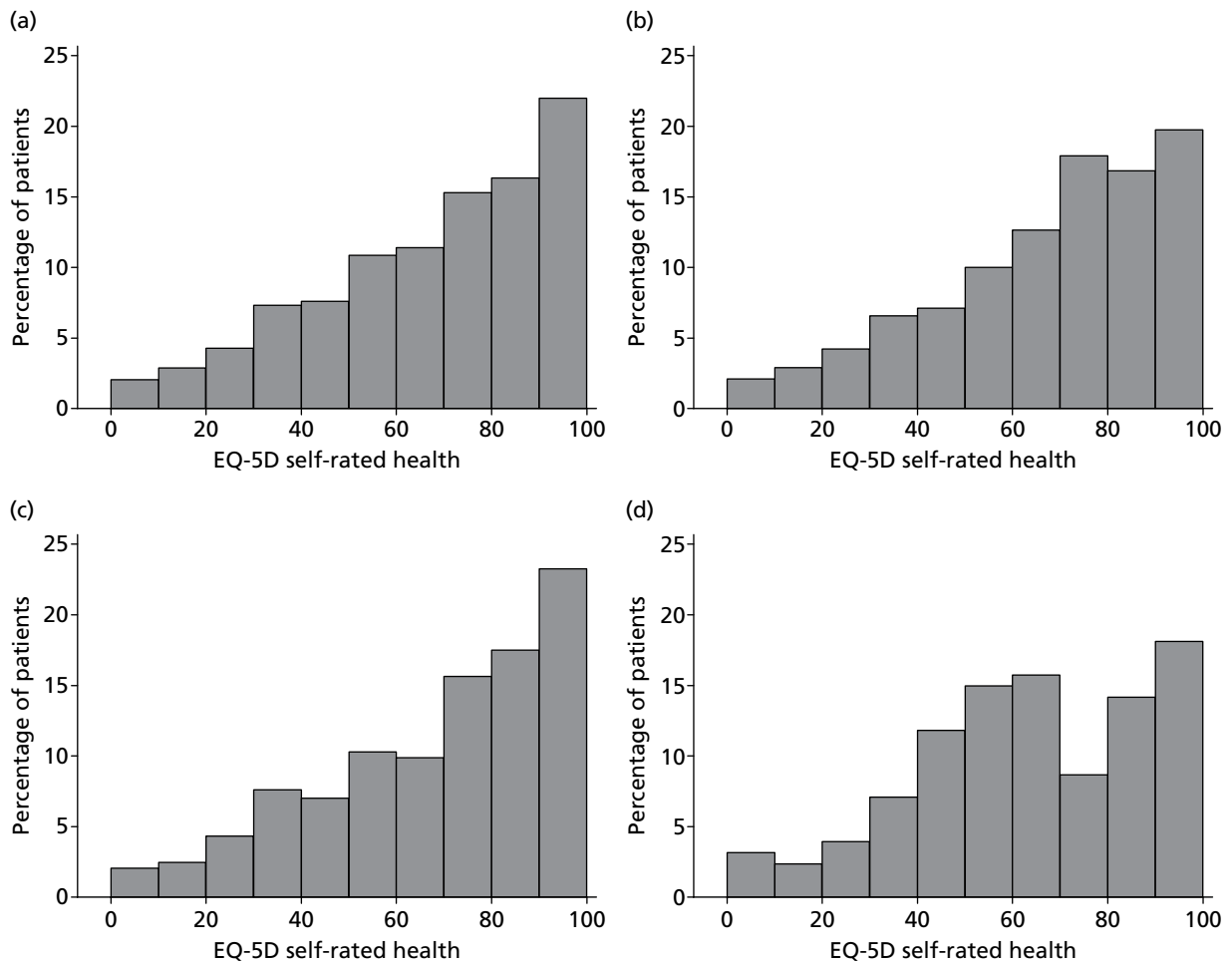


FIGURE 24 Self-rated health at 6 months following TBI, overall and by cause. (a) Overall; (b) RTA; (c) fall; (d) assault.

Discussion

Principal findings

Patients with acute TBI admitted to UK critical care units participating in the RAIN study were predominantly admitted following RTA (33%), fall (47%) or assault (12%). Characteristics and outcomes varied markedly by cause of TBI. The RAIN study demonstrated a substantial burden of poor neurological outcomes and QOL 6 months after TBI for adult patients admitted to critical care. Mortality at discharge from acute hospital was 16% for assault, 21% for RTA and 30% for falls, rising to 17%, 22% and 32%, respectively, at 6 months following the TBI. Of survivors at 6 months with known a known GOS-E category, 44% had severe disability, 30% had moderate disability, and only 26% had made a good recovery. When combined with the 26% mortality at 6 months, 61% of patients with known outcome had an unfavourable outcome (death or severe disability) at 6 months. In addition, between 35% and 70% of survivors reported problems across the five domains of the EQ-5D-3L. Despite this, self-rated health was remarkably good, with an overall median of 70 out of 100 and 22% of respondents rating their current health as 90 out of 100 or higher.

Comparison with other studies

Little literature exists reporting specifically on multicentre cohorts of patients with acute TBI receiving critical care. A previous study from the CMP reported on over 11,000 admissions to 169 general critical care units (including combined neuro/general critical care units) and two dedicated neurocritical care units between 1995 and 2005 with a primary reason for admission to the critical care unit of 'primary brain

injury', 'extradural haematoma' or 'subdural haematoma'.⁶ Three-quarters of admissions were male and the mean age was 44 years, corresponding very closely with the overall figures in the RAIN study. Patients were followed up to ultimate discharge from acute hospital, with mortality of 33.5% – considerably higher than the 24.5% acute hospital mortality observed in the RAIN study. A prospective study from Australia and New Zealand reported on 635 patients admitted to the critical care units of 16 major trauma centres following acute TBI.⁷³ The age and sex distribution was again similar to that of the RAIN study (mean age 42 years, 74% male). However, there was a different distribution of cause of TBI with 61% RTA, 25% falls, 8% assault and 8% other/unknown; 57% of TBIs were severe (GCS score 3–8) based on the first at hospital GCS score compared with 46% of those in the RAIN study with a first at hospital GCS score recorded. A remarkably high proportion of patients had no visible pathology on CT scan (24% overall including 23% of severe TBI) and of those with abnormal CT scans, diffuse injuries predominated (63%), consistent with the higher proportion of patients admitted following RTA. Mortality was similar to that in the RAIN study (15.1% vs 18.4% at discharge from the critical care unit and 24.4% vs 26.0% at 6 months following TBI).

The proportion of survivors with severe disability at 6 months in the RAIN study (44%) is high compared with previous studies, for example 26% for patients with severe TBI from a study in the Netherlands⁷⁴ and 27% among critically ill patients following TBI in Australia and New Zealand.⁷³ Some of these patients will still be on a trajectory of improving neurological outcome; the proportion with a good recovery increased from 38% at 6 months to 46% at 12 months in the study from the Netherlands,⁷⁴ and from 27% to 42% in the study from Australia and New Zealand.⁷³ However, for many patients, these are likely to represent long-term disabilities, for example a long-term follow-up study in Glasgow found that of 96 patients with severe disability at 1 year following TBI, 44 (46%) had died, 30 (31%) still had severe disability, 15 (16%) had moderate disability and seven (7%) had made a good recovery when followed up 5–7 years following injury.⁷⁵

Chapter 5 External validation of risk prediction models for acute traumatic brain injury among critically ill patients

Introduction

This chapter reports the statistical validation of the risk prediction models identified following the updated systematic review (see *Chapter 2*) using the data collected for the RAIN study (see *Chapters 3 and 4*). In addition, this chapter reports a nested substudy testing the inter-rater reliability (reproducibility) of CT scan reporting in the RAIN study.

Methods

Summary of risk prediction models

Following the updated systematic review (see *Chapter 2*) and review by the RAIN Study Steering Group, three families of risk prediction models were selected for validation in the RAIN study – the models of Hukkelhoven *et al.* (Hukkelhoven models);⁴⁸ the MRC CRASH trial collaborators (CRASH models);³⁰ and Steyerberg *et al.* (IMPACT models).³⁵ A total of 10 models were included in the RAIN study validation (*Figure 25*): four predicting mortality at 6 months (one Hukkelhoven and three IMPACT) and six predicting unfavourable outcome at 6 months (one Hukkelhoven, two CRASH and three IMPACT). Details of the development and validation of these models were reported in *Chapter 2*. A brief summary of the development data sources, inclusion/exclusion criteria and included variables is presented for each model below.

Hukkelhoven models

The Hukkelhoven models were developed using data from two multicentre RCTs, one from North America and one from Europe.^{49,50} Inclusion criteria for both trials were patients aged 15–65 years with severe TBI (GCS score of <9) regardless of CT findings or moderate TBI (GCS score of 9–12) with an abnormal CT scan. Patients with an absent motor score were excluded. Randomisation had to take place within 4 hours of injury. Two risk prediction models were developed: one for mortality at 6 months and one for unfavourable outcome at 6 months.⁴⁸ The variables included in the risk prediction models were: age (linear and quadratic terms); motor score; pupil reactivity; pre-hospital hypotension; pre-hospital hypoxia; Marshall CT classification; and traumatic SAH. Model coefficients were obtained from the published paper.⁴⁸

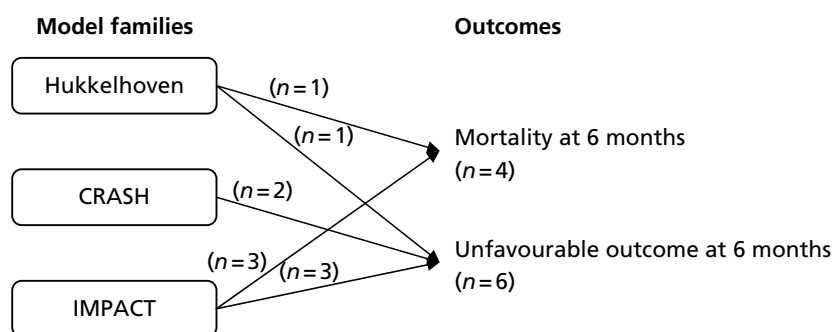


FIGURE 25 Overview of risk prediction models.

CRASH models

The CRASH models were developed using data from one multinational, multicentre RCT.^{53,54,62} Inclusion criteria for the trial were patients aged ≥ 16 years with TBI and a GCS score of < 15 and no clear contraindication to receiving corticosteroids. Randomisation had to take place within 8 hours of injury. In total, eight risk prediction models were developed, for each combination of setting (low-/middle- and high-income countries), outcome (mortality at 14 days and unfavourable outcome at 6 months) and model complexity ('Basic' and 'CT' models).³⁰ Patients with no CT scan available were excluded from the development samples for the CT models. As the setting for the RAIN study was the UK NHS, and the importance of longer-term outcomes was identified at the outset of the study, the models of interest for the RAIN study were the two models based on data from high-income countries predicting unfavourable outcome at 6 months. The variables included in the Basic models were age (linear > 40 years); GCS score (linear); pupil reactivity; and major extracranial injury (requiring hospital admission independent of the TBI). The additional variables included in the CT models were one or more small petechial haemorrhages; obliteration of the third ventricle or basal cisterns; subarachnoid bleed (traumatic SAH); midline shift of > 5 mm; and non-evacuated haematoma. Model coefficients were obtained from the authors.

IMPACT models

The IMPACT models were developed using data from the IMPACT database, a pooled database of data from eight RCTs and three observational studies of patients with moderate or severe TBI (GCS score of < 13).⁵⁵ Individual data sets had different inclusion criteria. Six risk prediction models were developed for each combination of outcome (mortality at 6 months and unfavourable outcome at 6 months) and model complexity ('Core', 'Extended' and 'Lab' models).³⁵ Patients from one of the constituent data sets of the IMPACT database, which did not record hypoxia, hypotension or CT classification, were excluded from the development sample for the extended models and patients from a further six data sets, which did not record laboratory values, were excluded from the development sample for the Laboratory models. Missing data for individual patients in the development samples for each model were imputed. The variables included in the Core models were age (linear); motor score; and pupil reactivity. The additional variables included in the Extended models were Marshall CT classification; traumatic SAH; epidural (extradural) haematoma; pre-hospital hypoxia; and pre-hospital hypotension. The additional variables included in the Laboratory models were glucose (linear); and haemoglobin (linear). Model coefficients were obtained from the published paper.³⁵

Data sources and risk factors definitions

Patients were selected from the RAIN study database if their last pre-sedation GCS score was < 15 . Definitions for fields in the RAIN study are provided in *Appendix 3*. Risk factor variables were calculated from the raw data as follows:

- *Age* Age in whole years at the time of TBI, calculated from the date of birth and date of TBI.
- *GCS score* The last recorded GCS score prior to sedation, which may have been either the pre-hospital GCS score, the first recorded-at-hospital GCS score or a subsequent measurement prior to sedation and admission to the critical care unit.
- *Motor score* The motor score component of the last pre-sedation GCS score.
- *Pupil reactivity* The first recorded-at-hospital pupil reactivity, if available, or the pre-hospital pupil reactivity if no first at hospital value was available. Pupil reactivity was recorded for the left and right eye separately and combined as either 'both reactive', 'one reactive' or 'neither reactive'. If only one eye could be assessed, pupil reactivity was assigned as 'both reactive' if this eye was reactive, and 'neither reactive' if this eye was not reactive.
- *Major extracranial injury* Recorded as a specific field in the RAIN study data set, defined as an injury requiring hospital admission in its own right.
- *Pre-hospital hypoxia* Defined as either a pre-hospital oxygen saturation of $< 90\%$, or pre-hospital hypoxia strongly suspected if there was clinical evidence of hypoxia (e.g. tension pneumothorax) but no pre-hospital oxygen saturation was recorded.

- *Pre-hospital hypotension* Defined as either a pre-hospital systolic blood pressure of <90 mmHg, or pre-hospital hypotension strongly suspected if there was clinical evidence of hypotension (e.g. multiple trauma with massive blood loss) but no pre-hospital systolic blood pressure was recorded.
- *Marshall CT classification* Based on the first CT scan following the TBI, and defined as (1) diffuse injury I – no visible pathology seen on CT scan (first CT scan result normal); (2) diffuse injury II – basal cisterns present, midline shift of 0–5 mm, no high- or mixed-density lesion of >25 ml; (3) diffuse injury III – basal cisterns compressed or absent, midline shift of 0–5 mm, no high- or mixed-density lesion of >25 ml; (4) diffuse injury IV – midline shift of >5 mm, no high- or mixed-density lesion >25 ml; (5) evacuated mass lesion – any high- or mixed-density lesion of >1 ml – surgically evacuated; (6) non-evacuated mass lesion of >25 ml – high- or mixed-density lesion of >25 ml not surgically evacuated.⁵⁶
- *Traumatic SAH* Recorded as a specific field in the RAIN study data set.
- *One or more small petechial haemorrhages* Recorded as a specific field in the RAIN study data set.
- *Obliteration of the third ventricle or basal cisterns* Third ventricle recorded as 'obliterated' or basal cisterns recorded as 'absent'.
- *Midline shift of >5 mm* Recorded as a specific field in the RAIN study data set.
- *Non-evacuated haematoma* Any high- or mixed-density lesion of >1 ml – not surgically evacuated.
- *Extradural haematoma* Recorded as a specific field in the RAIN study data set.
- *First at hospital glucose* Recorded as a specific field in the RAIN study data set.
- *First at hospital haemoglobin* Recorded as a specific field in the RAIN study data set.

Handling of missing data

Missing data in the RAIN study data set were addressed with multiple imputation.^{76,77} Multiple imputation aims to allow for the uncertainty about missing data by creating multiple copies of the data set with the missing values in each data set replaced by imputed values, sampled from their predicted distribution.⁷⁸ Analyses are conducted on each of the imputed data sets and combined together. As GOSE category is conditional on survival status, the imputation was conducted in two stages. In the first stage, imputation models were specified for risk factors and mortality at 6 months, according to observed covariates. In the second stage, for each of the previously imputed data sets, imputation models were specified for GOSE category for those patients who were either known to be alive at 6 months or were predicted to be alive by the first stage imputation model. Each multiple imputation model assumed that the data were 'missing at random', i.e. conditional on the variables included in the imputation models.⁷⁶ Each imputation model considered including, for example baseline characteristics (e.g. age) and resource use at 6 months (e.g. LOS in critical care). Five imputed data sets were generated for each stage of the imputation,⁷⁸ giving 25 imputed data sets in total. All multiple imputation models were implemented in R (The R Foundation for Statistical Computing, Vienna, Austria: www.r-project.org) using Multivariate Imputation by Chained Equations (MICE).⁷⁹

Validation data sets

For the primary analyses, each model was validated in the multiply imputed data sets, using (1) all patients in the RAIN study with a last pre-sedation GCS score of <15 and (2) only those patients meeting the original inclusion criteria for each model. As secondary analyses, and to reflect use of the models in real life settings, the validation was repeated in the original RAIN study data set prior to imputation using (3) all patients; (4) only those patients meeting the original inclusion criteria for each model; and (5) only those patients meeting the original inclusion criteria for each model and with complete data for all variables in the model. For analyses 3 and 4, missing values were assumed to be in the lowest risk category and laboratory data were singly imputed to a normal value.

As a sensitivity analysis, the analysis for models predicting unfavourable outcome in all patients in the RAIN study data set [data set (1) above] was repeated excluding those patients assigned to the GOSE category of severe disability that was either pre-existing or not due to the TBI.

Statistical analysis

The case mix and outcomes of patients reported for the original development sample for each family of models (Hukkelhoven, CRASH and IMPACT) was compared with those for the patients in the RAIN study data set that met the original inclusion criteria for the particular family of models, and with all patients in the RAIN study data set. The case mix factors included in these comparisons were those included in the papers reporting development of the models. Owing to the level of detail of reporting in the papers, it was possible to summarise the overall case mix and outcome for only each full development sample, and not specifically to the patients actually included in each development sample for each individual model.

The completeness of data for each risk factor included in each of the risk prediction models and the outcomes of mortality and unfavourable outcome at 6 months was assessed in the full RAIN study data set. Univariable analyses were conducted to assess the relationship between each risk factor and the outcomes.

Each risk prediction model was then validated in each of the five RAIN study validation data sets using measures of calibration, discrimination and overall fit, as described below. For the validation of risk prediction models for mortality at 6 months, the five data sets from the first stage imputation were used. For the validation of risk prediction models for unfavourable outcome at 6 months, the 25 data sets from the second stage imputation were used. In each case, measures of model performance were calculated in each imputed data set and combined using Rubin's rules,⁷⁶ which recognise uncertainty both within and between imputations.

Discrimination describes the ability of the model to correctly separate the patients into different groups (survivors from non-survivors or favourable from unfavourable outcomes). Discrimination was assessed by the c-index,⁸⁰ which is equivalent to the area under the ROC curve.⁸¹ When $c = 1$ there is perfect discrimination between the groups (i.e. every patient that died has a higher predicted risk than every patient that survived, or every patient with an unfavourable outcome has a higher predicted risk than every patient with a favourable outcome) and when $c = 0.5$ the discrimination is no better than chance.

Calibration describes the degree of correspondence between the probability predicted by the model, and the observed proportion with the outcome. Calibration was assessed by graphical plots of observed against expected risk in 10 equal-sized groups by predicted risk. The Hosmer–Lemeshow test was used to test the hypothesis of perfect calibration.⁸² However, the Hosmer–Lemeshow test does not provide a measure of the magnitude of miscalibration and is highly sensitive to sample size.⁸³ Therefore, the magnitude and direction of miscalibration was assessed using Cox's calibration regression.⁸⁴ Cox's calibration regression fits a logistic regression model to the predicted log odds from the risk prediction model to estimate the intercept, α , and slope, β . If the model is perfectly calibrated then $\alpha = 0$ and $\beta = 1$. The value of α represents the calibration at a predicted risk of 0.5, and calibration more generally if $\beta = 1$. If $0 < \beta < 1$, the predictions vary too much; if $\beta > 1$, the predictions 'show the right general pattern of variation but do not vary enough'.

The overall fit (or accuracy) of the model describes how close the predictions are to the actual outcomes for individual patients. Overall fit was assessed using Brier's score, the mean squared error between the outcome and prediction.⁸⁵ Lower values of Brier's score represent better fit, with perfect predictions corresponding to $B = 0$ and a constant prediction of 0.5 for all patients corresponding to $B = 0.25$.

Inter-rater reliability of computerised tomography scan reporting

It is essential to know whether the data obtained from local reporting of CT scans are adequate for accurate risk adjustment, as this will have significant implications on the practicability of using any particular risk prediction model. Data collectors were therefore asked to record appropriate identifiers to allow access to CT scans for rereview at a later date, and were requested not to discard or destroy the films or digital imaging data for these patients until 5 years after entry into the RAIN study. Copies of the first CT scan following presentation at hospital were requested for a randomly selected sample of 10% of

patients, weighted to include more patients from outside neuroscience centres, where patient throughput was lower, and including at least one patient from each site participating in the RAIN study (provided at least one patient had CT data available). Data collectors were requested to send anonymised CT scans to the WBIC. Images were transferred either electronically using the Image Exchange Portal or by recorded delivery or secure courier. The images were centrally viewed and assessed by four neurosurgical specialist registrars/research fellows experienced in assessing CT scans, working under the supervision of two of the clinical co-investigators (DKM, PJH). Each CT scan was assessed independently by two raters, working in two teams of two, and data were recorded using the same secure, web-based data entry system as for the original RAIN study data entry. Each rater was blinded to the site from which the CT scan originated, the original RAIN study data reported by that site, and the assessment of their co-rater.

Inter-rater reliability (reproducibility) was assessed by κ -statistics⁸⁶ for each individual CT field in the RAIN study data set between:

1. each group of three ratings comprising the original RAIN study data and the two independent ratings from WBIC; and
2. each pair of ratings: RAIN compared with WBIC rater 1, RAIN compared with WBIC rater 2 and WBIC rater 1 compared with WBIC rater 2, separately for the two teams of two raters within WBIC.

Subgroup analyses were conducted to compare inter-rater reliability by the specialty and grade of assessor in the original RAIN study data, and by whether the scan was from a neuroscience centre or a non-neuroscience centre.

Confidence intervals for κ -statistics were calculated using the method of Donner and Eliasziw⁸⁷ for two raters rating a binary outcome, the method of Zou and Donner⁸⁸ for more than two raters rating a binary outcome, and using bootstrap resampling for more than two raters rating an outcome with more than two levels.⁸⁹

All statistical analyses were conducted using Stata/SE version 10.1 (StataCorp LP, College Station, TX, USA).

Results

Comparison of model development samples with the RAIN study data set

Tables 12–14 describe the case mix and outcomes of the development samples for the families of Hukkelhoven, CRASH and IMPACT models compared with patients from the RAIN study, both those meeting the original inclusion criteria for the respective model and all patients in the RAIN study data set. Compared with patients in the Hukkelhoven development sample (see Table 12), patients in the RAIN study were, on average, older (mean 45 years vs 33 years), more likely to have had a fall (47% vs 17%) and less likely to have had an RTA (33% vs 58%) as the cause of their TBI, had worse GCS motor scores (32% vs 13% with motor score 1 or 2) and were more likely to have had either an evacuated or non-evacuated mass lesion (Marshall class 5/6, 50% vs 32%). They were, however, less likely to have either pre-hospital hypoxia (13% vs 21%) or hypotension (7% vs 18%). These differences remained, but were generally reduced, after applying the Hukkelhoven inclusion criteria to the RAIN study data set, with the exception of the GCS motor score in which the difference became more extreme (42% vs 13% with motor score 1 or 2). Mortality at 6 months was slightly higher in the RAIN study than in the Hukkelhoven development sample (26% vs 22%) but was similar (23% vs 22%) after applying the inclusion criteria. Unfavourable outcome at 6 months was substantially higher in the RAIN study both before (61% vs 40%) and after (60% vs 40%) applying the inclusion criteria.

Compared with patients in the CRASH development sample (see Table 13), patients in the RAIN study were, on average, slightly older (mean 45 vs 41 years), more likely to have had a fall (47% vs 20%) and less likely to have had an RTA (33% vs 50%) as the cause of their TBI, had worse GCS scores (59% vs 44% severe TBI,

TABLE 12 Case mix and 6-month outcomes for the Hukkelhoven models development sample compared with the RAIN study data set

Case mix and outcomes	Hukkelhoven	RAIN (meeting Hukkelhoven inclusion)	RAIN (all)
Number of admissions	2269	1806	2975
Age (years), mean (SD) [N]	33.2 (13.5) [2269]	38.0 (14.4) [1806]	44.7 (18.9) [2975]
Male, <i>n</i> (%) [N]	1757 (77.4) [2269]	1414 (78.3) [1806]	2263 (76.1) [2975]
Cause of TBI, <i>n</i> (%) [N]	[2269]	[1806]	[2975]
RTA	1319 (58.1)	708 (39.2)	971 (32.6)
Fall	386 (17.0)	699 (38.7)	1399 (47.0)
Other ^a	564 (24.9)	399 (22.1)	605 (20.3)
GCS motor score, <i>n</i> (%) [N]	[2269]	[1806]	[2907]
5/6 (localises/obeys)	933 (41.1)	672 (37.2)	1409 (48.5)
4 (normal flexion)	659 (29.0)	242 (13.4)	349 (12.0)
3 (abnormal flexion)	374 (16.5)	140 (7.8)	209 (7.2)
1/2 (none/extension)	303 (13.4)	752 (41.6)	940 (32.3)
Pupil reactivity, <i>n</i> (%) [N]	[2269]	[1806]	[2975]
Both reactive	1401 (61.7)	1275 (70.6)	2215 (74.5)
One reactive	279 (12.3)	122 (6.8)	167 (5.6)
Neither reactive	308 (13.6)	283 (15.7)	378 (12.7)
Unable/not assessed	281 (12.4)	126 (7.0)	215 (7.2)
Hypoxia, <i>n</i> (%) [N]	429 (21.4) [2006]	260 (15.2) [1709]	354 (12.6) [2800]
Hypotension, <i>n</i> (%) [N]	395 (17.9) [2208]	141 (8.3) [1703]	190 (6.8) [2791]
Marshall CT classification, <i>n</i> (%) [N]	[2249]	[1710]	[2773]
1/2 (diffuse injury I/II)	1006 (44.7)	674 (39.4)	1051 (37.9)
3 (diffuse injury III)	426 (18.9)	193 (11.3)	248 (8.9)
4 (diffuse injury IV)	88 (3.9)	51 (3.0)	78 (2.8)
5/6 (evacuated mass lesion/non-evacuated mass lesion >25 ml)	729 (32.4)	792 (46.3)	1396 (50.3)
Traumatic SAH, <i>n</i> (%) [N]	1090 (49.0) [2223]	1006 (58.4) [1724]	1565 (56.0) [2797]
Six-month outcome, <i>n</i> (%) [N]:			
Mortality	500 (22.0) [2269]	397 (22.7) [1746]	748 (26.0) [2881]
Unfavourable outcome	862 (40.1) [2149]	867 (60.0) [1444]	1481 (61.3) [2420]

SD, standard deviation.

^a Includes 'Assault' and 'Unknown'.

TABLE 13 Case mix and 6-month outcome for the CRASH models development sample compared with the RAIN study data set

Case mix and outcomes	CRASH ^a	RAIN (meeting CRASH inclusion)	RAIN (all)
Number of admissions	2,482	2710	2975
Age (years), mean (SD) [N]	40.6 (19.4)	43.9 (18.8) [2710]	44.7 (18.9) [2975]
Male, <i>n</i> (%) [N]	(78.9)	2069 (76.4) [2710]	2263 (76.1) [2975]
Cause of TBI, <i>n</i> (%) [N]		[2710]	[2975]
RTA	(50.2)	949 (35.0)	971 (32.6)
Fall	(20.0)	1218 (44.9)	1399 (47.0)
Other ^b	(29.8)	543 (20.0)	605 (20.3)
Hours since injury, mean (SD) [N]	2.8 (2.0)	0.4 (4.1) [2710]	7.1 (46.6) [2975]
GCS score, <i>n</i> (%) [N]		[2710]	[2975]
13–14 (mild TBI)	(32.6)	398 (14.7)	447 (15.0)
9–12 (moderate TBI)	(23.6)	677 (25.0)	765 (25.7)
3–8 (severe TBI)	(43.8)	1635 (60.3)	1763 (59.3)
Pupil reactivity, <i>n</i> (%) [N]		[2710]	[2975]
Both reactive	(80.7)	2016 (74.4)	2215 (74.5)
One reactive	(6.3)	154 (5.7)	167 (5.6)
Neither reactive	(9.1)	350 (12.9)	378 (12.7)
Unable/not assessed	(3.9)	190 (7.0)	215 (7.2)
Major extracranial injury, <i>n</i> (%) [N]	(22.5)	1163 (42.9) [2709]	1213 (40.8) [2974]
CT scan available, <i>n</i> (%) [N]	(88.0)	2583 (95.3) [2710]	2817 (94.7) [2975]
Traumatic SAH, <i>n</i> (%) [N]	(26.4)	1456 (56.8) [2563]	1565 (56.0) [2797]
Obliteration of third ventricle or basal cisterns, <i>n</i> (%) [N]	(9.6)	641 (25.0) [2560]	717 (25.7) [2793]
Midline shift, <i>n</i> (%) [N]	(11.1)	753 (29.4) [2563]	880 (31.5) [2796]
Haematoma, <i>n</i> (%) [N]		[2580]	[2813]
Evacuated	(7.9)	831 (32.2)	964 (34.3)
Non-evacuated	(26.5)	1341 (52.0)	1432 (50.9)
Six-month outcome, <i>n</i> (%) [N]			
Unfavourable outcome	(38.5)	1340 (61.0) [2198]	1481 (61.3) [2420]

SD, standard deviation.

^a Note that absolute numbers were not reported, only percentages.^b Includes 'Assault' and 'Unknown'.

TABLE 14 Case mix and 6-month outcome for the IMPACT models development sample compared with the RAIN study data set

Case mix and outcomes	IMPACT	RAIN (meeting IMPACT inclusion)	RAIN (all)
Number of admissions	8509	2528	2975
Age (years), median (IQR) [N]	30 (21 to 45) [8509]	44 (28 to 59) [2528]	44 (28 to 59) [2975]
GCS motor score, n (%) [N]	[8509]	[2528]	[2975]
5/6 (localises/obeys)	2591 (30.5)	974 (38.5)	1409 (47.4)
4 (normal flexion)	1940 (22.8)	345 (13.6)	349 (11.7)
3 (abnormal flexion)	1085 (12.8)	209 (8.3)	209 (7.0)
2 (extension)	1042 (12.2)	219 (8.7)	219 (7.4)
1 (none)	1395 (16.4)	721 (28.5)	721 (24.2)
Untestable/missing	456 (5.4)	60 (2.4)	68 (2.3)
Pupil reactivity, n (%) [N]	[8509]	[2528]	[2975]
Both reactive	4486 (52.7)	1828 (72.3)	2215 (74.5)
One reactive	886 (10.4)	152 (6.0)	167 (5.6)
Neither reactive	1754 (20.6)	367 (14.5)	378 (12.7)
Unable/not assessed	1383 (16.3)	181 (7.2)	215 (7.2)
Hypoxia, n (%) [N]	1116 (20.5) [5452]	327 (13.8) [2379]	354 (12.6) [2800]
Hypotension, n (%) [N]	1171 (18.2) [6420]	169 (7.1) [2370]	190 (6.8) [2791]
Marshall CT classification, n (%) [N]	[5192]	[2355]	[2773]
1 (diffuse injury I)	360 (6.9)	94 (4.0)	113 (4.1)
2 (diffuse injury II)	1838 (35.4)	770 (32.7)	938 (33.8)
3 (diffuse injury III)	863 (16.6)	214 (9.1)	248 (8.9)
4 (diffuse injury IV)	187 (3.6)	64 (2.7)	78 (2.8)
5 (evacuated mass lesion)	1435 (27.6)	834 (35.4)	964 (34.8)
6 (non-evacuated mass lesion >25 ml)	509 (9.8)	379 (16.1)	432 (15.6)
Traumatic SAH, n (%) [N]	3313 (44.8) [7393]	1365 (57.5) [2375]	1565 (56.0) [2797]
Extradural haematoma(s), n (%) [N]	999 (13.5) [7409]	373 (15.6) [2392]	469 (16.7) [2816]
Glucose (mmol/l), median (IQR) [N]	8.2 (6.7 to 10.4) [4830]	7.7 (6.3 to 9.5) [2142]	7.6 (6.3 to 9.5) [2496]
Haemoglobin (g/dl), median (IQR) [N]	12.7 (10.8 to 14.3) [4376]	13.4 (11.8 to 14.6) [2280]	13.4 (11.9 to 14.6) [2683]
Six-month outcome, n (%) [N]			
Mortality	2396 (28.2) [8509]	685 (27.9) [2455]	748 (26.0) [2881]
Unfavourable outcome	4082 (48.0) [8509]	1323 (64.3) [2059]	1481 (61.3) [2420]

GCS score 3–8; 15% vs 33% mild TBI, GCS score 13–14), were more likely to have unreactive pupils (13% vs 9%) and major extracranial injury (41% vs 23%), and had higher rates of all risk factors on CT. The rate of unfavourable outcome at 6 months was substantially higher in the RAIN study (61% vs 39%). There was very little change after applying the CRASH inclusion criteria to the RAIN study data set, as the majority of patients in the RAIN study met CRASH inclusion.

Compared with patients in the IMPACT development sample (see *Table 14*), patients in the RAIN study were, on average, older (median 44 vs 30 years), more likely to have GCS motor scores at the extremes of the range (24% vs 16% with motor score 1 and 47% vs 30% with motor score 6), and were less likely to have unreactive pupils (13% vs 21%), hypoxia (13% vs 21%) and hypotension (7% vs 18%). The distributions of CT findings and laboratory results were broadly similar. Mortality at 6 months was similar (26% vs 28%) but the rate of unfavourable outcome at 6 months was higher in the RAIN study (61% vs 48%). There was little change after applying the IMPACT inclusion criteria to the RAIN study data set.

Data completeness

Table 15 reports the data completeness for risk factors and outcomes in the RAIN study data set. Age and GCS score were 100% complete (due to their requirement for meeting RAIN study inclusion criteria), and major extracranial injury was missing for only one patient (and assumed absent). All other risk factors and outcomes were included in the multiple imputation. The core risk factors were available for between 92.8% (pupil reactivity) and 97.7% (motor score) of patients. The first CT scan was available for 2817 patients (94.7%) and the majority of these had all CT fields recorded. Overall, 93.2% of CT scans could be assigned to a Marshall class; of the remaining 6.8%, 5.3% could not be assigned as no CT data were available and 1.5% were due to individual missing CT fields. Laboratory variables were the least complete with 83.9% completeness for glucose and 90.2% for haemoglobin. There was 96.8% follow-up for mortality at 6 months (being unknown only for patients who were homeless or a non-UK resident and could not be linked with the MRIS database; see *Chapter 3*). There was 81.4% follow-up overall for unfavourable outcome at 6 months (see *Chapter 4*). Following multiple imputation, the overall mortality at 6 months was estimated to be 25.7% and the rate of unfavourable outcomes 57.4% (note that this is lower than the observed rate owing to being more likely to observe outcomes for non-survivors).

Univariable associations between risk factors and outcomes

Tables 16–18 report the univariable associations between risk factors and outcomes for core, CT and laboratory variables. The majority of core risk factors demonstrated similar patterns of associations with outcomes as in the risk prediction models (see *Table 16*). Mortality at 6 months was relatively flat below the age of 40 years and increased from the age of 40 years (reflecting the structure used in the CRASH models), whereas unfavourable outcome increased across the whole range of age (reflecting the structure used in the IMPACT models). The range of outcomes across categories of GCS motor score (16–40% for mortality and 45–75% for unfavourable outcome) was almost as wide as that seen across the total GCS score (15–43% and 44–78%), reflecting the consensus that the majority of prognostic information in the GCS score, for patients with TBI, comes from the motor score component. Non-reactive pupils and pre-hospital hypoxia and hypotension were associated with substantially worse outcomes. However, major extracranial injury was not associated with any increase in mortality or unfavourable outcome at 6 months.

For CT variables (see *Table 17*), mortality increased substantially across the four categories of diffuse injury in the Marshall CT classification, was lower for category 5 (evacuated mass lesion) and substantially higher for category 6 (non-evacuated mass lesion >25 ml). This pattern does not appear to support the modelling approach taken in both the Hukkelhoven and IMPACT models of combining categories 5 and 6, although the relationship may be different once adjusted for other variables (e.g. the separate variable for extradural haematoma included in the IMPACT models). All other CT factors were associated with increased mortality and unfavourable outcome except small petechial haemorrhages and extradural haematoma. There was no univariable association between small petechial haemorrhages and outcomes. However, it should be noted that in the CRASH CT model, this variable was associated only with a small, and not statistically

TABLE 15 Data completeness for variables included in the risk prediction models ($n = 2975$)

Variable	Hukkelhoven	CRASH Basic	CRASH CT	IMPACT Core	IMPACT Extended	IMPACT Lab	Completeness, n (%)
Predictors							
Age	✓	✓	✓	✓	✓	✓	2975 (100)
GCS score		✓	✓				2975 (100)
GCS motor score	✓			✓	✓	✓	2907 (97.7)
Pupil reactivity	✓	✓	✓	✓	✓	✓	2760 (92.8)
Major extracranial injury		✓	✓				2974 (>99.9)
Hypoxia	✓			✓	✓	✓	2800 (94.1)
Hypotension	✓			✓	✓	✓	2791 (93.8)
Marshall CT classification	✓				✓	✓	2773 (93.2)
Traumatic SAH	✓		✓		✓	✓	2797 (94.0)
Small petechial haemorrhages			✓				2814 (94.6)
Obliteration of third ventricle/ basal cisterns			✓				2793 (93.9)
Midline shift			✓				2796 (94.0)
Non-evacuated haematoma			✓				2813 (94.6)
Extradural haematoma					✓	✓	2816 (94.7)
Glucose						✓	2496 (83.9)
Haemoglobin						✓	2683 (90.2)
Outcomes							
Mortality at 6 months	✓			✓	✓	✓	2881 (96.8)
Unfavourable outcome at 6 months	✓	✓	✓	✓	✓	✓	2422 (81.4)

significant, increase in risk in high-income countries and was retained in the model because of the more substantial effect observed in low- and middle-income countries. Extradural haematoma was associated with a decreased risk of mortality and unfavourable outcome, consistent with the negative coefficient for this variable in the IMPACT Extended and IMPACT Lab models.

For the laboratory variables (see *Table 18*), there was a substantial increasing risk of both mortality and unfavourable outcome at 6 months associated with both increasing glucose and decreasing haemoglobin, consistent with the relationships in the IMPACT Lab models.

TABLE 16 Univariable associations between risk factors and outcomes for variables included in the risk prediction models: core variables

Variable	Mortality at 6 months		Unfavourable outcome at 6 months	
	n/N	% (95% CI)	n/N	% (95% CI)
Age (years)				
16–29	125/807	15.5 (13.2 to 18.1)	303/669	45.3 (41.6 to 49.1)
30–39	61/394	15.5 (12.2 to 19.4)	181/325	55.7 (50.3 to 61.0)
40–49	109/533	20.5 (17.2 to 24.1)	269/444	60.6 (56.0 to 65.0)
50–59	115/421	27.3 (23.3 to 31.8)	228/343	66.5 (61.3 to 71.3)
60–69	149/362	41.2 (36.2 to 46.3)	232/315	73.7 (68.5 to 78.2)
70–79	127/258	49.2 (43.2 to 55.3)	186/229	81.2 (75.7 to 85.8)
80+	62/106	58.5 (49.0 to 67.4)	82/97	84.5 (76.0 to 90.4)
GCS score				
13–14	63/426	14.8 (11.7 to 18.5)	158/362	43.6 (38.6 to 48.8)
9–12	135/740	18.2 (15.6 to 21.2)	308/613	50.2 (46.3 to 54.2)
4–8	301/1137	26.4 (24.0 to 29.1)	625/944	66.2 (63.1 to 69.2)
3	249/578	43.1 (39.1 to 47.1)	390/503	77.5 (73.7 to 81.0)
GCS motor score				
6	78/486	16.0 (13.1 to 19.6)	189/416	45.4 (40.7 to 50.2)
5	166/871	19.1 (16.6 to 21.8)	377/713	52.9 (49.2 to 56.5)
4	76/341	22.3 (18.2 to 27.0)	173/283	61.1 (55.3 to 66.6)
3	59/200	29.5 (23.6 to 36.2)	112/166	67.5 (60.0 to 74.1)
2	77/215	35.8 (29.7 to 42.4)	141/176	80.1 (73.6 to 85.3)
1	282/701	40.2 (36.7 to 43.9)	453/608	74.5 (70.9 to 77.8)
Pupil reactivity				
Both reactive	450/2146	21.0 (19.3 to 22.7)	996/1785	55.8 (53.5 to 58.1)
One reactive	41/159	25.8 (19.6 to 33.1)	92/135	68.1 (59.9 to 75.4)
Neither reactive	202/371	54.4 (49.4 to 59.4)	282/328	86.0 (81.8 to 89.3)
Major extracranial injury				
No	460/1714	26.8 (24.8 to 29.0)	872/1429	61.0 (58.5 to 63.5)
Yes	288/1166	24.7 (22.3 to 27.3)	608/992	61.3 (58.2 to 64.3)
Pre-hospital hypoxia				
No	577/2361	24.4 (22.7 to 26.2)	1184/1978	59.9 (57.7 to 62.0)
Yes	133/347	38.3 (33.4 to 43.5)	209/297	70.4 (64.9 to 75.3)
Pre-hospital hypotension				
No	631/2516	25.1 (23.4 to 26.8)	1264/2105	60.0 (57.9 to 62.1)
Yes	76/184	41.3 (34.4 to 48.5)	124/163	76.1 (69.0 to 82.0)

TABLE 17 Univariable associations between risk factors and outcomes for variables included in the risk prediction models: CT variables

Variable	Mortality at 6 months		Unfavourable outcome at 6 months	
	n/N	% (95% CI)	n/N	% (95% CI)
Marshall CT classification				
1	7/109	6.4 (3.1 to 12.7)	36/85	42.4 (32.4 to 53.0)
2	117/896	13.1 (11.0 to 15.4)	337/727	46.4 (42.8 to 50.0)
3	79/240	32.9 (27.3 to 39.1)	136/211	64.5 (57.8 to 70.6)
4	30/78	38.5 (28.4 to 49.6)	50/74	67.6 (56.3 to 77.1)
5	252/948	26.6 (23.9 to 29.5)	523/797	65.6 (62.3 to 68.8)
6	212/420	50.5 (45.7 to 55.2)	299/372	80.4 (76.0 to 84.1)
Traumatic SAH				
No	239/1193	20.0 (17.9 to 22.4)	546/987	55.3 (52.2 to 58.4)
Yes	462/1522	30.4 (28.1 to 32.7)	846/1298	65.2 (62.5 to 67.7)
Small petechial haemorrhages				
No	422/1614	26.1 (24.1 to 28.3)	834/1366	61.1 (58.4 to 63.6)
Yes	284/1118	25.4 (22.9 to 28.0)	568/935	60.7 (57.6 to 63.8)
Obliteration of third ventricle/basal cisterns				
No	383/1999	19.2 (17.5 to 20.9)	906/1650	54.9 (52.5 to 57.3)
Yes	315/712	44.2 (40.6 to 47.9)	483/631	76.5 (73.1 to 79.7)
Midline shift of >5 mm				
No	363/1843	19.7 (17.9 to 21.6)	840/1529	54.9 (52.4 to 57.4)
Yes	338/871	38.8 (35.6 to 42.1)	552/755	73.1 (69.8 to 76.2)
Non-evacuated haematoma				
No	313/1350	23.2 (21.0 to 25.5)	690/1133	60.9 (58.0 to 63.7)
Yes	394/1381	28.5 (26.2 to 31.0)	714/1170	61.0 (58.2 to 63.8)
Extradural haematoma				
No	612/2278	26.9 (25.1 to 28.7)	1203/1926	62.5 (60.3 to 64.6)
Yes	94/456	20.6 (17.2 to 24.6)	200/377	53.1 (48.0 to 58.0)

External validation of the risk prediction models

For the primary analysis, following multiple imputation, all 2975 patients were included in the validation of the risk models among all patients in the RAIN study data set and between 1868 (63%) and 2711 (91%) were included in the validation among patients eligible for each model (*Table 19*). Owing to multiple imputation of missing data, the sample sizes were the same for the validation data sets for mortality and for unfavourable outcome for each model, where relevant.

The discrimination (c-index) of the four models predicting mortality at 6 months is reported in *Table 20*. Discrimination was similar for the Hukkelhoven, IMPACT Extended and IMPACT Lab models (c-index 0.78) and higher than that for the IMPACT Core model (0.75). Inspection of the calibration plots (*Figure 26*) showed good calibration for the Hukkelhoven and IMPACT Lab models, whereas the IMPACT Core and Extended models tended to overestimate the risk of mortality at 6 months (i.e. observed mortality was

TABLE 18 Univariable associations between risk factors and outcomes for variables included in the risk prediction models: laboratory variables

Variable	Mortality at 6 months		Unfavourable outcome at 6 months	
	n/N	% (95% CI)	n/N	% (95% CI)
First at hospital glucose (mmol/l)				
<6	68/459	14.8 (11.9 to 18.4)	178/377	47.2 (42.2 to 52.3)
6–6.9	80/449	17.8 (14.6 to 21.6)	190/362	52.5 (47.3 to 57.6)
7–7.9	114/446	25.6 (21.7 to 29.8)	225/373	60.3 (55.3 to 65.2)
8–9.9	162/554	29.2 (25.6 to 33.2)	303/473	64.1 (59.6 to 68.3)
10+	203/509	39.9 (35.7 to 44.2)	346/449	77.1 (73.0 to 80.7)
First at hospital haemoglobin (g/dl)				
<10	100/235	42.6 (36.4 to 48.9)	160/204	78.4 (72.3 to 83.5)
10–11.9	146/429	34.0 (29.7 to 38.6)	261/362	72.1 (67.3 to 76.5)
12–12.9	101/390	25.9 (21.8 to 30.5)	225/332	67.8 (62.6 to 72.6)
13–13.9	123/539	22.8 (19.5 to 26.5)	237/462	51.3 (46.7 to 55.8)
14–14.9	122/488	25.0 (21.4 to 29.0)	258/420	61.4 (56.7 to 66.0)
15+	97/516	17.6 (14.6 to 21.2)	202/408	49.5 (44.7 to 54.3)

TABLE 19 Numbers of admissions and events included in validation data sets for the primary analysis, post imputation

Risk model	All patients, validation data set (1)	Eligible for model, validation data set (2)
Number of admissions		
Hukkelhoven	2975	1868
CRASH Basic	2975	2711
CRASH CT	2975	2584
IMPACT Core	2975	2528
IMPACT Extended	2975	2393
IMPACT Lab	2975	2393
Mortality at 6 months (%)		
Hukkelhoven	25.7	22.2
IMPACT Core	25.7	27.6
IMPACT Extended	25.7	27.6
IMPACT Lab	25.7	27.6
Unfavourable outcome at 6 months (%)		
Hukkelhoven	57.4	55.9
CRASH Basic	57.4	57.0
CRASH CT	57.4	56.9
IMPACT Core	57.4	60.0
IMPACT Extended	57.4	59.9
IMPACT Lab	57.4	59.9

TABLE 20 Discrimination: mortality at 6 months

Risk model	All patients	Eligible for model
c-index (95% CI)		
Hukkelhoven	0.784 (0.764 to 0.805)	0.773 (0.745 to 0.801)
IMPACT Core	0.754 (0.733 to 0.774)	0.750 (0.728 to 0.772)
IMPACT Extended	0.780 (0.760 to 0.799)	0.780 (0.760 to 0.801)
IMPACT Lab	0.777 (0.756 to 0.798)	0.779 (0.758 to 0.800)

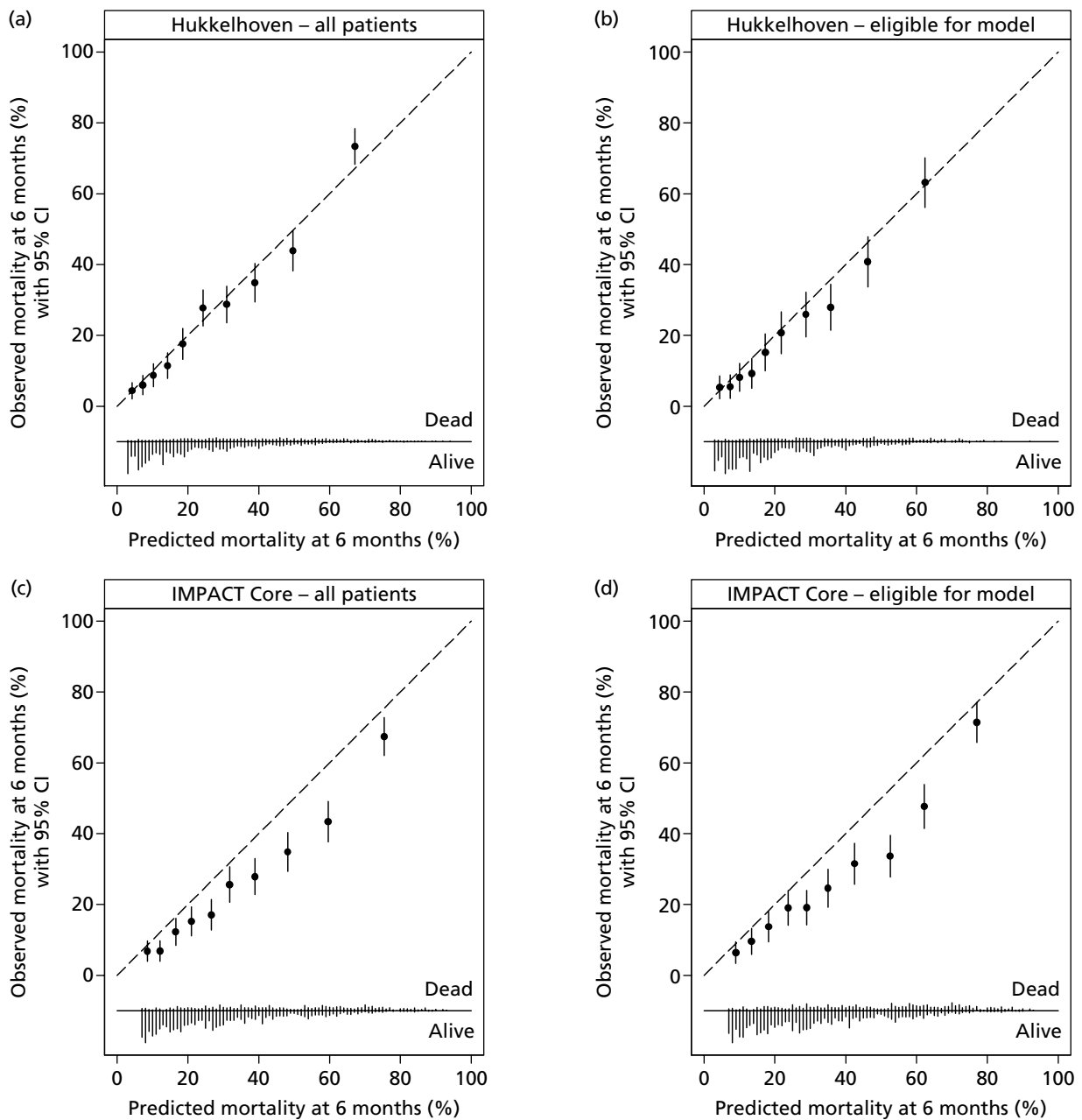


FIGURE 26 Calibration plots: mortality at 6 months. Each point represents the observed mortality (with 95% CI) plotted against the predicted mortality from the model for 10 equal-sized groups based on the predicted mortality. Bars at the foot of each figure ('rug plots') illustrate the distribution of predictions for survivors and non-survivors.

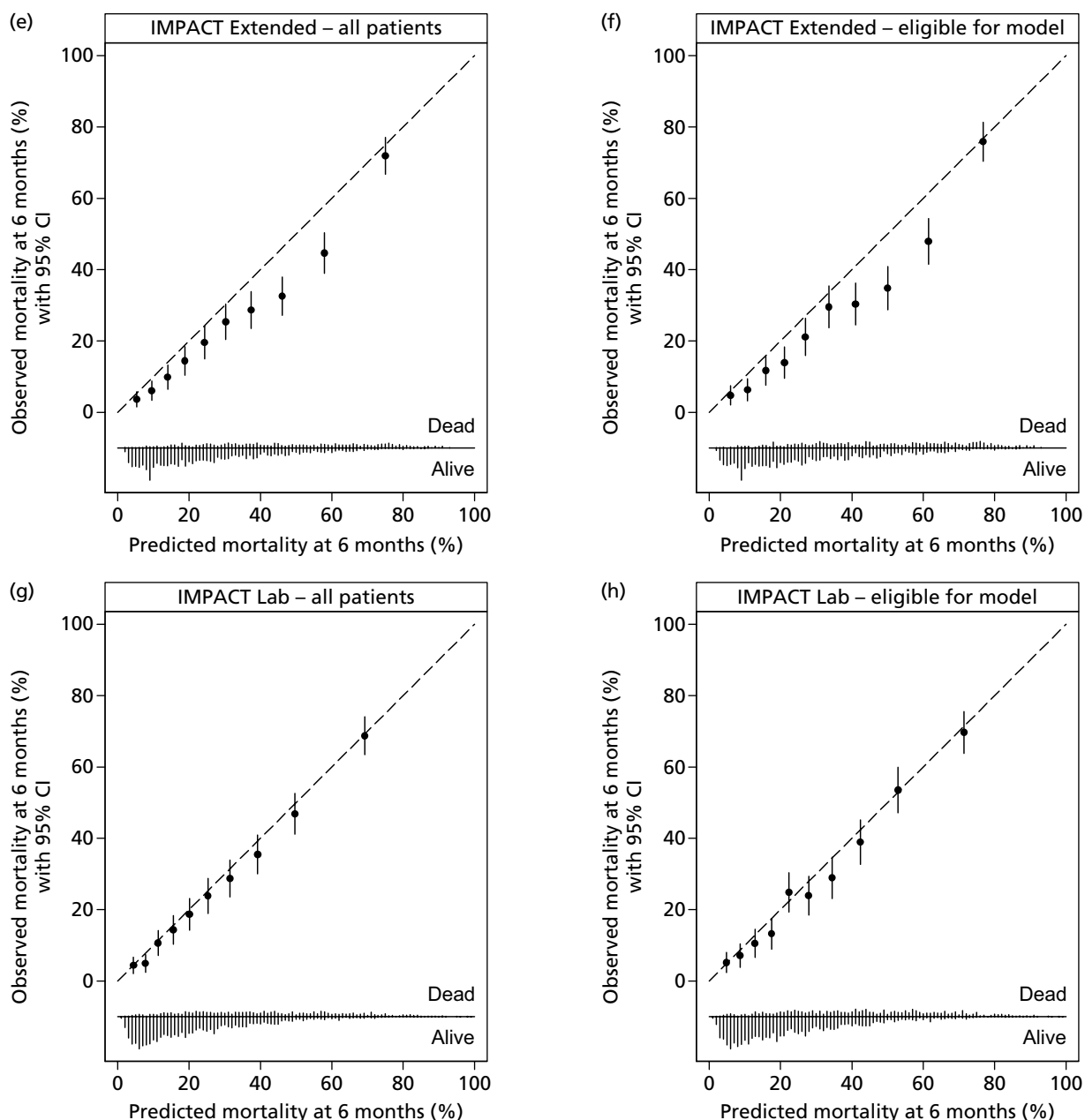


FIGURE 26 Calibration plots: mortality at 6 months. Each point represents the observed mortality (with 95% CI) plotted against the predicted mortality from the model for 10 equal-sized groups based on the predicted mortality. Bars at the foot of each figure ('rug plots') illustrate the distribution of predictions for survivors and non-survivors. (Continued.)

lower than predicted). This visual interpretation is supported by the measures and tests of calibration (Table 21). Brier's score (Table 22), summarising the overall fit of the predictions, was best for the Hukkelhoven model and worst for the IMPACT Core model. There was little difference in any measures of model performance between assessment among all patients and among those eligible for the model.

Each point represents the observed mortality (with 95% CI) plotted against the predicted mortality from the model for 10 equal-sized groups based on the predicted mortality. Bars at the foot of each figure ('rug plots') illustrate the distribution of predictions for survivors and non-survivors.

The discrimination of the models for predicting unfavourable outcome at 6 months was worse than for mortality at 6 months, with c-index values ranging from 0.69 to 0.71 (Table 23). The IMPACT Lab

TABLE 21 Calibration: mortality at 6 months

Risk model	All patients	Eligible for model
Hosmer–Lemeshow test, chi-squared statistic (p-value)		
Hukkelhoven	18.8 [0.042]	15.3 [0.12]
IMPACT Core	117 [<0.001]	112 [<0.001]
IMPACT Extended	76.7 [<0.001]	74.8 [<0.001]
IMPACT Lab	10.6 [0.39]	14.0 [0.17]
Cox calibration regression, α (95% CI) β (95% CI) [p-value]		
Hukkelhoven	–0.01 (–0.13 to 0.11) 1.06 (0.96 to 1.16) [0.22]	–0.13 (–0.29 to 0.04) 1.06 (0.92 to 1.20) [0.011]
IMPACT Core	–0.50 (–0.60 to –0.40) 0.95 (0.86 to 1.05) [<0.001]	–0.51 (–0.61 to –0.40) 0.94 (0.84 to 1.05) [<0.001]
IMPACT Extended	–0.37 (–0.48 to –0.27) 1.02 (0.92 to 1.11) [<0.001]	–0.39 (–0.50 to –0.28) 1.03 (0.93 to 1.13) [<0.001]
IMPACT Lab	–0.11 (–0.23 to 0.01) 1.00 (0.90 to 1.11) [0.051]	–0.11 (–0.23 to 0.01) 1.01 (0.90 to 1.12) [0.059]

TABLE 22 Overall fit: mortality at 6 months

Risk model	All patients	Eligible for model
Brier's score		
Hukkelhoven	0.150	0.141
IMPACT Core	0.166	0.175
IMPACT Extended	0.156	0.163
IMPACT Lab	0.153	0.159

model had slightly better discrimination (0.714), followed by the models making use of CT findings (Hukkelhoven, CRASH CT and IMPACT Extended; c-index 0.708) with the models using only core variables (CRASH Basic and IMPACT Core) having the worst discrimination (c-index 0.69–0.70). All models were poorly calibrated, substantially underestimating the risk of unfavourable outcome at 6 months, particularly at low predicted risk (*Figure 27* and *Table 24*). The lack of calibration resulted in very poor values for Brier's score – little better than (and, in the case of the CRASH Basic model, worse than) the value of 0.25 that would be observed from predicting a constant risk of 0.5 for all patients (*Table 25*). The sensitivity analysis excluding patients with severe disability – either pre-existing or not due to the TBI – resulted in very small improvements in discrimination and no discernible change to calibration or overall fit (*Table 26*). Results were very similar when the analyses were repeated for the secondary analyses in the data sets prior to multiple imputation (see *Appendix 6*).

Each point represents the observed proportion with unfavourable outcome (with 95% CI) plotted against the predicted risk of unfavourable outcome from the model for 10 equal-sized groups based on the predicted risk. Bars at the foot of each figure ('rug plots') illustrate the distribution of predictions for patients with favourable and unfavourable outcomes.

TABLE 23 Discrimination: unfavourable outcome at 6 months

Risk model	All patients	Eligible for model
c-index (95% CI)		
Hukkelhoven	0.708 (0.686 to 0.730)	0.688 (0.660 to 0.716)
CRASH Basic	0.699 (0.677 to 0.721)	0.697 (0.675 to 0.720)
CRASH CT	0.708 (0.686 to 0.729)	0.710 (0.687 to 0.733)
IMPACT Core	0.693 (0.671 to 0.716)	0.689 (0.665 to 0.713)
IMPACT Extended	0.708 (0.686 to 0.730)	0.706 (0.683 to 0.730)
IMPACT Lab	0.714 (0.692 to 0.736)	0.713 (0.689 to 0.737)

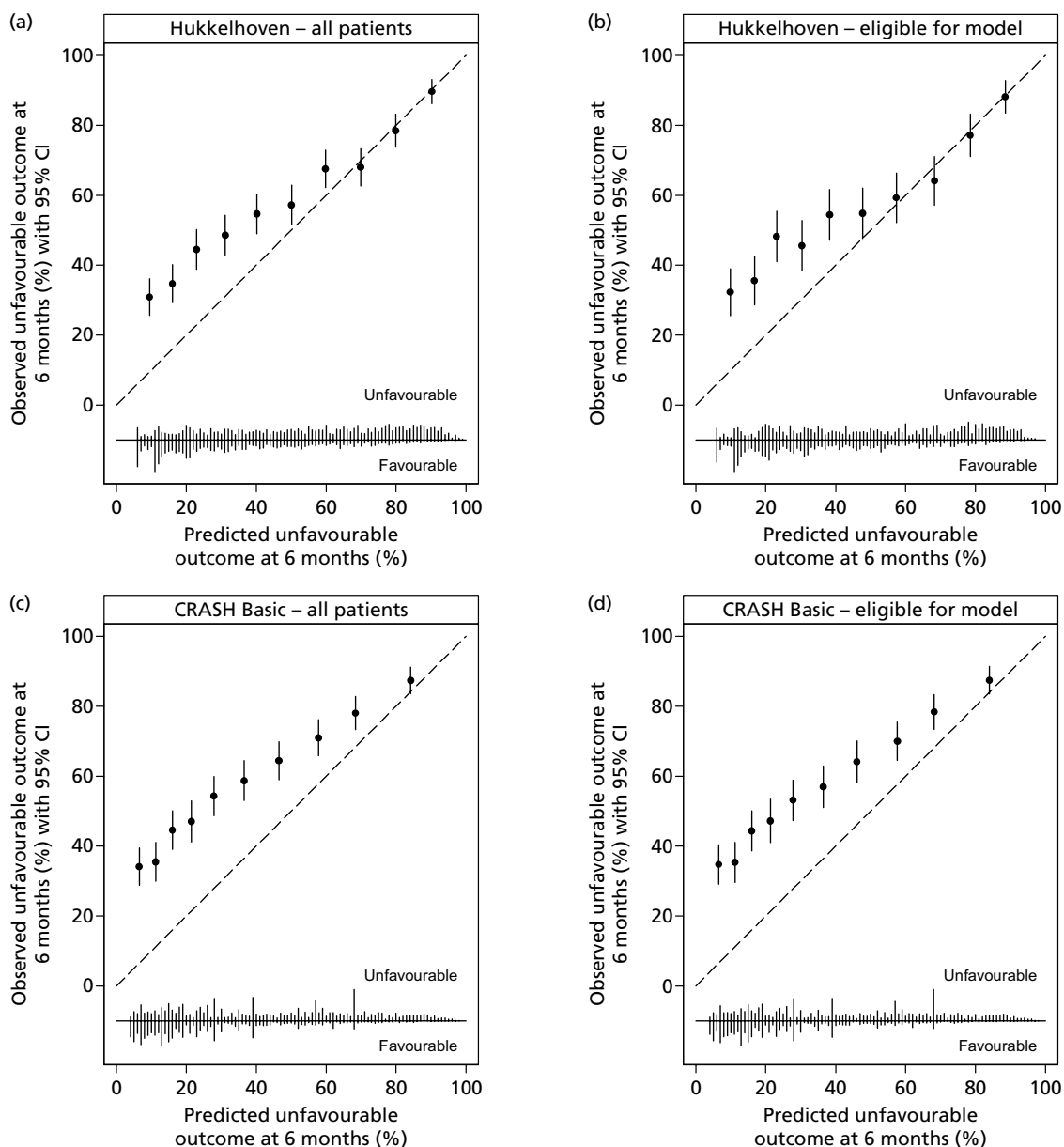


FIGURE 27 Calibration plots: unfavourable outcome at 6 months. Each point represents the observed proportion with unfavourable outcome (with 95% CI) plotted against the predicted risk of unfavourable outcome from the model for 10 equal-sized groups based on the predicted risk. Bars at the foot of each figure ('rug plots') illustrate the distribution of predictions for patients with favourable and unfavourable outcomes. (*Continued.*)

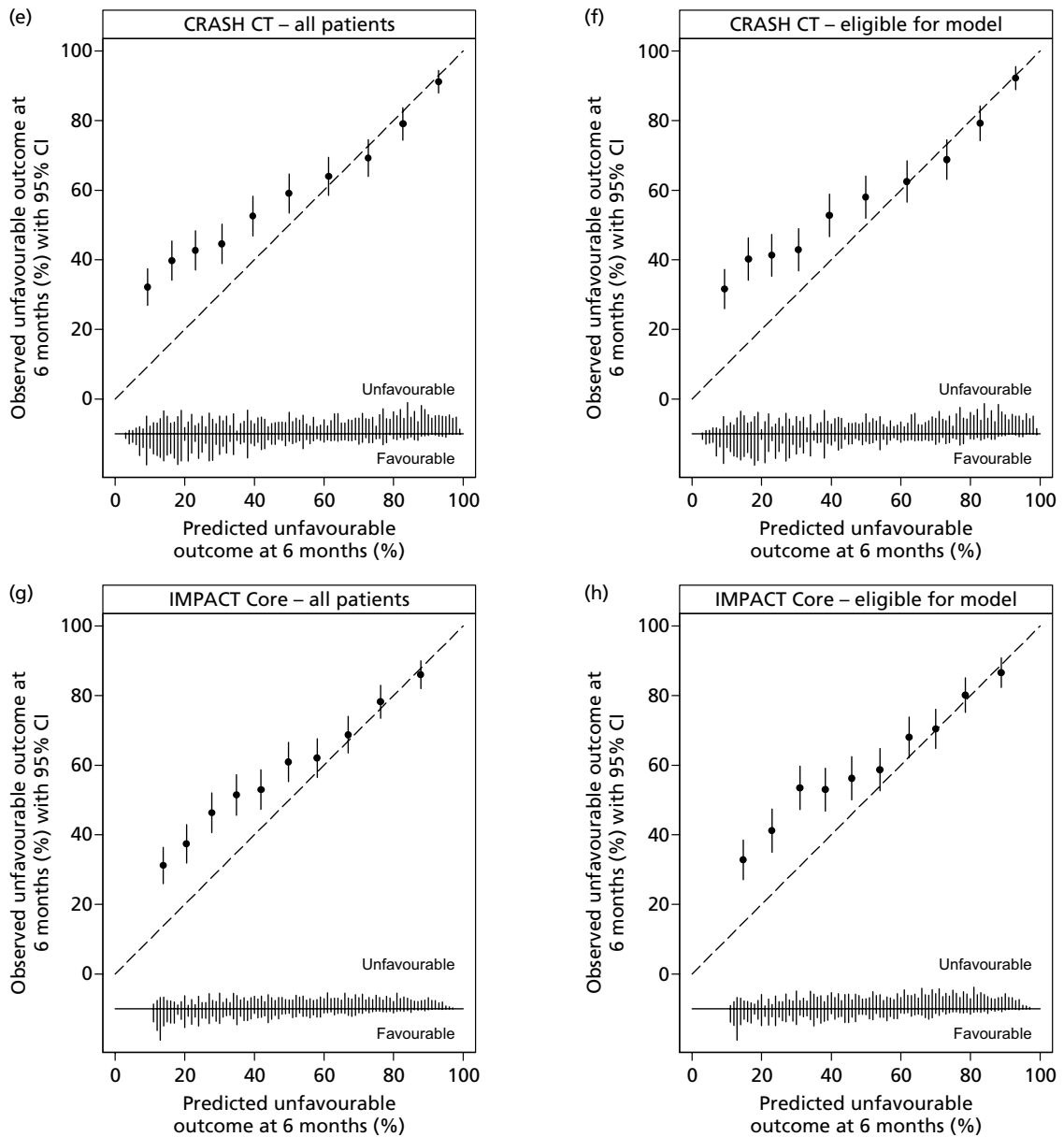


FIGURE 27 Calibration plots: unfavourable outcome at 6 months. Each point represents the observed proportion with unfavourable outcome (with 95% CI) plotted against the predicted risk of unfavourable outcome from the model for 10 equal-sized groups based on the predicted risk. Bars at the foot of each figure ('rug plots') illustrate the distribution of predictions for patients with favourable and unfavourable outcomes.

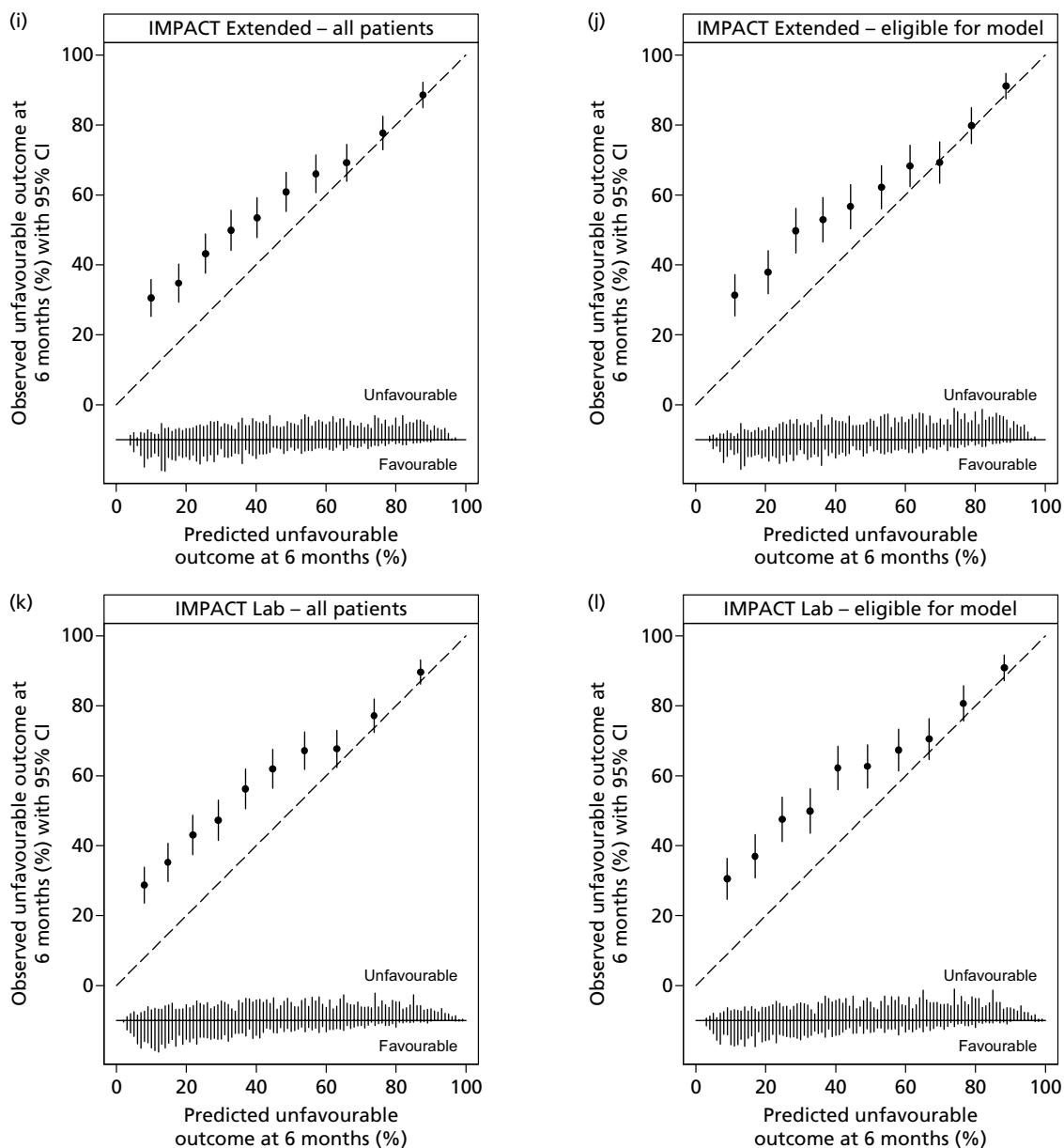


FIGURE 27 Calibration plots: unfavourable outcome at 6 months. Each point represents the observed proportion with unfavourable outcome (with 95% CI) plotted against the predicted risk of unfavourable outcome from the model for 10 equal-sized groups based on the predicted risk. Bars at the foot of each figure ('rug plots') illustrate the distribution of predictions for patients with favourable and unfavourable outcomes. (*Continued.*)

TABLE 24 Calibration: unfavourable outcome at 6 months

Risk model	All patients	Eligible for model
Hosmer–Lemeshow test, chi-squared statistic [p-value]		
Hukkelhoven	401 [<0.001]	272 [<0.001]
CRASH Basic	1102 [<0.001]	997 [<0.001]
CRASH CT	437 [<0.001]	362 [<0.001]
IMPACT Core	253 [<0.001]	219 [<0.001]
IMPACT Extended	341 [<0.001]	252 [<0.001]
IMPACT Lab	515 [<0.001]	384 [<0.001]
Cox calibration regression, α (95% CI) β (95% CI) [p-value]		
Hukkelhoven	0.44 (0.35 to 0.53) 0.60 (0.52 to 0.68) [<0.001]	0.39 (0.28 to 0.50) 0.57 (0.47 to 0.66) [<0.001]
CRASH Basic	0.74 (0.64 to 0.85) 0.59 (0.52 to 0.67) [<0.001]	0.73 (0.62 to 0.84) 0.60 (0.52 to 0.67) [<0.001]
CRASH CT	0.40 (0.31 to 0.49) 0.56 (0.49 to 0.63) [<0.001]	0.38 (0.28 to 0.47) 0.57 (0.50 to 0.64) [<0.001]
IMPACT Core	0.41 (0.32 to 0.50) 0.66 (0.58 to 0.75) [<0.001]	0.43 (0.34 to 0.52) 0.65 (0.55 to 0.74) [<0.001]
IMPACT Extended	0.47 (0.38 to 0.56) 0.66 (0.58 to 0.75) [<0.001]	0.48 (0.38 to 0.58) 0.66 (0.57 to 0.75) [<0.001]
IMPACT Lab	0.58 (0.48 to 0.67) 0.65 (0.57 to 0.73) [<0.001]	0.59 (0.49 to 0.74) 0.65 (0.56 to 0.74) [<0.001]

TABLE 25 Overall fit: unfavourable outcome at 6 months

Risk model	All patients	Eligible for model
Brier's score		
Hukkelhoven	0.232	0.239
CRASH Basic	0.262	0.262
CRASH CT	0.232	0.230
IMPACT Core	0.232	0.230
IMPACT Extended	0.230	0.227
IMPACT Lab	0.236	0.233

TABLE 26 Sensitivity analysis: discrimination, calibration and overall fit for unfavourable outcome at 6 months, for all patients excluding severe disability, pre-existing or not due to the TBI ($n = 2918$)

Model	c-index (95% CI)	Hosmer–Lemeshow test, χ^2 (p -value)	Cox calibration regression, α , β (p -value)	Brier's score
Hukkelhoven	0.711 (0.689 to 0.733)	353 (<0.001)	0.40 to 0.61 (<0.001)	0.230
CRASH Basic	0.701 (0.679 to 0.722)	1015 (<0.001)	0.71 to 0.60 (<0.001)	0.259
CRASH CT	0.710 (0.689 to 0.732)	394 (<0.001)	0.36 to 0.57 (<0.001)	0.230
IMPACT Core	0.695 (0.672 to 0.717)	224 (<0.001)	0.37 to 0.67 (<0.001)	0.231
IMPACT Extended	0.711 (0.689 to 0.733)	302 (<0.001)	0.44 to 0.67 (<0.001)	0.228
IMPACT Lab	0.718 (0.696 to 0.740)	454 (<0.001)	0.54 to 0.66 (<0.001)	0.233

Inter-rater reliability of computerised tomography scan reporting

Computerised tomography scans were available for 312 (91%) of 342 patients randomly selected for inclusion in the substudy evaluating inter-rater reliability of CT scan reporting, including at least one scan from 64 of the 66 critical care units that recruited at least one patient to the RAIN study. The main reason cited for failure to provide a CT scan was the need to obtain the scan from a referring hospital. κ -Statistics ranged from 0.19 to 0.78 across the individual CT fields (*Table 27*). The majority of fields used in the risk model were found to have moderate to good inter-rater reliability (κ -statistic 0.4–0.8). The worst inter-rater reliability was found for the presence of small petechial haemorrhages, which may partly explain why no association was found between this factor and outcomes. Agreement between the WBIC assessors (WBIC1 vs WBIC2 and WBIC3 vs WBIC4; median κ -statistic 0.70, IQR 0.58 to 0.76) was generally better than between the original RAIN study data and the WBIC assessors (RAIN vs WBIC1, RAIN vs WBIC2, etc.; 0.52, 0.37–0.62). κ -Statistics for subgroup analyses are reported in *Tables 28* and *29*. There was little discernible variation in inter-rater reliability of CT scan assessments according to the specialty and grade of the assessor for the original RAIN study data (see *Table 28*). CT scans that originated from RAIN study critical care units within neuroscience centres had similar inter-rater reliability compared with CT scans that originated from non-neuroscience centres (see *Table 29*).

Discussion

Principal findings

The RAIN study has demonstrated that the Hukkelhoven, CRASH and IMPACT risk prediction models for mortality and unfavourable outcome at 6 months have acceptable levels of discrimination when applied in a UK cohort of adult patients admitted to critical care units following acute TBI. Although the Hukkelhoven and IMPACT Lab models for mortality at 6 months had good calibration, the other IMPACT models for mortality at 6 months overpredicted risk, and all models for unfavourable outcome at 6 months underpredicted risk particularly at the lower end of the risk spectrum.

Strengths and weaknesses

The main strengths of the RAIN study are the large, representative sample with high levels of data completeness and the rigorous statistical methods. The RAIN study included 84% of all neuroscience centres in the UK plus representation from the important, but often overlooked, cohort of critically ill patients with acute TBI managed outside neuroscience centres. Although the completeness of follow-up for unfavourable outcome at 6 months (81%) was lower than ideal, this reflects the difficulties inherent in following up such a population (see *Chapter 4*). Furthermore, consent was obtained at the point of follow-up rather than prior to enrolment (as would be the case in an RCT), so patients who declined follow-up were still included within the initial study population. The low follow-up rate was addressed

TABLE 27 κ -Statistics (95% CIs) for inter-rater reliability of CT scan reporting

CT variable	Three-way comparison (n = 312)	WBIC team 1 (n = 156)		WBIC team 2 (n = 155)		
		RAIN vs WBIC1	RAIN vs WBIC2	RAIN vs WBIC3	RAIN vs WBIC4	
CT scan result (normal/abnormal)	0.59 (0.46 to 0.70)	0.60 (0.40 to 0.75)	0.62 (0.42 to 0.76)	0.61 (0.41 to 0.77)	0.54 (0.31 to 0.71)	0.73 (0.48 to 0.87)
Traumatic SAH	0.44 (0.36 to 0.52)	0.34 (0.15 to 0.46)	0.49 (0.33 to 0.61)	0.54 (0.39 to 0.67)	0.37 (0.18 to 0.48)	0.61 (0.46 to 0.73)
Brainstem pathology	0.20 (0.10 to 0.34)	0.08 (-0.06 to 0.28)	0.03 (-0.08 to 0.23)	-0.01 (-0.02 to 0.50)	0.24 (0.04 to 0.41)	0.25 (0.08 to 0.42)
Basal cisterns (absent/compressed/present)	0.56 (0.52 to 0.64)	0.50 (0.42 to 0.64)	0.52 (0.39 to 0.67)	0.68 (0.59 to 0.80)	0.52 (0.39 to 0.62)	0.73 (0.62 to 0.83)
Obliteration of third ventricle	0.60 (0.49 to 0.69)	0.61 (0.44 to 0.74)	0.51 (0.32 to 0.66)	0.75 (0.59 to 0.86)	0.54 (0.34 to 0.70)	0.79 (0.61 to 0.90)
Midline shift of >5 mm	0.78 (0.71 to 0.84)	0.62 (0.47 to 0.74)	0.69 (0.55 to 0.80)	0.84 (0.71 to 0.92)	0.81 (0.67 to 0.90)	0.91 (0.79 to 0.96)
One or more small petechial haemorrhage(s) of ≤ 1 ml	0.18 (0.11 to 0.26)	0.14 (-0.06 to 0.26)	0.37 (0.20 to 0.49)	0.26 (-0.01 to 0.30)	0.09 (-0.07 to 0.25)	0.23 (0.07 to 0.38)
High-/mixed-density lesion(s) of >1 ml	0.68 (0.60 to 0.74)	0.68 (0.54 to 0.79)	0.63 (0.48 to 0.74)	0.74 (0.61 to 0.83)	0.63 (0.48 to 0.75)	0.78 (0.64 to 0.87)
Extradural haematoma	0.60 (0.49 to 0.70)	0.58 (0.37 to 0.74)	0.64 (0.43 to 0.79)	0.81 (0.62 to 0.91)	0.59 (0.41 to 0.73)	0.64 (0.45 to 0.78)
Subdural haematoma	0.67 (0.60 to 0.73)	0.64 (0.50 to 0.74)	0.67 (0.53 to 0.77)	0.84 (0.73 to 0.91)	0.59 (0.45 to 0.70)	0.71 (0.58 to 0.81)
Intracerebral haematoma/haemorrhage/contusion	0.51 (0.44 to 0.58)	0.52 (0.38 to 0.64)	0.39 (0.20 to 0.50)	0.58 (0.41 to 0.68)	0.47 (0.32 to 0.60)	0.68 (0.54 to 0.78)
Posterior fossa haematoma	0.36 (0.17 to 0.56)	0.53 (0.25 to 0.75)	0.18 (0.005, 0.53)	0.15 (-0.01 to 0.47)	0.21 (0.02 to 0.50)	0.65 (0.36 to 0.83)
Volume of largest high-/mixed-density lesion (>25 ml/ ≤ 25 ml)	0.65 (0.58 to 0.72)	0.56 (0.40 to 0.67)	0.60 (0.45 to 0.72)	0.76 (0.64 to 0.85)	0.61 (0.46 to 0.73)	0.71 (0.57 to 0.81)

TABLE 28 κ -Statistics (95% CIs) for inter-rater reliability of CT scan reporting by speciality and grade of assessor

CT variable	Speciality and grade of assessor					
	Critical care/ anaesthesia consultant (n = 32)	Neurocritical care/ neuroanaesthesia consultant (n = 71)	Neurosurgery/ neuroradiology consultant (n = 28)	Neurosurgery/ neuroradiology non- consultant (n = 25)	Radiology consultant (n = 87)	Radiology non- consultant (n = 49)
CT scan result (normal/ abnormal)	0.22 (0.00 to 0.74)	0.62 (0.28 to 0.83)	N/A	N/A	0.63 (0.45 to 0.77)	0.40 (0.13 to 0.67)
Traumatic SAH	0.46 (0.19 to 0.69)	0.48 (0.32 to 0.63)	0.17 (-0.03 to 0.47)	0.47 (0.18 to 0.72)	0.50 (0.36 to 0.63)	0.29 (0.10 to 0.49)
Brainstem pathology	0.37 (0.11 to 0.64)	0.22 (0.05 to 0.45)	0.14 (-0.01 to 0.67)	0.46 (0.07 to 0.82)	0.16 (0.01 to 0.48)	-0.05 (-0.03 to 0.39)
Basal cisterns (absent/ compressed/present)	0.54 (0.39 to 0.81)	0.55 (0.45 to 0.71)	0.39 (0.19 to 0.59)	0.49 (0.28 to 0.66)	0.64 (0.51 to 0.78)	0.50 (0.36 to 0.61)
Obliteration of third ventricle	0.59 (0.27 to 0.81)	0.48 (0.26 to 0.68)	0.46 (0.18 to 0.70)	0.66 (0.35 to 0.85)	0.68 (0.39 to 0.85)	0.72 (0.42 to 0.88)
Midline shift of >5 mm	0.84 (0.60 to 0.95)	0.75 (0.59 to 0.86)	0.57 (0.30 to 0.77)	0.84 (0.60 to 0.94)	0.90 (0.71 to 0.97)	0.74 (0.48 to 0.88)
One or more small petechial haemorrhage(s) of \leq 1 ml	0.17 (-0.02 to 0.41)	0.16 (0.02 to 0.33)	0.08 (-0.10 to 0.33)	0.10 (-0.08 to 0.39)	0.18 (0.05 to 0.33)	0.28 (0.09 to 0.49)
High-/mixed-density lesion(s) of > 1 ml	0.33 (0.07 to 0.62)	0.87 (0.70 to 0.94)	0.63 (0.26 to 0.86)	N/A	0.71 (0.58 to 0.81)	0.59 (0.40 to 0.75)
Extradural haematoma	0.32 (0.06 to 0.63)	0.70 (0.50 to 0.84)	0.80 (0.50 to 0.93)	0.52 (0.19 to 0.77)	0.57 (0.23 to 0.81)	0.56 (0.24 to 0.79)
Subdural haematoma	0.50 (0.26 to 0.69)	0.73 (0.59 to 0.84)	0.70 (0.45 to 0.86)	0.60 (0.33 to 0.80)	0.63 (0.49 to 0.75)	0.78 (0.61 to 0.88)
Intracerebral haematoma/ haemorrhage/contusion	0.24 (0.03 to 0.47)	0.66 (0.51 to 0.77)	0.22 (0.01 to 0.47)	0.44 (0.17 to 0.67)	0.57 (0.42 to 0.70)	0.48 (0.28 to 0.65)
Posterior fossa haematoma	0.58 (0.11 to 0.89)	0.38 (0.10 to 0.69)	N/A	0.49 (0.12 to 0.80)	0.31 (0.04 to 0.74)	N/A
Volume of largest high-/ mixed-density lesion (>25 ml/ \leq 25 ml)	0.76 (0.53 to 0.90)	0.76 (0.62 to 0.86)	0.42 (0.17 to 0.64)	0.39 (0.14 to 0.63)	0.57 (0.38 to 0.72)	0.63 (0.41 to 0.79)

N/A, Ratings did not vary sufficiently across assessors to allow reliable calculation of κ -statistic.

TABLE 29 κ -Statistics (95% CIs) for inter-rater reliability of CT scan reporting by origin of scan

CT variable	Neuroscience centre	
	Yes (<i>n</i> = 194)	No (<i>n</i> = 117)
CT scan result (normal/abnormal)	0.57 (0.35 to 0.74)	0.58 (0.41 to 0.72)
Traumatic SAH	0.40 (0.30 to 0.50)	0.51 (0.38 to 0.62)
Brainstem pathology	0.26 (0.12 to 0.43)	0.10 (−0.00 to 0.32)
Basal cisterns (absent/compressed/present)	0.53 (0.42 to 0.61)	0.61 (0.50 to 0.71)
Obliteration of third ventricle	0.52 (0.38 to 0.64)	0.75 (0.57 to 0.86)
Midline shift of >5 mm	0.76 (0.67 to 0.83)	0.82 (0.67 to 0.91)
One or more small petechial haemorrhage(s) of ≤1 ml	0.14 (0.05 to 0.24)	0.25 (0.13 to 0.37)
High/mixed density lesion(s) of >1 ml	0.68 (0.56 to 0.77)	0.64 (0.52 to 0.74)
Extradural haematoma	0.61 (0.47 to 0.72)	0.56 (0.31 to 0.75)
Subdural haematoma	0.67 (0.58 to 0.74)	0.66 (0.54 to 0.76)
Intracerebral haematoma/haemorrhage/contusion	0.48 (0.39 to 0.57)	0.54 (0.41 to 0.66)
Posterior fossa haematoma	0.38 (0.16 to 0.61)	0.30 (0.06 to 0.65)
Volume of largest high-/mixed-density lesion (>25 ml/≤25 ml)	0.65 (0.56 to 0.73)	0.60 (0.45 to 0.72)

by implementing a two-stage multiple imputation process – first imputing risk factors and mortality, and subsequently, for those alive or imputed to be alive at 6 months, imputing the GOSE categories.

Strengths and weaknesses in comparison with other studies

The RAIN study is the first prospective external validation of these risk prediction models, with all previous validations having been undertaken using existing data sources from either RCTs or trauma registries. Consequently, although many previous validation studies have been restricted to validating modified and refitted versions of the models due to differences between the available data for validation and the data used for model development, the RAIN study was able to define variables in advance to accurately implement all risk models as originally reported.

The discrimination of the risk prediction models in the RAIN study was generally within the range observed in previous development and validation populations. The Hukkelhoven models had *c*-indices of 0.78 and 0.71 for mortality and unfavourable outcome at 6 months, respectively, in the RAIN study compared with 0.78 and 0.80 in the original development sample.⁴⁸ The Hukkelhoven models have been validated in four external existing data sources. The model development paper reported validation of the model for mortality at 6 months in observational data sets from the EBIC and the TCDB with a *c*-index of 0.87 and 0.89, respectively.⁴⁸ The model for unfavourable outcome at 6 months was validated in the EBIC data set only (as the timing of GOS reporting in the TCDB data set was variable) with a *c*-index of 0.83. Subsequently, Hukkelhoven *et al.*⁹⁰ presented validation data from one further data source, the Selfotel RCT, with a *c*-index of 0.74 for both mortality and unfavourable outcome at 6 month. A recently reported study from a 10-year cohort of patients admitted to a single UK neuroscience centre reported a *c*-index around 0.83 for both mortality and unfavourable outcome at 1 year.⁹¹

The CRASH Basic model and CT model for unfavourable outcome at 6 months had *c*-indices of 0.70 and 0.71, respectively, in the RAIN study compared with 0.81 and 0.83 in the original development sample.³⁰ The model development paper reported validation of modified versions of both models (excluding major

extracranial injury and small petechial haemorrhages) in the IMPACT database with a c-index of 0.77 for both models. The CRASH models have subsequently been validated in three further existing data sources from previous RCTs in a joint study by the IMPACT, CRASH and TARN groups.⁹² These were, again, modified versions of the original models, refitted using only patients in the CRASH trial with GCS score of ≤ 8 and replacing total GCS with motor score and the CRASH CT variables with Marshall classification, resulting in a model structure substantially more similar to the Hukkelhoven and IMPACT models. The c-index for the modified CRASH Basic model in these three data sets was 0.68, 0.74 and 0.76, respectively; the c-index for the modified CRASH CT model was 0.71 in the only data set for which this could be calculated.

The IMPACT Core, Extended and Laboratory models for mortality at 6 months had c-indices of 0.75, 0.78 and 0.78, respectively, in the RAIN study compared with values of 0.66–0.84, 0.71–0.87 and 0.72–0.80 in cross-validation among the original data sets used for model development.³⁵ The corresponding figures for the models for unfavourable outcome at 6 months were 0.69, 0.71 and 0.71, respectively, in the RAIN study compared with 0.74–0.82, 0.73–0.84 and 0.75–0.82 in cross-validation among the original development data sets. The model development paper reported validation of the IMPACT Core model and a modified version of the Extended model (the 'Core + CT' model, excluding hypoxia, hypotension and extradural haematoma) in the CRASH trial data set with c-indices of 0.78 and 0.80, respectively, for mortality at 6 months, and the same results for unfavourable outcome at 6 months. The IMPACT models have subsequently been validated in six further data sets – a study from a single trauma centre in the USA,⁹³ and the joint study from the IMPACT, CRASH and TARN groups using data from three RCTs (as for the validation of the CRASH models) and two observational studies.⁹² The single-centre US study reported c-indices of 0.78, 0.83 and 0.83 for mortality at 6 months, and 0.76, 0.79 and 0.76 for unfavourable outcome at 6 months for the Core, Extended and Laboratory models, respectively.⁹³ The IMPACT/CRASH/TARN study reported a c-index for the IMPACT Core model ranging from 0.65–0.83 for mortality at 6 months across the five data sets, and 0.66–0.76 for unfavourable outcome at 6 months across four data sets in which this outcome was available.⁹² The best discrimination for mortality was from the UK TARN data set; however, the outcome assessed in this data set was mortality at discharge from hospital not mortality at 6 months. The IMPACT Extended model had a c-index of 0.86 for hospital mortality in the TARN data set, and 0.71 for both mortality and unfavourable outcome at 6 months in the one RCT data set in which it could be applied. The IMPACT Lab model had c-index of 0.71 and 0.70 for mortality and unfavourable outcome at 6 months, respectively, in the same data set.

In the RAIN study, the presence of major extracranial injury was found not to be associated with an increased risk of either mortality or unfavourable outcome at 6 months and this is at variance with some previous studies. A recent meta-analysis on the effect of major extracranial injury on mortality in TBI found an inverse relationship between major extracranial injury and mortality according to the severity of the TBI with odds ratios of 2.14, 1.46 and 1.18 in mild (GCS score of 13–14), moderate (GCS score of 9–12) and severe (GCS score of 3–8) TBI, respectively.⁹⁴ Although there are patients with a range of severity of TBI within the RAIN study, approximately two-thirds had GCS scores of 3–8 and all patients were admitted to a critical care unit, which may also represent an additional marker of severity. One may therefore anticipate that the effect of major extracranial injury within the RAIN study would be small. It is also possible, however, that the lack of effect of major extracranial injury in the RAIN study may be due to a lack of consistent application of the definition, taken from the CRASH trial, which was somewhat subjective. Collection of more detailed injury severity scoring, although time consuming, would permit more detailed investigation of the effect of major extracranial injury both more consistently across sites and according to severity.

Advantages and disadvantages of the alternative risk prediction models

In terms of the statistical assessment of model performance, there was very little to choose between models of similar complexity from Hukkelhoven, CRASH and IMPACT. The best discrimination overall was from the IMPACT Lab model – the only one of the models to include laboratory parameters – however, the improvement in performance over the models of the next level of complexity (Hukkelhoven, CRASH CT, IMPACT Extended) was very small. There was a larger difference in performance between these

models and the simplest models using core data only (CRASH Basic and IMPACT Core), suggesting that there is important prognostic information within the CT scan and the presence/absence of pre-hospital hypoxia/hypotension. The substudy on inter-rater reliability of CT scan reporting suggested that the CT findings included in the models could be assessed with acceptable reliability. The CRASH models included two variables – major extracranial injury and small petechial haemorrhages – that did not demonstrate any association with outcomes in the RAIN study. This may be seen as a reason to prefer the Hukkelhoven and IMPACT Extended models over the CRASH CT model; however, despite the inclusion of these apparently non-prognostic fields, the overall performance of the CRASH CT model was similar. For the subsequent analyses within the RAIN study, we therefore selected the IMPACT Lab model as the primary model for risk adjustment in the base-case analyses, with the CRASH CT model used for sensitivity analyses. The CRASH CT model was chosen over the Hukkelhoven model for sensitivity analyses as it included more substantially different predictor variables from the IMPACT Lab model.

Chapter 6 Evaluation of the costs, consequences and cost-effectiveness of alternative locations of care for critically ill patients with acute traumatic brain injury

Introduction

Acute TBI is a major cause of death and long-term disability.^{75,95–99} The economic burden of TBI is considerable; studies in the USA have reported societal costs of approximately US\$60B per year.¹⁰⁰ Care pathways for adult patients after acute TBI vary widely across regions within publicly funded health-care systems.^{101,102} These clinical practice variations are not informed by evidence on the relative costs and outcomes following alternative care pathways. Instead, the location of critical care following TBI may reflect bed availability, local variation and clinical assessment of the patient's prognosis. Variations in the care pathway may be important determinants of mortality and morbidity following TBI. Studies have reported that management of adult TBI patients in specialist neuroscience centres is associated with improved outcomes compared with non-neuroscience centres.^{15,16,103} Several case series have suggested that dedicated algorithms and protocols of care in neurocritical care settings can improve mortality and functional outcome following TBI.^{14,104,105} Possible improvements from more specialised care for patients with TBI may reflect more concentrated knowledge among health professionals, and greater numbers of patients.^{14,106} However, a common concern is that the evidence base on alternative locations of care following TBI is weak; in the absence of RCTs, confounding is a key concern, and previous studies have failed to undertake adequate risk-adjustment when comparing outcomes across settings. Further, few studies have compared the relative costs and cost-effectiveness of alternative locations of care following acute TBI.^{107–109}

Notwithstanding the lack of evidence, it has been recommended that, following a severe TBI, patients should be managed within a neuroscience centre.¹¹ Even within neuroscience centres, there are alternative models of critical care, with a recent report suggesting most TBI patients admitted to neuroscience centres are managed in neurocritical care units (about two-thirds of beds), or combined units that included neuro/general critical care beds (about one-third).¹²

The distinction between these two models of care within neuroscience centres is potentially important. Recent expansion of dedicated neurocritical care facilities^{13,14} has been based on evidence of the potential benefits from managing severe head injury in specialist centres.¹⁶ However, such evidence remains inconclusive, as these studies rely on risk prediction models that have not been validated, and fail to differentiate between any effects of specialist neurocritical care, per se, compared with rapid access to neurosurgical care. A key issue is whether any additional initial costs of dedicated compared with combined neuro/general critical care units, are justified by subsequent reductions in morbidity costs, mortality, or disability. Although there is some evidence that specific interventions for patients with TBI, such as aggressive intracranial pressure monitoring, can improve outcomes,¹⁴ these can be provided in either combined neuro/general critical care units or in dedicated neurocritical care units. The RAIN study compared the risk-adjusted costs, consequences and cost-effectiveness of dedicated neurocritical care units compared with combined neuro/general critical care units in neuroscience centres. In both settings, patients had access to other specialist resources, such as neurosurgery and neuroradiology.

A second key policy question is whether adult patients with TBI without an acute 'neurosurgical' lesion benefit from an 'early' decision to transfer to a neuroscience centre. The available evidence is

inconclusive.^{110–114} Although there is a consensus that those patients who have a space-occupying intracranial haematoma with worsening mass effect should be rapidly transferred to a neurosurgical centre,¹¹⁵ for other adult patients with TBI, there is little evidence on any relative gains from ‘early’ transfer. For critically ill TBI patients, in whom neurosurgery is not indicated, the risks from ‘early’ transfer and subsequent aggressive protocols of care may be substantial.^{116,117} Indeed, for adult TBI patients the relatively aggressive approaches adopted in neurocritical care within neuroscience compared with non-neuroscience centres could lead to worse outcomes,¹¹⁸ higher costs and may not be cost-effective.¹¹⁹ An alternative view is that an early decision to keep the patient within the non-neuroscience centre can lead to delayed transfers, for example if a critical lesion develops subsequently, with potentially higher risks.¹²⁰ Previous National Institute for Health and Care Excellence (NICE) guidelines for ‘non-neurosurgical’ patients with TBI recognised the importance of the issue of ‘early’ transfer by listing it as a key topic for future research.¹¹

A key challenge for such an evaluation is to choose an appropriate time point that reflects an ‘early’ decision to transfer. Here, an ‘early’ decision of whether or not to transfer the patient, is defined as one made immediately after the TBI has been diagnosed and the patient stabilised for transfer. Although limited NHS resources could delay transfer by several hours, transfer within 18 hours of hospital presentation still implies an early decision to transfer. A transfer more than 24 hours after hospital presentation implies a decision to delay transfer, rather than an intended early transfer delayed by logistics. In many cases the patient may not be transferred at all.¹⁶

We therefore had two distinct research objectives that addressed separate decision problems of key policy relevance but were complementary in using risk prediction models to adjust for observed confounders when assessing the costs, consequences and cost-effectiveness of alternative care locations following TBI. These objectives were to compare the relative costs, consequences and cost-effectiveness of:

1. management in a dedicated neurocritical care unit compared with a combined neuro/general critical care unit for adult patients with TBI presenting at a neuroscience centre
2. ‘early’ (within 18 hours of hospital presentation) transfer to a neuroscience centre compared with ‘no or late’ (after 24 hours) transfer, for adult patients with TBI who initially present at a non-neuroscience centre and do not require surgery for evacuation of a mass lesion.

These objectives are not easily addressed by RCTs but the variation in neurocritical care services across the NHS allowed us to undertake a rigorous non-randomised study. Such a non-randomised study requires valid, reliable and accurate risk prediction models. Earlier sections of this report suggest that pre-existing risk prediction models for patients with TBI can provide appropriate adjustment for patient factors at presentation.

Methods overview

This evaluation compared alternative care locations for adult patients admitted to critical care following TBI. The evaluation was undertaken in two phases. In the first phase, we compared the costs and consequences of the alternative care locations at 6 months following the TBI. In the second phase, we used estimates from these 6-month end points to project the lifetime cost-effectiveness of alternative care locations. The first phase cost–consequence study compared risk-adjusted 6-month health outcomes (mortality, GOSE and EQ-5D-3L) and costs across alternative care locations using data from the RAIN study. In the second phase, the cost-effectiveness analysis (CEA) followed NICE methods guidance and took a health and personal social perspective,⁶⁷ and reported cost-effectiveness over the lifetime. Future costs and outcomes were discounted at the current recommended rates of 3.5%.

The subsequent sections motivate the alternative care pathways and comparators considered, report the methods and results of the cost–consequence analysis and then report the methods and results of the lifetime CEA. Finally, we discuss the findings from both phases of the evaluation.

Motivating the comparators chosen for the research objectives

Alternative care pathways in the NHS for adult patients with traumatic brain injury

There are many possible pathways for patients admitted to NHS critical care units following acute TBI, but the vast majority of patients can broadly be classified into one of four pathways (*Figure 28*). Patients may either present at a non-neuroscience centre (pathways A, B and C), or directly to a neuroscience centre (pathway D). Patients who present to a non-neuroscience centre may either receive all of their critical care within that centre (pathway A) or transfer to a neuroscience centre either directly from the emergency department (pathway B), or critical care within the non-neuroscience centre (pathway C). (Note that pathway C will include both patients for whom the initial decision is to transfer to a neuroscience centre but who receive a period of critical care within the non-neuroscience centre either for stabilisation prior to transfer or while a suitable bed is located, and also patients for whom the initial decision is to manage within the non-neuroscience centre but a subsequent decision is made to transfer, e.g. owing to deterioration.) Patients who present directly to a neuroscience centre are generally managed within a neurocritical care unit in that neuroscience centre (pathway D), which may be either a dedicated neurocritical care unit or a combined neuro/general critical care unit. (Occasionally, when beds are unavailable patients may be transferred to a general critical care unit in a neuroscience centre.)

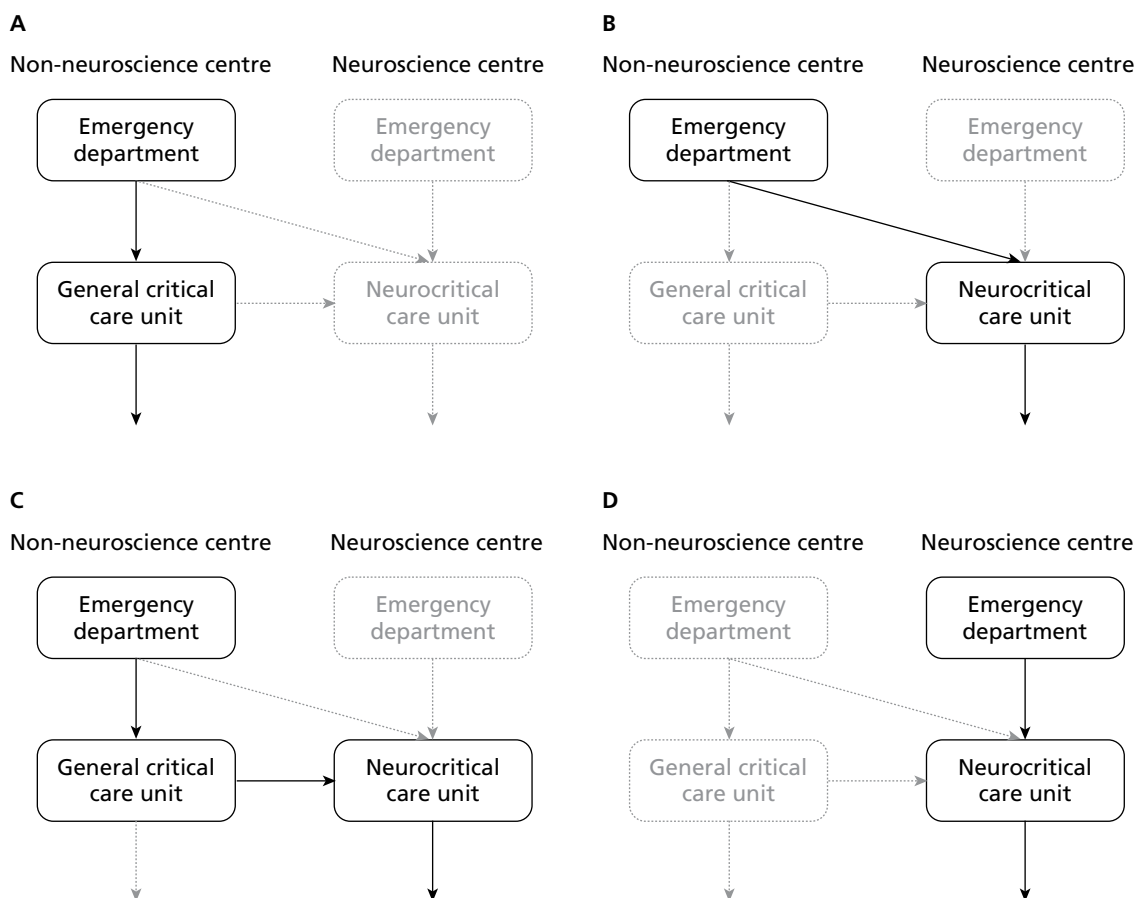


FIGURE 28 Simplified patient pathways.

Comparators for addressing research objective 1

Research objective 1 considered alternative ways of organising and delivering neurocritical care services *within* a neuroscience centre for patients admitted following acute TBI (Figure 29). The population of interest was defined by all RAIN study patients who were admitted to critical care within a neuroscience centre, regardless of whether they initially presented at a neuroscience centre (pathway D) or were transferred from a non-neuroscience centre (pathways B or C). Patients who received all their critical care within a non-neuroscience centre were excluded (i.e. pathway A). The decision problem contrasted care in neuroscience centres with a *dedicated* neurocritical care unit (see Figure 29a) compared with a *combined* neuro/general critical care unit (see Figure 29b). Hence, patients within each neuroscience centre were only included in one of the comparator groups, analogous to a cluster randomised trial in which individuals within a cluster are all randomised to the same 'treatment'.

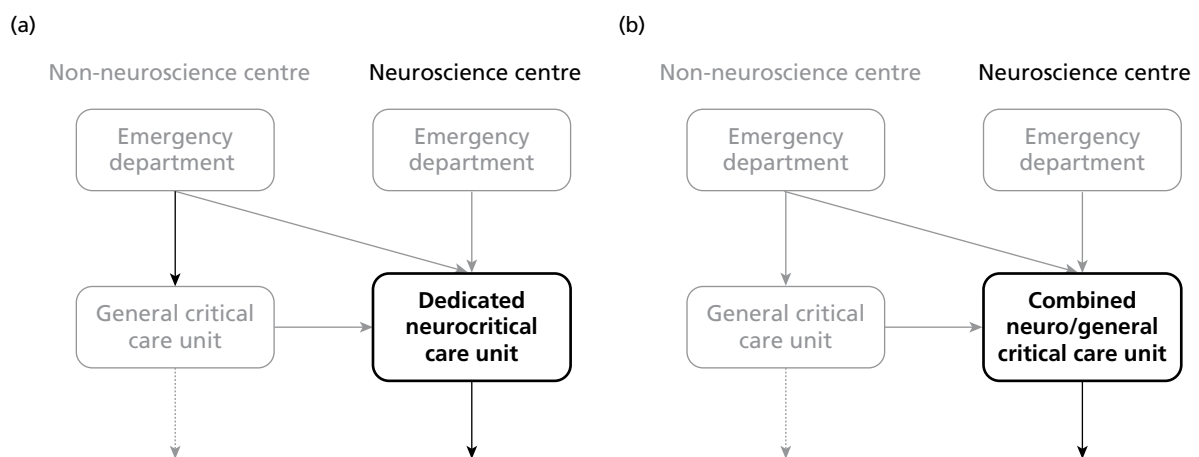


FIGURE 29 Comparators for research objective 1: organisation of care within neuroscience centres. (a) Dedicated neuro unit; (b) combined neuro/general unit.

Comparators for addressing research objective 2

The second research objective considered whether, for those patients who presented at a non-neuroscience centre, the intention to undertake an early transfer to a neuroscience centre was cost-effective. This population was characterised by all RAIN study patients who presented at a non-neuroscience centre (i.e. pathways A, B and C) apart from those who underwent neurosurgery for evacuation of a mass lesion within 24 hours following presentation. These comparators were selected to contrast an initial decision to transfer the patient to a neuroscience centre (Figure 30a) compared with an initial decision to manage the patient within the non-neuroscience centre (see Figure 30b). The 'early' transfer group comprised patients transferred directly to a neuroscience centre from an emergency department in a non-neuroscience centre, and transfers from a critical care unit that were within 18 hours of initial hospital presentation. The 'no or late' transfer group comprised patients who received all their critical care within a non-neuroscience centre, and also patients from critical care units in non-neuroscience centres, who were transferred to a neuroscience centre more than 24 hours after initial hospital presentation. To ensure separation between the comparator arms, we excluded patients transferred between 18 and 24 hours following initial hospital presentation. The cut-off times were chosen by consensus among the clinical experts on the RAIN Study Steering Group. Patients within each participating critical care unit could be included within either comparator group.

As part of research objective 2, three sets of prespecified subgroup analyses were undertaken: the first according to age, the second according to presence of major extracranial injury and the third by GCS score at baseline. The justification for reporting results by age group was that several recent studies have reported worse outcomes following TBI for older patients, defined as those above an age threshold

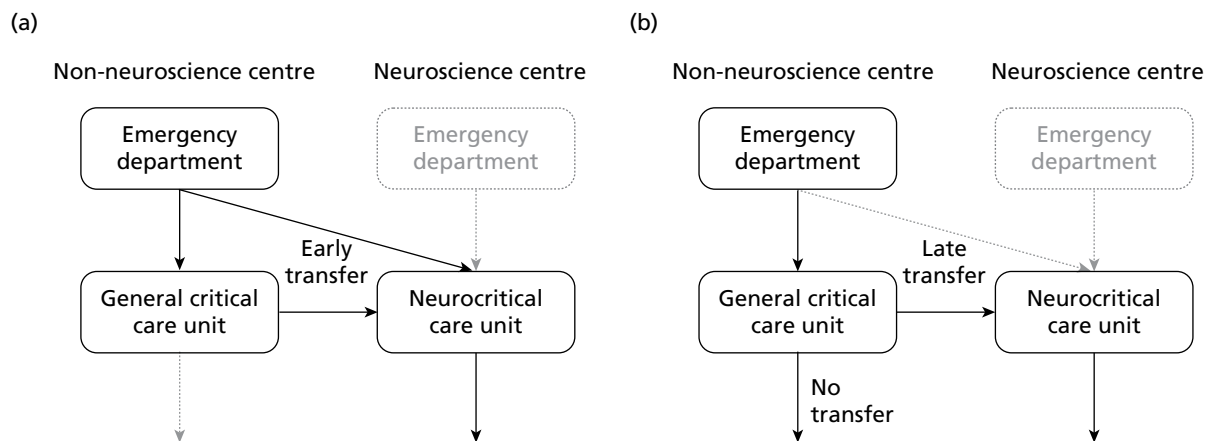


FIGURE 30 Comparators for research objective 2: 'early' vs 'no or late' transfer to a neuroscience centre. (a) Early transfer; (b) no or late transfer.

ranging from 65 to 80 years.^{121–124} This raises the hypothesis that 'early' transfer for an older subgroup may not be cost-effective. We categorised age groups according to a cut-off of 70 years, which is in the middle of the range of age thresholds used previously, and was anticipated to ensure sufficient sample sizes in each subgroup.

Major extracranial injury frequently accompanies TBI and can increase mortality.^{16,94,125–127} However, it is unclear whether the presence of major extracranial injury will modify the effect of an early transfer to neuroscience centres on mortality, morbidity or cost. Hence, we reported the costs, consequences and cost-effectiveness of 'early' compared with 'no or late' transfer for subgroups with and without major extracranial injury, defined as an injury that would require hospital admission in its own right.

The third subgroup analysis was motivated by NICE guidance, which recommended transfer to a neuroscience centre for all patients with severe TBI, defined as a TBI with GCS score of ≤ 8 , regardless of the need for neurosurgery.¹¹ We therefore reported the costs, consequences and cost-effectiveness of 'early' compared with 'no or late' transfer for subgroups with a last pre-sedation GCS scores of 3–8 and 9–14.

Methods for the cost–consequence analysis of alternative care locations at 6 months

Settings, inclusion criteria and measurement of case mix

Each critical care unit within the RAIN study was classified according to whether they were in a neuroscience centre and, if so, whether they were a dedicated neurocritical care unit or a combined neuro/general critical care unit (*Table 30*). (The one 'major injuries unit' participating in the RAIN study was classified as a dedicated neurocritical care unit due to the specialist nature of their case mix and the presence of a separate general critical care unit within the same hospital.) All dedicated neurocritical care units in the UK participated in the RAIN study, along with 74% of combined neuro/general critical care units and 16% of general critical care units in non-neuroscience centres. Dedicated neurocritical care units had a similar distribution of bed numbers to general critical care units in non-neuroscience centres, whereas combined neuro/general critical care units were larger. The throughput of TBI cases was similar for dedicated neurocritical care units and combined neuro/general critical care units, and substantially higher than for general critical care units in non-neuroscience centres.

Data were extracted from the RAIN study data set for all patients with acute TBI and a last pre-sedation GCS score of < 15 . For research objective 1, all patients with RAIN study data submitted from a

TABLE 30 Description of critical care units participating in the RAIN study

Hospital type	Neuroscience centre ^a		Non-neuroscience centre
	Dedicated neurocritical care unit	Combined neuro/general critical care unit	General critical care unit
Number of units (% of all in UK)	13 (100)	14 (73.7)	36 (16.1)
Number of beds, <i>n</i> (%)			
5–9	5 (38.5)	0 (0)	17 (47.2)
10–14	5 (38.5)	1 (7.1)	14 (38.9)
15–19	3 (23.1)	5 (35.7)	4 (11.1)
20+	0 (0)	8 (57.1)	1 (2.8)
Number of admissions in RAIN study	1565	1621	440
Admissions per unit per year (IQR across units)	90 (60 to 103)	84 (54 to 110)	9 (6 to 11)
Number of patients in analysis	1324	1341	310

^a Includes data from four additional critical care units within neuroscience centres (i.e. not the unit where patients with TBI would routinely be managed); these units have not been included in the reported numbers of units and their admissions have been counted with those of the neurocritical care unit.

neuroscience centre were included in the analysis. All patients who met the inclusion criteria within an eligible critical care unit were then assigned to either comparator group according to whether the neurocritical care unit met the criteria for a dedicated critical care or combined neuro/general critical care unit.^{13,14}

For research objective 2, all patients initially presenting at a non-neuroscience centre were included in the analysis. Patients included in this analysis came from RAIN study data submitted either from non-neuroscience centres or from neuroscience centres where the location prior to admission field indicated that the patient had been transferred from another acute hospital. Patients were assigned to either comparison group according to the time of transfer to a neuroscience centre. Patients transferred to a neuroscience centre between 18 and 24 hours following initial presentation at an acute hospital were excluded from the analysis.

Risk factor data for the IMPACT Lab³⁵ and CRASH CT³⁰ models were taken from the time of injury and initial presentation at acute hospital, and were defined in the same way as for the external validation of the risk prediction models (see *Chapter 5*).

Resource use before 6 months

For research objective 1, resource use was considered from the first admission to critical care *within* the neuroscience centre, i.e. any resource use before this critical care admission, was excluded. For the second research objective, resource use was considered from the first critical care admission following the TBI. For both research objectives, the RAIN study prospectively recorded the LOS in critical care for each admission, according to days in a dedicated neurocritical care unit within a neuroscience centre, days in a combined neuro/general critical care unit within a neuroscience centre, and days in a general critical care unit within a non-neuroscience centre. The RAIN study also recorded whether or not the patient had intracranial neurosurgery for evacuation of a mass lesion. We recorded the LOS following transfer to other wards, both within the same acute hospital or to other hospitals including rehabilitation centres (all termed LOS on general medical wards). Any readmissions to critical care within the RAIN study were recorded. We also extracted data on readmissions to critical care units that were not in the RAIN study via data linkage

with the CMP database. Each day during critical care was assigned to the appropriate Healthcare Resource Group (HRG) using daily organ support data recorded for the CCMDs.

The 6-month follow-up in the RAIN study (see *Chapter 3*) included a Health Services Questionnaire to ascertain use of other hospital and personal social services up to 6 months following the TBI. These postal questionnaires asked patients or their carers to report any hospital and personal service use between discharge from hospital and 6 months. We adapted a questionnaire¹²⁸ to report service use following a TBI. The items of service use included subsequent hospital readmissions (excluding critical care), visits to hospital outpatients, and community health services (contacts with the GP, health visitor, district nurse, physiotherapist, occupational therapist, psychologist and speech therapist) (see *Appendix 5*). The patients eligible for this questionnaire were those known to be alive, and discharged from hospital by the date of the 6-month follow-up.

Health outcomes at 6 months

Data on 6-month outcomes were collected centrally as detailed in *Chapter 3*. EQ-5D-3L profiles were combined with health-state preference values from the UK general population, to give an EQ-5D-3L utility index score on a scale anchored at 0 (death) and 1 (perfect health).¹²⁹ QALYs at 6 months were then reported for each patient by combining information on survival and utility score at 6 months. Patients who died before 6 months were assigned zero QALYs. For patients alive at 6 months who completed an EQ-5D-3L questionnaire, their utility score at 6 months was multiplied by 0.5 life-years (6/12 months) to give their 6-month QALY.

Unit costs

For all critical care admissions, each bed-day was costed with the corresponding unit cost per bed-day from the 'Payment by Results' database.¹³⁰ Each set of unit costs distinguished between the alternative care locations; for research objective 1, separate unit costs were extracted for neuroscience centres with dedicated neurocritical care units compared with neuroscience centres with combined neuro/general critical care units (*Table 31*). For research objective 2, separate unit costs were applied to critical care in non-neuroscience centres (general critical care) compared with neuroscience centres (dedicated neurocritical care or combined neuro/general critical care). The unit cost of transfer to a neuroscience centre was taken as the cost of an emergency transfer.¹³⁰ For those admissions that included an intracranial procedure, to recognise the additional costs of theatre time and consumables, we included an additional unit cost corresponding to neurosurgery for cases with complications or comorbidities.¹³⁰ Each set of unit costs was reported as an average across the centres in the RAIN study. Unit costs for general medical bed-days were taken across all categories of elective, excess bed-days, weighted for their relative prevalence.¹³¹ Other unit costs of health and personal social services were taken from the literature (*Table 32*).¹³² All unit costs were reported in 2010–11 prices.

Each item of resource use was combined with the appropriate unit cost to report a cost per patient for each cost category (inpatient, outpatient, community and total costs). Resource use was estimated at the individual patient-level for each specific location of care. The unit costs were average unit costs across the centres in the RAIN study specific to each location of care (see *Table 32*).

Analysis of 6-month costs and consequences

For both research objectives, we described baseline characteristics, unadjusted outcomes, resource use and costs for each comparator. For each end point we employed regression analysis to adjust for baseline differences between the comparators using the individual risk factor variables from the IMPACT Laboratory model.³⁵ For the mortality and unfavourable outcome end points, we report odds ratios with logistic regression. For research objective 1, where each patient within a critical care unit was by definition within the same comparison group, we specified multilevel models that included random effects for centre to recognise any between-centre differences.^{133,134} For the EQ-5D-3L, QALY and cost end points, the multilevel model reported incremental effects of the alternative care locations, after adjusting for case mix. The multilevel models assumed that both individual and centre level residuals were drawn from normal

TABLE 31 Unit costs (£) of inpatient care

Resource use	Unit costs (£) of inpatient care		
	Neuroscience centre with dedicated neurocritical care unit	Neuroscience centre with combined neuro/general critical care unit	Non-neuroscience centre with general critical care unit
Critical care bed-day			
One organ supported	865	800	738
Two organs supported	888	1269	899
Three organs supported	1354	1181	1348
Four organs supported	1369	1324	1553
Five organs supported	1433	1360	1685
Six organs supported	1481	1570	1895
Seven organs supported	1448	1570	2204
General medical bed-day ^a	252	252	252
Transfer to neuroscience centre	253	253	N/A
Intracranial procedure	5796	4570	6174 ^b

N/A, not applicable.
a Cost of excess bed-day.
b National average of NHS reference cost.
Source: NHS reference costs 2010–11.¹³⁰

distributions. For research objective 2, where patients within each critical care unit could be assigned to either comparison arm, we repeated the above analysis but with single-level regression models estimated by maximum likelihood. These models reported incremental effects of the alternative care locations, together with 95% CIs, assuming that individual level residuals followed normal distributions. For research objective 2, we undertook prespecified subgroup analyses to report: incremental effects according to age (aged ≤ 70 years or > 70 years), major extracranial injury (yes or no) and GCS score (3–8 or 9–14). All analyses were implemented in R using the General Linearized Models (GLM) package.¹³⁵

For those patients who did not complete the 6-month follow-up questionnaires, data were unavailable for GOSE (approximately 20%), EQ-5D-3L and health service use (both approximately 50%). For a minority of patients, information was missing for baseline characteristics (between 2% and 17%) and mortality (3%). We addressed missing data with multiple imputation following a similar approach to that applied in *Chapter 5*.^{76,78,136} The EQ-5D-3L, GOSE and cost end points were conditional on survival status, so we conducted the imputation in two stages. In the first stage, we specified imputation models for baseline characteristics and mortality according to observed covariates. In the second stage, for each of the previously imputed data sets, we specified imputation models for GOSE, EQ-5D-3L and health service use for those patients who were either known to be alive at 6 months, or were predicted to be alive by the first stage imputation model. (Owing to the high number of health service use categories, we specified multiple imputation models only for three aggregated categories: inpatient, outpatient and 'other' service use. In order to present disaggregated descriptions of mean service use across all the patients sampled in each arm, we also undertook mean imputation. Here we replaced missing observations in each category with the unconditional mean resource use for each category by treatment arm, among those patients with the relevant resource use observed.)

TABLE 32 Unit cost (£) of contacts with outpatient and community health services

Community health service	Unit cost (£)
Hospital outpatient	147
GP practice visit	47
GP home visit	99
GP practice nurse	11
Hospital staff nurse	11
Health visitor	11
District nurse	11
Psychologist	16
Speech and language therapist	8
Occupational therapist	10
Physiotherapist	8
Counsellor	60
Hospital discharge co-ordinator	8
Child psychologist	16
Dietitian	8
Mental health service	27
Cognitive-behavioural therapist	8
Social worker	9
Art therapy	10

Source: Curtis.¹³²

Each multiple imputation model assumed that the data were ‘missing at random’, that is conditional on the variables included in each imputation model.⁷⁶ Each imputation model considered including baseline covariates (e.g. risk factor variables from the IMPACT Lab model), resource use (e.g. LOS in critical care), and end points (e.g. we used data for those patients who completed the GOSE questionnaire to predict missing EQ-5D-3L). For research objective 1, we developed multilevel imputation models to recognise the hierarchical structure of the data.¹³⁷ For research objective 2, we used standard multiple imputation.⁷⁷ As the missingness pattern may differ across treatment groups, we specified separate imputation models for each comparator, and five imputed data sets were generated for each stage of the imputation, giving a total of 25 imputed data sets for each arm. After imputation, we applied the analytical models to each imputed data set, and combined the resultant estimates with Rubin’s rules,⁷⁶ which recognise uncertainty both within and between imputations. All multiple imputation models were implemented in R using MICE.⁷⁹

Results of the cost–consequence analysis of alternative care locations at 6 months

Research objective 1: Dedicated neurocritical care unit compared with combined neuro/general critical care unit

The baseline characteristics of the patients were broadly similar between the dedicated neurocritical care units and combined neuro/general critical care units (*Table 33*). In particular, the median predicted risk of unfavourable outcome, according to the IMPACT Lab model, was 40% for those dedicated critical care units compared with 41% in the combined units.

Table 34 describes the main items of hospital resource use recorded from the RAIN study and the CMP database. Although the overall mean hospital LOS was similar between the groups, the dedicated neurocritical care unit group had a higher average LOS in critical care.

Table 35 shows the flow of patients through the study. As the EQ-5D-3L and the Health Services Questionnaire were administered only by post, and not by telephone, the completion rates were lower for these questionnaires.

Mortality at 6 months was similar between the groups (*Table 36*). The dedicated neurocritical care unit group had a higher mean EQ-5D-3L utility index score for survivors, a lower proportion of patients with unfavourable outcomes and higher mean QALYs, although none of these differences was statistically significant, after case mix adjustment.

Table 37 reports the results from the Health Services Questionnaire for all patients sampled in each comparison group. The mean numbers of contacts were similar between the groups. For both groups, relatively low use, on average, was made of community health services.

Table 38 reports the mean total costs at 6 months for each comparison arm. On average, critical care costs were higher for the dedicated neurocritical care units, and this led to a positive incremental cost compared with combined neuro/general critical care units.

TABLE 33 Description of baseline covariates included in the risk models and additional potential confounders for research objective 1

Baseline covariates	Combined neuro/general critical care unit	Dedicated neurocritical care unit
Number of admissions	1341	1324
Age (years)		
Mean (SD)	44.4 (18.8)	43.9 (18.7)
Median (IQR)	43 (28 to 58)	43 (26 to 59)
Male, <i>n</i> (%)	1023 (76.3)	1002 (75.7)
Major extracranial injury, <i>n</i> (%)	590 (44.0)	488 (36.9)
Pre-hospital hypoxia, ^a % ^b	13.4	11.5
Pre-hospital hypotension, ^a % ^b	8.1	4.8
Last pre-sedation GCS score, <i>n</i> (%)		
13–14 (mild TBI)	166 (12.4)	232 (17.5)
9–12 (moderate TBI)	352 (26.2)	340 (25.7)
3–8 (severe TBI)	823 (61.4)	752 (56.8)

TABLE 33 Description of baseline covariates included in the risk models and additional potential confounders for research objective 1 (*continued*)

Baseline covariates	Combined neuro/general critical care unit	Dedicated neurocritical care unit
GCS motor score, % ^b		
6 (obeys)	15.9	19.8
5 (localises)	32.2	30.8
4 (normal flexion)	12.3	12.0
3 (abnormal flexion)	8.1	6.9
2 (extension)	8.3	6.7
1 (none)	23.2	23.7
Pupil reactivity, % ^b		
Both reactive	79.8	80.9
One reactive	6.4	6.8
Neither reactive	13.8	12.3
Marshall CT classification, % ^b		
1 (diffuse injury I)	2.7	4.3
2 (diffuse injury II)	35.0	30.4
3 (diffuse injury III)	8.4	9.6
4 (diffuse injury IV)	2.5	3.3
5 (evacuated mass lesion)	37.3	39.3
6 (non-evacuated mass lesion >25 ml)	14.1	13.1
Traumatic SAH, % ^b	57.1	56.6
Extradural haematoma, % ^b	16.7	17.5
Predicted risk (%) at 6 months, median (IQR) ^b		
Death (IMPACT Lab model)	22.8 (11.5 to 39.6)	22.5 (11.3 to 36.9)
Unfavourable outcome (IMPACT Lab model)	41.0 (22.9 to 64.2)	40.0 (21.1 to 60.7)
Unfavourable outcome (CRASH CT model)	44.2 (24.3 to 72.2)	42.5 (22.4 to 70.3)

SD, standard deviation.

a Observed (hypoxia, SaO₂ <90%; hypotension, systolic blood pressure <90 mmHg) or strongly suspected.

b Summaries presented are after multiple imputation; number (%) missing each field were hypoxia 171 (6.4); hypotension 179 (6.7); motor score 65 (2.4); pupil reactivity 198 (7.4); Marshall CT classification 189 (7.1); traumatic SAH 175 (6.6); and extradural haematoma 156 (5.9).

c First recorded values after hospital presentation or, if unavailable, last recorded values pre-hospital.

d From first CT scan following presentation at hospital.

TABLE 34 Hospital resource use up to 6 months for research objective 1

Resource	Combined neuro/general critical care unit (n = 1341)	Dedicated neurocritical care unit (n = 1324)
Index admission		
Mean (SD) days in critical care	11.08 (10.83)	13.19 (15.07)
Mean (SD) days on general medical wards	26.26 (36.03)	24.69 (33.96)
Mean (SD) total hospital days	37.34 (40.49)	37.89 (39.62)
Neurosurgery, ^a n (%)	477 (35.57)	478 (36.10)
Readmission		
n (%) readmission	66 (4.92)	100 (7.55)
Mean (SD) days on critical care	0.46 (3.27)	0.59 (2.94)
Mean (SD) days on general wards	0.22 (3.28)	0.22 (3.41)
Mean (SD) total days	0.68 (5.24)	0.80 (5.05)
Mean (SD) total hospital days up to 6 months	38.02 (41.27)	38.69 (40.49)

SD, standard deviation.

a Intracranial procedure for evacuation of mass lesion.

Source: RAIN study and CMP database.

TABLE 35 Flow of patients (n) from hospital presentation to 6-month follow-up for research objective 1

Stage of follow-up	Combined neuro/general critical care unit	Dedicated neurocritical care unit
Hospital presentation	1341	1324
Total deaths before 6 months	331	305
Missing data on death before 6 months	42	45
Eligible for Your Health Questionnaire	968	974
GOSE questionnaire completed	750 (77%)	796 (82%)
EQ-5D-3L questionnaire completed	471 (49%)	508 (52%)
Initial hospital episode of 6 months or more	27	20
Eligible for Health Services Questionnaire	941	954
Health Services Questionnaire completed	495 (53%)	529 (55%)

TABLE 36 Six-month outcomes for research objective 1, unadjusted and adjusted for case mix (after multiple imputation)

Six-month outcomes	Combined neuro/general critical care unit (n = 1341)	Dedicated neurocritical care unit (n = 1324)	Odds ratio/incremental effect ^a (95% CI)	
			Unadjusted	Adjusted
Death before 6 months, n (%)	341 (25%)	312 (24%)	0.982 (0.95 to 1.02)	0.942 (0.77 to 1.16)
Mean (SD) EQ-5D (survivors)	0.43 (0.41)	0.48 (0.41)	0.049 (−0.001 to 0.098)	0.048 (−0.002 to 0.099)
GOSE category, n (%)				
Upper good recovery	155 (12%)	169 (13%)		
Lower good recovery	76 (6%)	71 (5%)		
Upper moderate disability	145 (11%)	166 (13%)		
Lower moderate disability	123 (9%)	125 (9%)		
Upper severe disability	181 (14%)	165 (12%)		
Lower severe disability	283 (21%)	289 (22%)		
Pre-existing severe disability	36 (3%)	27 (2%)		
Dead	341 (25%)	312 (24%)		
Unfavourable outcome, n (%)	841 (63%)	793 (60%)	0.888 (0.69 to 1.15)	0.902 (0.74 to 1.10)
Mean (SD) QALY	0.16 (0.20)	0.18 (0.21)	0.023 (0.002 to 0.043)	0.020 (−0.001 to 0.040)

SD, standard deviation.

^a Odds ratio for death and unfavourable outcome, and incremental for other estimates.**TABLE 37** Mean (SD) resource use from Health Services Questionnaire between discharge from hospital and 6 months following the TBI^a

Resource use	Combined neuro/general critical care unit (n = 1341)	Dedicated neurocritical care unit (n = 1324)
Inpatient days (general medical)	8.3 (16.7)	8.2 (17.6)
Outpatient visits	3.3 (4.6)	2.7 (3.7)
GP contacts	2.1 (2.2)	2.3 (2.4)
Nurse contacts	1.3 (2.4)	1.2 (2.1)
Occupational therapist contacts	2.3 (3.6)	2.5 (3.9)
Health visitor contacts	0.8 (2.2)	0.8 (2.1)
Clinical psychologist contacts	1.3 (3.3)	1.1 (3.0)
Speech therapist contacts	1.4 (3.5)	1.5 (3.9)
Physiotherapist contacts	3.4 (3.9)	3.4 (4.0)
Mental health service contacts	0.4 (2.0)	0.4 (1.6)
Cognitive-behavioural therapist contacts	0.3 (1.3)	0.2 (1.0)

SD, standard deviation.

^a For patients with missing values who were known to be alive at 6 months, we applied imputed means for each item of service use.

TABLE 38 Unadjusted mean (SD) costs (£), and incremental costs at 6 months for research objective 1, after adjusting for case mix

Source of costs	Combined neuro/general critical care unit (n = 1341)	Dedicated neurocritical care unit (n = 1324)	Incremental cost (95% CI)
Index admission ^a			
Critical care	15,066 (15,190)	18,225 (21,638)	
General medical	6619 (9081)	6223 (8558)	
Subsequent admissions			
Critical care ^a	559 (3958)	722 (3664)	
General medical ^a	56 (827)	55 (860)	
General medical ^b	757 (2468)	782 (2503)	
Outpatient care ^b	445 (1405)	407 (1322)	
Community costs ^b	332 (1274)	364 (1375)	
Grand total ^{ab}	25,466 (21,468)	28,855 (25,970)	3694 (1899 to 5489)

SD, standard deviation.

a Source: RAIN study and CMP database.

b Source: Health Services Questionnaire.

Research objective 2: 'early' compared with 'no or late' transfer to a neuroscience centre

There were substantial differences in case mix between patients in the 'early' transfer group and the 'no or late' transfer group (*Table 39*). The patients in the 'early' transfer group were on average younger but were generally of less severe case mix than the 'no or late' transfer group. The 'no or late' transfer group had a higher proportion of patients with a GCS score of 3–8, for whom neither pupil was reactive, and who had a Marshall CT classification of 'non-evacuated mass lesion'. The net effect was that the median predicted risk of death at 6 months was higher for the 'no or late' transfer group than for the 'early' transfer group.

Figure 31 presents a histogram of the time from initial presentation at hospital to transfer to a neuroscience centre, for all patients transferred. Each bin on the histogram represents a time period of 1 hour; the vertical line at 18 hours represent the maximum time to transfer for the 'early' group, and the line at 24 hours, the minimum transfer time for the 'late' group. In the 'no or late' transfer group, 94% of patients were not transferred to a neuroscience centre. The majority of transfers were between 3 and 10 hours from hospital presentation. For 77 patients transferred directly from an emergency department a time of transfer was not available; these patients were defined as in the 'early' transfer group.

The 'early' transfer group had mean LOS in critical care, on general wards and in total that was approximately double that of the 'no or late' transfer group (*Table 40*). In addition, a higher proportion of patients in the 'early' transfer group had an intracranial procedure for evacuation of a mass lesion, at least 24 hours after initial presentation.

Table 41 shows the flow of patients through the study, and highlights that around half the eligible patients completed the postal questionnaires for the EQ-5D-3L and service use.

The proportion of patients who died before 6 months was substantially lower in the 'early' compared with the 'no or late' transfer group (odds ratio after case mix adjustment 0.52, 95% CI 0.34 to 0.80; *Table 42*). Although the CI on the odds ratio for unfavourable outcome included 1, the 'early' transfer

TABLE 39 Description of baseline covariates included in the risk models and additional potential confounders for research objective 2

Baseline covariates	'No or late' transfer to neuroscience centre	'Early' transfer to neuroscience centre
Number of admissions	263	584
Age (years)		
Mean (SD)	40.0 (17.4)	50.7 (20.1)
Median (IQR)	39 (24 to 53)	49 (35 to 69)
Male, <i>n</i> (%)	207 (78.7)	455 (77.9)
Major extracranial injury, <i>n</i> (%)	110 (41.8)	209 (35.8)
Pre-hospital hypoxia, ^a % ^b	15.0	13.5
Pre-hospital hypotension, ^a % ^b	9.7	5.2
Last pre-sedation GCS score, <i>n</i> (%)		
13–14 (mild TBI)	41 (15.6)	105 (18.0)
9–12 (moderate TBI)	62 (23.6)	173 (29.6)
3–8 (Severe TBI)	160 (60.8)	306 (52.4)
Motor score from last pre-sedation GCS score, % ^b		
6 (obeys)	14.1	20.8
5 (localises)	26.5	35.4
4 (normal flexion)	10.3	11.2
3 (abnormal flexion)	4.9	4.9
2 (extension)	7.3	5.9
1 (none)	36.7	21.8
Pupil reactivity, ^c % ^b		
Both reactive	77.0	83.8
One reactive	1.4	6.1
Neither reactive	21.6	10.0
Marshall CT classification, ^d % ^b		
1 (diffuse injury I)	10.9	2.4
2 (diffuse injury II)	45.6	42.4
3 (diffuse injury III)	8.4	16.7
4 (diffuse injury IV)	2.7	4.3
5 (evacuated mass lesion)	0.6	9.6
6 (non-evacuated mass lesion >25ml)	31.8	24.6
Traumatic SAH, ^d % ^b	47.1	60.3
Extradural haematoma, ^d % ^b	9.6	14.8

TABLE 39 Description of baseline covariates included in the risk models and additional potential confounders for research objective 2 (*continued*)

Baseline covariates	'No or late' transfer to neuroscience centre	'Early' transfer to neuroscience centre
Predicted risk (%) at 6 months, median (IQR) ^b		
Death (IMPACT Lab model)	24.6 (9.6 to 48.1)	18.3 (9.4 to 32.7)
Unfavourable outcome (IMPACT Lab model)	47.8 (20.8 to 73.6)	33.8 (17.7 to 54.3)
Unfavourable outcome (CRASH CT model)	56.4 (21.8 to 83.1)	35.6 (19.1 to 58.4)

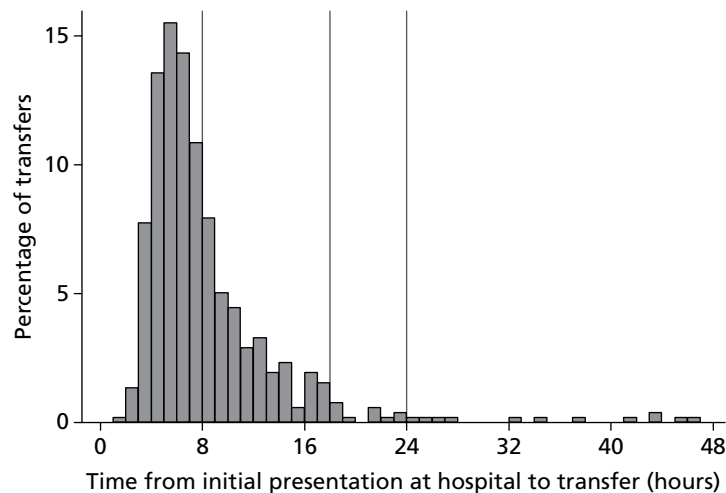
SD, standard deviation.

a Observed (hypoxia, $\text{SaO}_2 < 90\%$; hypotension, systolic blood pressure < 90 mmHg) or strongly suspected.

b Summaries presented are after multiple imputation; number (%) missing each field were hypoxia 29 (3.4); hypotension 33 (3.9); motor score 9 (1.1); pupil reactivity 72 (8.5); Marshall CT classification 89 (10.5); traumatic SAH 74 (8.7); and extradural haematoma 68 (8.0).

c First recorded values following presentation at hospital or, if unavailable, last recorded values pre-hospital.

d From first CT scan following presentation at hospital.

**FIGURE 31** Distribution of time from initial presentation at hospital to transfer to a neuroscience centre. Note: 10 transfers beyond 48 hours are not shown; 77 transfers direct from the emergency department had missing transfer times and were assumed to be early.

group reported a higher mean EQ-5D-3L utility index score for survivors, and higher mean QALYs after case mix adjustment.

Table 43 shows the hospital and community health service use reported by the patients at 6 months, averaged across the whole sample including those who died. The 'early' transfer group reported higher average LOS after readmissions to general medical wards, and had higher mean contacts with outpatient and community health services.

The higher proportion of patients surviving in the early transfer arm is reflected in the estimates of the total costs at 6 months (Table 44); the mean costs of critical care and the total costs were twice as high in the early transfer group, with a positive incremental cost of approximately £15,000, after case mix adjustment.

TABLE 40 Hospital resource use up to 6 months for research objective 2

Resource use	'No or late' transfer to neuroscience centre (n = 263)	'Early' transfer to neuroscience centre (n = 584)
Index admission		
Mean (SD) days in critical care	5.67 (6.66)	13.93 (15.68)
Mean (SD) days on general medical wards	12.73 (23.94)	24.31 (34.09)
Mean (SD) total hospital days	18.40 (26.98)	38.24 (40.37)
Neurosurgery, ^a n (%)	1 (0.38)	48 (8.22)
Readmission		
n (%) readmission	9 (3.42)	38 (6.51)
Mean (SD) days on critical care	0.28 (2.03)	0.57 (3.18)
Mean (SD) days on general wards	0.03 (0.31)	0.13 (1.55)
Mean (SD) total hospital days	0.31 (2.24)	0.69 (3.98)
Mean (SD) total hospital days up to 6 months	18.71 (27.02)	38.94 (40.86)

SD, standard deviation.

a Intracranial procedure for evacuation of mass lesion.

Source: RAIN study and CMP database.

TABLE 41 Flow of patients (n) from hospital presentation to 6-month follow-up for research objective 2

Stage of follow-up	'No or late' transfer to neuroscience centre	'Early' transfer to neuroscience centre
Hospital presentation	263	584
Total deaths before 6 months	104	106
Missing data on deaths by 6 months	7	23
Eligible for Your Health Questionnaire	152	455
GOSE questionnaire completed	114 (75%)	363 (80%)
EQ-5D-3L questionnaire completed	70 (46%)	233 (51%)
Initial hospital episode of 6 months or more	2	7
Eligible for Health Services Questionnaire	150	448
Health Services Questionnaire completed	76 (51%)	236 (53%)

Table 45 presents the results of the subgroup analyses for the 6-month end points, after case mix adjustment. Patients aged >70 years had, on average, a higher odds of death in the 'early' compared with the 'no or late' transfer group, but the CIs around the odds ratios were wide and included 1. For older survivors, the mean odds ratio for death at 6 months was <1 whether or not patients had a major extracranial injury but the subgroup with major extra cranial injury had very low odds of death in the 'early' transfer group.

TABLE 42 Six-month outcomes for research objective 2, unadjusted and adjusted for case mix

Six-month outcomes	'No or late' transfer to neuroscience centre (n = 263)	'Early' transfer to neuroscience centre (n = 584)	Odds ratio/incremental effect ^a (95% CI)	
			Unadjusted	Adjusted
Death before 6 months, n (%)	107 (41%)	109 (19%)	0.334 (0.242 to 0.462)	0.52 (0.34 to 0.80)
Mean (SD) EQ-5D (survivors)	0.44 (0.37)	0.55 (0.41)	0.108 (0.011 to 0.205)	0.129 (0.032 to 0.225)
GOSE category, n (%)				
Upper good recovery	40 (15%)	80 (14%)		
Lower good recovery	9 (3%)	45 (8%)		
Upper moderate disability	20 (7%)	88 (15%)		
Lower moderate disability	25 (9%)	65 (11%)		
Upper severe disability	19 (7%)	74 (13%)		
Lower severe disability	34 (13%)	117 (20%)		
Pre-existing severe disability	11 (4%)	7 (1%)		
Dead	107 (41%)	109 (19%)		
Unfavourable outcome, n (%)	169 (65%)	307 (53%)	0.61 (0.17 to 2.15)	0.88 (0.28 to 2.79)
Mean (SD) QALY	0.13 (0.18)	0.22 (0.21)	0.093 (0.056 to 0.130)	0.051 (0.015 to 0.086)

SD, standard deviation.

a Odds ratio for death and unfavourable outcome, and incremental for other estimates.

TABLE 43 Mean (SD) resource use from Health Services Questionnaire between discharge from hospital and 6 months following the TBI^a

Resource use	'No or late' transfer to neuroscience centre (n = 263)	'Early' transfer to neuroscience centre (n = 584)
Inpatient days (general medical)	6.4 (13.8)	7.9 (15.5)
Outpatient visits	1.8 (2.3)	2.4 (2.4)
GP contacts	2.2 (2.3)	2.3 (2.0)
Nurse contacts	1.1 (2.6)	1.1 (2.0)
Occupational therapist contacts	1.4 (3.3)	2.5 (3.7)
Health visitor contacts	0.9 (2.1)	0.7 (1.9)
Clinical psychologist contacts	0.6 (2.1)	1.0 (2.5)
Speech therapist contacts	0.5 (1.6)	1.1 (2.4)
Physiotherapist contacts	2.6 (3.2)	2.8 (3.2)
Mental health service contacts	0.4 (1.4)	0.2 (0.8)
Cognitive-behavioural therapist contacts	0.2 (1.1)	0.2 (0.8)

SD, standard deviation.

a For patients with missing values who were known to be alive at 6 months, we applied imputed means for each item of service use.

TABLE 44 Unadjusted mean (SD) costs (£) and incremental costs at 6 months after adjusting for case mix

Source of costs	'No or late' transfer to neuroscience centre (n = 263)	'Early' transfer to neuroscience centre (n = 584)	Incremental cost (95% CI)
Index admission ^a			
Critical care	8330 (10,016)	19,352 (22,874)	
General medical	3209 (6033)	6126 (8589)	
Subsequent admissions			
Critical care ^a	395 (2939)	720 (3957)	
General medical ^a	8 (79)	33 (391)	
General medical ^b	616 (2247)	836 (2547)	
Outpatient care ^b	289 (1114)	573 (1740)	
Community costs ^b	288 (1177)	604 (1885)	
Grand total ^{a,b}	13,152 (14,563)	28,525 (27,100)	15,001 (11,123 to 18,880)

SD, standard deviation.

a Source: RAIN study and CMP database.

b Source: Health Services Questionnaire.

TABLE 45 Odds ratio for death, incremental EQ-5D-3L, incremental QALY and cost at 6 months (adjusted for case mix) of 'early' vs 'no or late' transfer, for subgroups of patients by age, major extracranial injury and GCS score

Subgroups	Odds ratio for death (95% CI)	Incremental EQ-5D-3L (95% CI)	Incremental QALY (95% CI)	Incremental cost (95% CI)
Overall	0.521 (0.34 to 0.80)	0.129 (0.032 to 0.225)	0.051 (0.015 to 0.086)	15,001 (11,123 to 18,880)
Age (years)				
≤70	0.471 (0.289 to 0.766)	0.132 (0.027 to 0.237)	0.066 (0.014 to 0.118)	15,770 (11,492 to 20,047)
>70	1.528 (0.441 to 5.299)	0.074 (-0.334 to 0.483)	0.037 (-0.167 to 0.241)	5136 (-3604 to 13,876)
Major extracranial injury				
No	0.797 (0.448 to 1.420)	0.131 (-0.001 to 0.262)	0.066 (-0.000 to 0.131)	11,756 (6774 to 16,737)
Yes	0.215 (0.098 to 0.468)	0.119 (-0.019 to 0.256)	0.059 (-0.009 to 0.128)	20,481 (14,374 to 26,588)
GCS score				
Mild or moderate TBI	0.733 (0.358 to 1.498)	0.127 (-0.004 to 0.259)	0.064 (-0.002 to 0.130)	9195 (4076 to 14,314)
Severe TBI	0.431 (0.237 to 0.783)	0.135 (-0.005 to 0.275)	0.067 (-0.003 to 0.137)	18,293 (12,573 to 24,013)

Methods for the lifetime cost-effectiveness analysis

Overview

For each research objective, we reported incremental cost-effectiveness of the alternative care locations over the lifetime. Such lifetime CEA requires information on long-term survival, QOL and cost of alternative interventions. Hence, it was necessary to make assumptions about the long-term prognosis of patients with TBI based on the 6-month data from the RAIN study, but also drawing on evidence from the literature. We tested whether the results were robust to alternative assumptions in extensive sensitivity analyses.

To calculate lifetime QALYs, long-term survival for each patient was calculated from observed survival for each patient within the first 6 months, and from their predicted survival after 6 months. Survival after 6 months was predicted for each patient by applying age-/sex-adjusted excess death rates for the RAIN study patients compared with those for the general population. This was undertaken in two steps. First, we calculated the excess death rates for RAIN study patients who survived after 6 months, compared with the age-/sex-matched UK general population. Second, these excess death rates were applied to predict life expectancy for each RAIN study patient alive at 6 months according to their age and sex.

Long-term survival

Patients in the RAIN study had their vital status followed up until September 2011, and dates of all cause death before that cut-off were provided by MRIS. For each patient the total survival time was calculated up to death or September 2011. We plotted Kaplan–Meier survival curves showing the number of patients who died over time until the last available time point, which was 800 days after the initial admission. For each comparator, the majority of deaths were within the first 30 days, as shown in *Figure 32* for research objective 1.

We followed methodological guidance and considered alternative parametric approaches for extrapolating the observed survival.¹³⁸ When considering alternative parametric specifications we excluded the first 30 days of follow-up, as during this time period, patients had high risks of death; it was judged inappropriate to use this portion of the data for predicting the long-term probability of death. *Figure 33* shows alternative parametric extrapolations for research objective 1, for the two comparator arms combined.

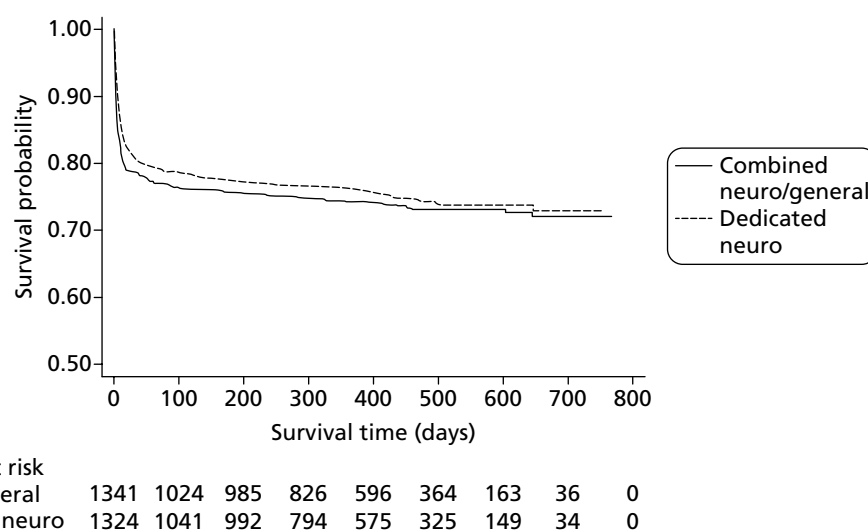


FIGURE 32 Kaplan–Meier survival curves for research objective 1.

We compared the relative goodness of fit of the alternative parametric survival functions, for the remaining period of observed survival according to the Akaike information criterion (AIC) and Bayesian information criterion (BIC), the fit was similar with the logistic, log-normal or Weibull models (*Table 46*).

We compared the survival predicted by the alternative extrapolation approaches at 6–12 months with that for the age-/sex-matched general population.¹³⁹ We used each parametric extrapolation to report the predicted probability of death at 6–12 months for all the 30-day survivors included in RAIN for research objective 1, and report the ratio of these probabilities of death compared with those for the age-/sex-matched general population, also over a 6-month period. *Table 47* shows, for the older age group each of the parametric survival curves tended to predict lower mortality compared with the general population.

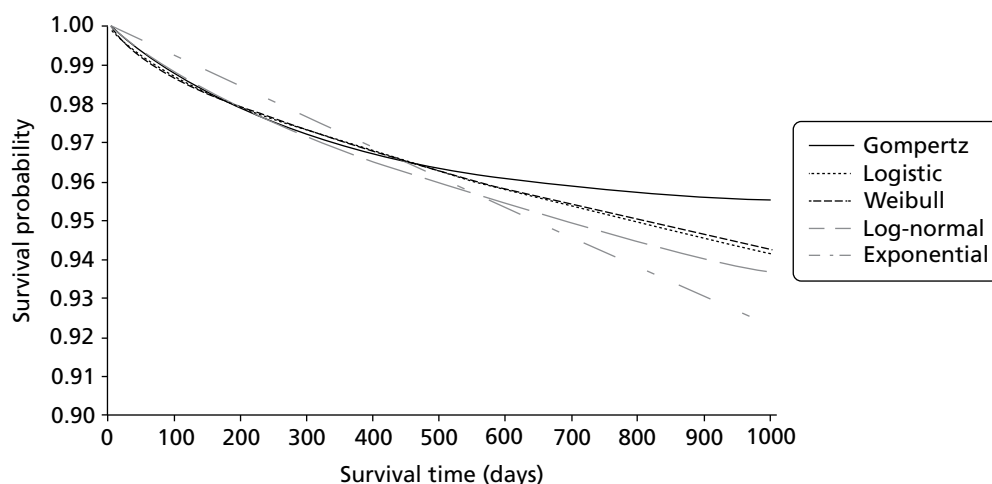


FIGURE 33 Comparison of alternative parametric extrapolations of survival for research objective 1.

TABLE 46 Fit of alternative parametric survival functions applied to the RAIN study data after day 30 for research objective 1

Distribution	AIC	BIC
Gompertz	1302.839	1421.721
Log-normal	1285.765	1404.647
Logistic	1285.889	1404.771
Weibull	1287.583	1406.465
Exponential	1325.173	1438.394

TABLE 47 Ratios of the death rates from applying alternative parametric extrapolations for patients from the RAIN study for research objective 1, compared with the age-/sex-matched general population^a

Age group (years)	Gompertz	Log-normal	Logistic	Weibull	Exponential
16–44	1.34 (1.26 to 1.43)	1.24 (1.13 to 1.35)	1.27 (1.18 to 1.36)	1.29 (1.21 to 1.38)	1.07 (1.00 to 1.14)
45–59	1.15 (1.05 to 1.25)	1.13 (1.02 to 1.23)	1.09 (0.99 to 1.19)	1.11 (1.01 to 1.21)	0.91 (0.83 to 1.00)
60+	0.70 (0.64 to 0.76)	0.69 (0.64 to 0.74)	0.69 (0.63 to 0.74)	0.67 (0.61 to 0.73)	0.58 (0.53 to 0.64)

^a Death rates are by age band and for 6–12 months following TBI for RAIN study patients, and for a 6-month period for the general population. Numbers in parentheses are 95% CIs.

In the base case we therefore decided that the most plausible approach was to apply age-/sex-matched general population death rates after 6 months for each comparator. Hence, in each of the comparator arms for research objective 1, a similar proportion of patients were assumed to die each year. Of the alternative parametric functions, the Gompertz was judged the most plausible and so we applied this extrapolation as a sensitivity analysis.

For research objective 2, the Kaplan–Meier survival curves (Figure 34) highlight that differences in survival between the comparator groups were observed within the first 30 days, and were maintained over time. Here when the alternative parametric specifications were applied to the RAIN data (excluding the first 30 days after TBI), the fit was similar (Table 48). Each of the extrapolation approaches predicted death rates lower than those for the general population for 6–12 months for the younger age group (Table 49). In the base case, we again applied age-/sex-matched general population death rates after 6 months, and used the Gompertz extrapolation in a sensitivity analysis. For this decision problem, both approaches assumed that the differences between the comparison groups observed within the RAIN study were maintained over time.

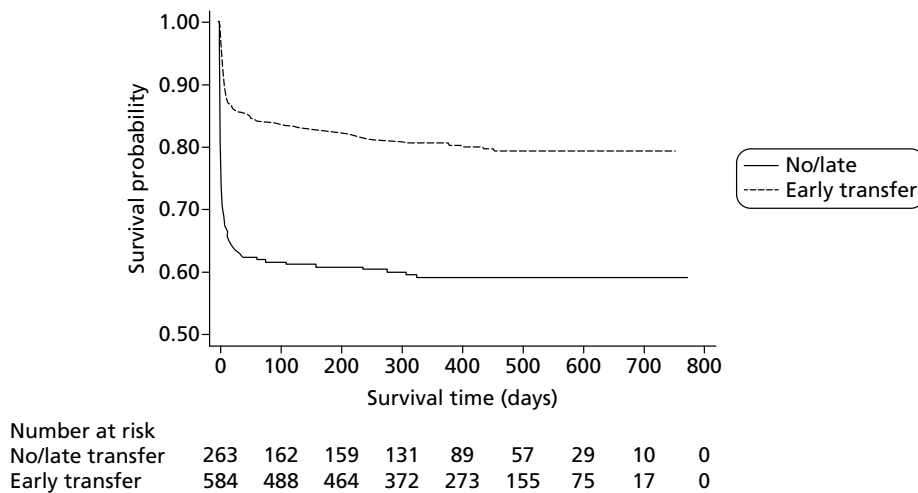


FIGURE 34 Kaplan–Meier survival curves for research objective 2.

TABLE 48 Fit of alternative parametric extrapolations of survival for research objective 2

Distribution	AIC	BIC
Gompertz	358.0628	448.0886
Log-normal	363.7754	458.3024
Logistic	366.0875	460.6145
Weibull	368.5472	463.0743
Exponential	374.2425	464.2683

TABLE 49 Ratios of the death rates from applying alternative parametric extrapolations for patients from the RAIN study for research objective 2, compared with the age-/sex-matched general population^a

Age group (years)	Gompertz	Log-normal	Logistic	Weibull	Exponential
16–44	0.61 (0.55 to 0.68)	0.43 (0.35 to 0.50)	0.52 (0.45 to 0.58)	0.55 (0.49 to 0.61)	0.47 (0.41 to 0.52)
45–59	1.02 (0.80 to 1.24)	0.83 (0.62 to 1.04)	0.89 (0.66 to 1.11)	0.92 (0.72 to 1.11)	0.79 (0.61 to 0.96)
60+	0.96 (0.78 to 1.13)	0.93 (0.78 to 1.07)	0.92 (0.76 to 1.08)	0.89 (0.72 to 1.06)	0.81 (0.64 to 0.98)

^a Death rates are by age band and for 6 to 12 months following TBI for RAIN study patients, and for a 6-month period for the general population. Numbers in parentheses are 95% CIs.

Long-term quality of life

The lifetime CEA required estimates of QOL over time according to the initial locations of critical care. Ideally, CEAs are populated with longitudinal estimates of QOL reported using a generic, preference-based utility measure such as the EQ-5D-3L. We reviewed the literature to find appropriate evidence on QOL for this research objective. However, we did not find any studies that reported QOL over time with a preference-based measure. Our review did find two studies that reported QOL assessed with the Short Form questionnaire-36 items (SF-36) at approximately 10 years after TBI compared with the general population. Jacobsson *et al.*¹⁴⁰ collected data for 67 individuals in Sweden 10 years after acute TBI. This sample included 50% of patients defined as having had a mild TBI (GCS score of 13–15 at admission to the emergency department) and 50% who had either a moderate (GCS score of 9–12) or severe (GCS score of 3–8) TBI. However, the study did not find any differences in QOL according to initial severity. The main finding was that for the whole sample of patients with TBI, general health assessed by the SF-36 was approximately 15% lower than that for the age-/sex-matched general population ($n = 1224$). Andelic *et al.*¹⁴¹ described QOL (SF-36) for a sample of 62 survivors 10 years after moderate (GCS score of 9–12; 52%) to severe (GCS score of 3–8; 48%) TBI in Norway. The main finding was that the study patients had systematically lower scores on each dimension of the SF-36 than the age-/sex-matched general population ($n = 2323$). The mean SF-36 score for general health was similar to that for a moderate to severe TBI sample in the USA ($n = 228$), and approximately 15% less than that of the general Norwegian population. A similar decrement to the general populations was reported for the moderate and the severe TBI groups. Other studies have considered disability over time for TBI survivors,⁷⁵ and found that in patients admitted to hospital 5–7 years after a TBI, rates of disability were high (53%) and similar to those reported at 1 year (57%). Our review did not find any studies that estimated long-term QOL or disability for TBI patients managed in alternative locations of neurocritical care.

In light of the lack of evidence on long-term QOL following alternative locations of critical care, our estimates of QOL over time for each comparator were based on the 6-month data from the RAIN study. However, rather than assuming that the differences in QOL between the comparators at 6 months were maintained, we made the conservative assumption that the differences in QOL attenuated over time. For each comparator we predicted the mean QOL at 6 months for patients aged 40 years (approximately the median age of RAIN patients) with the same risk adjustment applied as in the cost–consequence analysis. We predict mean QOL for each treatment arm between year 1 and year 10 with a linear interpolation, such that after 10 years the mean for each treatment arm was 15% lower than that for the age-matched general population. After 10 years we assumed that for each comparator, the 15% decrement compared with the age-matched population was maintained. As *Figure 35* shows, this implies that the relative gains in QOL at 6 months attenuate over time (see also *Sensitivity analyses*).

For each individual, we combined their predicted life expectancy (see *Long-term survival*), with their predicted QOL over time to give their projected lifetime QALY.

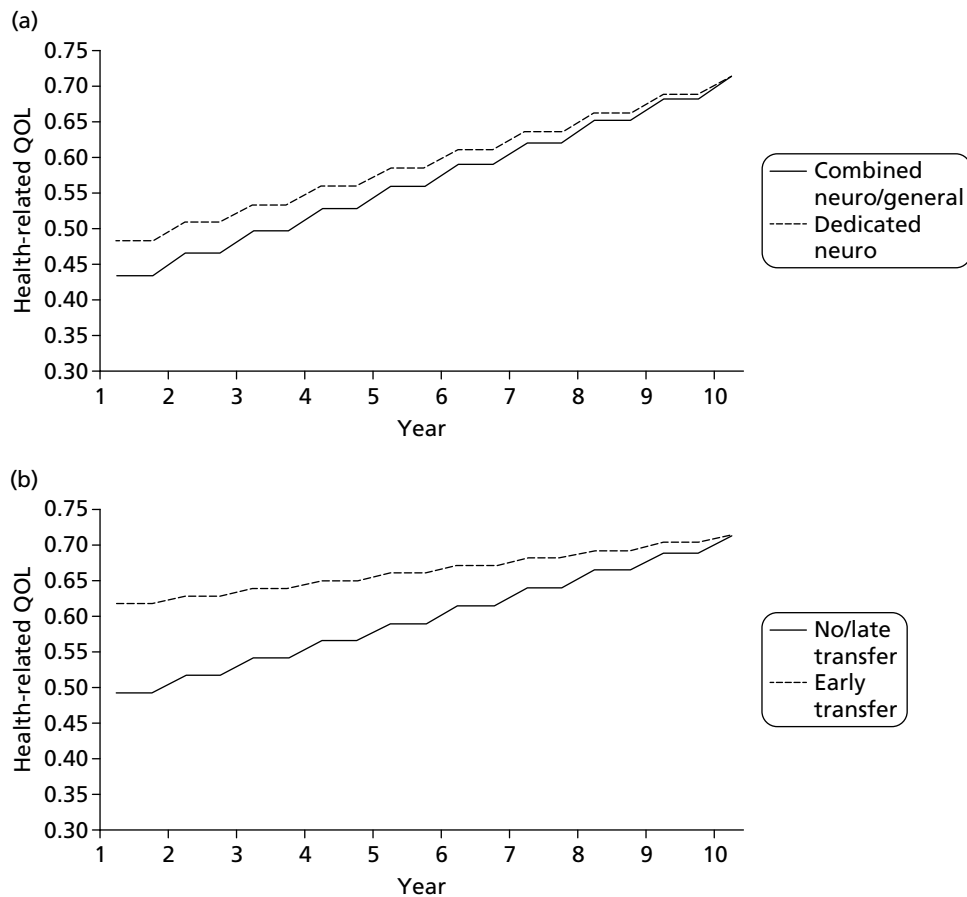


FIGURE 35 Attenuation of relative QOL over time for (a) research objective 1 and (b) research objective 2.

Long-term costs

The lifetime CEA also required costs to be projected for each individual for those surviving beyond 6 months. We reviewed the literature but did not find any relevant information on the relative costs of alternative care locations for patients who were alive 6 months after TBI. We therefore considered long-term costs based on the costs estimated in the RAIN study at 6 months. The costs considered fell into four categories: inpatient costs incurred after admission to critical care, inpatient costs on general wards, outpatient costs and community care costs.

We calculated inpatient costs incurred after critical care admission by recording ongoing admissions and readmissions to critical care units that participated in the RAIN study between 6 and 12 months after the TBI. We also considered admissions to critical care units that did not participate in the RAIN study but were included in the CMP, and to critical care units that participated in the CMP after patient recruitment to the RAIN study ended. The mean costs for each comparator group were then calculated for those patients who survived at least 6 months and were not censored between 6 and 12 months. These mean costs were used to impute mean costs between 6 and 12 months for the censored observations. For each comparator, these mean costs were relatively small (*Tables 50 and 51*). After 1 year it was assumed that there were no further readmissions to critical care that were attributable to the original TBI.

For the other cost categories, we took each individual's inpatient, outpatient and community costs up to 6 months estimated from the Health Services Questionnaires. For each comparator arm we then reported the mean cost between initial hospital discharge and the 6-month time point but only for those surviving up to 6 months. We then applied these 6 monthly costs for each survivor to each subsequent 6-month period up to 3 years. After 3 years we assumed that there were no further costs attributable to the acute TBI (see *Sensitivity analyses*).

TABLE 50 Mean (SD) costs (£) assumed for lifetime CEA for research objective 1

Source of costs	Measurement time frame	Combined neuro/general critical care unit	Dedicated neurocritical care unit	Assumptions: base case (sensitivity analysis)
Critical care admissions ^a	6–12 months	207 (794)	398 (1602)	0 after 12 months
General medical admissions ^b	Discharge to 6 months	1410 (4828)	1478 (5093)	For 3 years (for 5 years)
Outpatient visits ^b	Discharge to 6 months	337 (815)	303 (653)	For 3 years (for 5/10 years)
Community care ^b	Discharge to 6 months	176 (382)	188 (351)	For 3 years (for 5/10 years)

SD, standard deviation.

a Source: RAIN study/CMP database, 12 month survivors.

b Source: Health Services Questionnaire, 6-month survivors.

TABLE 51 Mean (SD) costs (£) assumed for lifetime CEA for research objective 2

Source of costs	Measurement time frame	'No or late' transfer to neuroscience centre	'Early' transfer to neuroscience centre	Assumptions: base case (sensitivity analysis)
Critical care admissions ^a	6–12 months	77 (647)	497 (2106)	0 after 12 months
General medical admissions ^b	Discharge to 6 months	1059 (3459)	1809 (4925)	For 3 years (for 5 years)
Outpatient visits ^b	Discharge to 6 months	211 (359)	300 (472)	For 3 years (for 5/10 years)
Community care ^b	Discharge to 6 months	168 (361)	221 (326)	For 3 years (for 5/10 years)

SD, standard deviation.

a RAIN study/CMP database, 12-month survivors.

b Health Services Questionnaire, 6-month survivors.

Base-case analysis

We reported mean lifetime costs (£) and QALYs per patient for each comparison group by predicting costs and outcomes for each individual as described above. Each incremental effect was reported using the risk factors from the IMPACT Lab risk prediction model to adjust for case mix. For research objective 1, incremental QALYs and costs were estimated with bivariate multilevel models to allow for clustering and any correlation between the end points.^{133,134} For research objective 2, the correlation between the end points was recognised with Seemingly Unrelated Regression.¹⁴²

For each research objective, incremental net monetary benefits (INBs) were estimated by valuing incremental QALYs at a threshold of £20,000 per QALY and subtracting from this the incremental costs. For each lifetime end point (costs, QALYs and INBs) we used bivariate regression analysis to recognise correlation between individuals' costs and QALYs.⁷⁷ Each of these regression models was applied to each of the 25 imputed data sets from the analysis of the 6-month end points (see *Analysis of 6-month costs and consequences*). We again combined the resultant estimates of the incremental effectiveness, costs and cost-effectiveness with Rubin's rules. Hence, CIs for incremental costs, QALYs and INBs again recognised the within- and between-imputation variation. Cost-effectiveness acceptability curves (CEACs) were calculated by reporting the probability that each alternative was the most cost-effective (i.e. had a positive INB) at different levels of willingness to pay for a QALY gain (£0–50,000 per QALY gained). For research objective 2, analyses were repeated for the previously defined subgroups using stratified analyses.

Sensitivity analyses

The base case made the following assumptions that, a priori, were judged to be potentially important: (a) costs attributable to the TBI were only incurred for up to 3 years; (b) the differences in unit costs across care locations represented genuine differences in resource inputs across settings; (c) QOL from the 6-month follow-up applied irrespective of the actual time of follow-up (which ranged from 4 to 10 months after initial presentation); (d) the QOL for survivors at 10 years post TBI was 15% of that of the general population; (e) transfers up to 18 hours following initial hospital presentation were categorised as 'early'; (f) costs were normally distributed; (g) all-cause death rates applied from 6 months following hospital presentation; and (h) the IMPACT Lab risk prediction model was the most appropriate for case mix adjustment. The sensitivity analyses tested whether the base-case results were robust if the following alternative standpoints were taken:

- (a) *Extending the period over which costs were attributable to the acute TBI* To test whether the results were sensitive to the duration over which costs were attributable to the acute TBI, we repeated the analysis assuming that (i) inpatient costs in general medical wards, outpatient and community costs were incurred for 5 years, and (ii) outpatient and community costs continued for up to 10 years.
- (b) *Using the same unit costs across all critical care locations* We assumed that all critical care units in the RAIN study had the unit costs for combined neuro/general critical care units.
- (c) *Limiting use of QOL data from the RAIN study to those patients whose QOL was measured at close to 6 months* To assess the impact of only using QOL information from those patients in the RAIN study followed up between 150 and 220 days, we assumed that those patients who had QOL measured outside these time points had missing 6-month QOL and GOSE questionnaire data. We then applied a multiple imputation model to impute 6-month end points for these patients.
- (d) *Assuming that the QOL decrement observed in RAIN was maintained* Some studies have suggested that the level of residual disability reported at 12 months is maintained for 5–7 years.⁷⁵ Here we assumed that the decrement in QOL reported in the RAIN study at 6 months compared with the general population was maintained over the patients' lifetime.
- (e) *Taking a stricter definition of 'early' transfer for research objective 2* To test whether or not the results for research objective 2 were robust to the arbitrary definition of 'early' transfer, we repeated the analyses defining an 'early' transfer as within 8 hours of hospital presentation and excluding patients transferred between 8 and 18 hours.
- (f) *Assuming that individual patient costs were drawn from a gamma distribution compared with a normal distribution* The assumption that costs are normally distributed may not be plausible,¹⁴³ so here we allow costs to follow a gamma distribution.¹⁴⁴
- (g) *Using a Gompertz survival function* To test whether the results were robust to the choice of extrapolation approach we applied age-stratified death rates using a Gompertz survival function.
- (h) *Undertaking risk adjustment with CRASH CT risk prediction model* We reran the analytical models estimating incremental costs and QALYs using the variables from the CRASH CT model³⁰ rather than the IMPACT Lab model³⁵ to adjust for case mix.

Results of the lifetime cost-effectiveness analysis

Base-case results for research objective 1

The base-case lifetime cost-effectiveness results for the first research objective are shown in *Table 52*. Dedicated neurocritical care units had higher mean lifetime QALYs at small additional mean costs, with an incremental cost-effectiveness ratio (ICER) of approximately £14,000 per QALY. At a ceiling ratio of £20,000 per QALY the INB was positive (approximately £1300). The CEAC suggested that at ceiling ratios of £20,000 to £30,000 per QALY, the probability that dedicated compared with combined neurocritical care units are cost-effective for patients following acute TBI, is around 60% (*Figure 36*).

TABLE 52 Lifetime cost-effectiveness: mean (SD) costs (£), QALYs and incremental net benefit for research objective 1

Parameter	Combined neuro/general critical care unit	Dedicated neurocritical care unit	Incremental effect ^a (95% CI)
Lifetime costs	31,007 (22,471)	34,909 (26,834)	3167 (–464 to 6797)
Lifetime QALYs	9.49 (6.52)	9.99 (6.56)	0.224 (–0.332 to 0.780)
Lifetime cost per QALY			14,128
INB ^b			1316 (–9857 to 12,489)

SD, standard deviation.

a Incremental effects are after case mix adjustment.

b INB can be calculated by following methods guidance and multiplying the mean QALY gain (or loss) by £20,000, and subtracting from this the incremental cost.

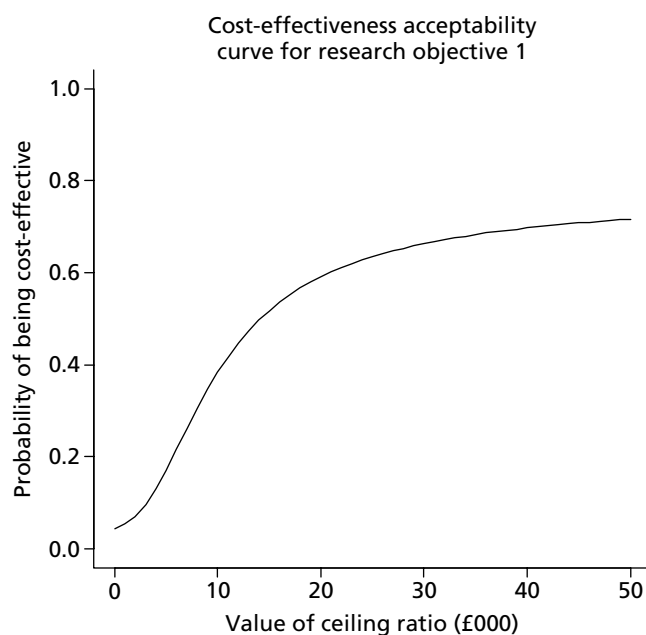


FIGURE 36 Probability that care following acute TBI is more cost-effective in a dedicated neurocritical care unit vs a combined neuro/general critical care unit at alternative levels of willingness to pay for a QALY gain.

Sensitivity analysis results for research objective 1

The sensitivity analysis shows that the base-case finding, that dedicated critical care units were on average more cost-effective, is robust to the alternative approaches taken (Figure 37). Where the higher mean QOL for the dedicated neurocritical compared with the combined units observed in the RAIN study is maintained for the lifetime, the positive incremental QALY and INB in favour of the dedicated units increased. Here, sampling uncertainty is greater than in the base case as this approach recognises more fully individual-level variation in QOL across the sample. However, as for the other scenarios considered, the point estimate of the INB is consistent with that reported in the base case.

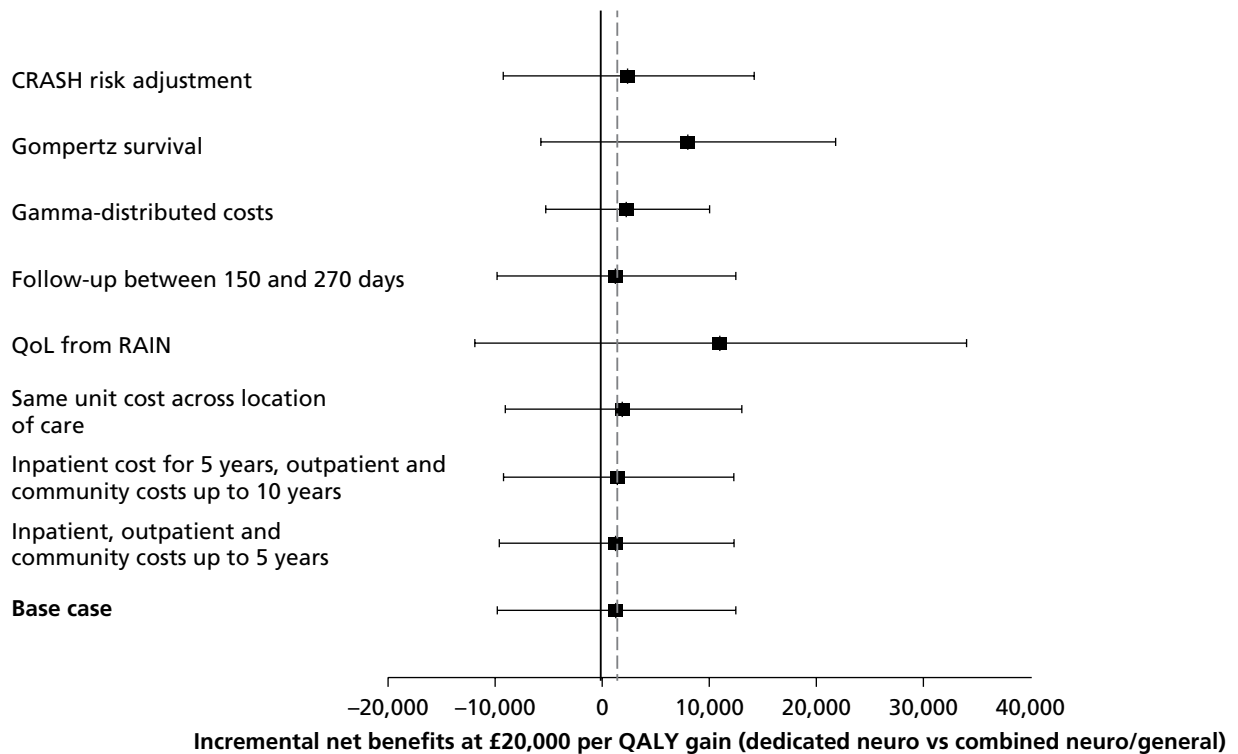


FIGURE 37 Sensitivity analyses reporting mean (95% CI) INB comparing care for dedicated neurocritical care units vs combined neuro/general critical care units. Vertical dashed line indicates incremental net benefits in the base case analysis. Solid vertical line indicates no difference in net monetary benefits between comparator groups.

Base-case results for research objective 2

Table 53 reports the base-case results for the lifetime CEA comparing 'early' transfer compared with 'no or late' transfer to a neuroscience centre.

The results show that, after adjusting for differences in observed baseline characteristics the 'early' transfer group reported higher lifetime QALYs, at an additional cost, with an ICER of approximately £11,000 per QALY. The CEAC suggested that at the standard thresholds of £20,000–30,000 per QALY, the probability that early transfer was cost-effective is close to 100% (Figure 38).

TABLE 53 Lifetime cost-effectiveness: mean (SD) costs (£), QALYs and incremental net benefit for research objective 2

Parameter	'No or late' transfer to neuroscience centre	'Early' transfer to neuroscience centre	Incremental effect ^a (95% CI)
Lifetime costs	16,105 (15,041)	36,422 (28,030)	19,209 (15,234 to 23,184)
Lifetime QALYs	7.19 (6.88)	11.55 (6.43)	1.795 (1.049 to 2.541)
Lifetime cost per QALY			10,704
INB ^b			16,682 (2574 to 30,791)

SD, standard deviation.

a Incremental effects are after case mix adjustment.

b INB can be calculated by following methods guidance and multiplying the mean QALY gain (or loss) by £20,000, and subtracting from this the incremental cost.

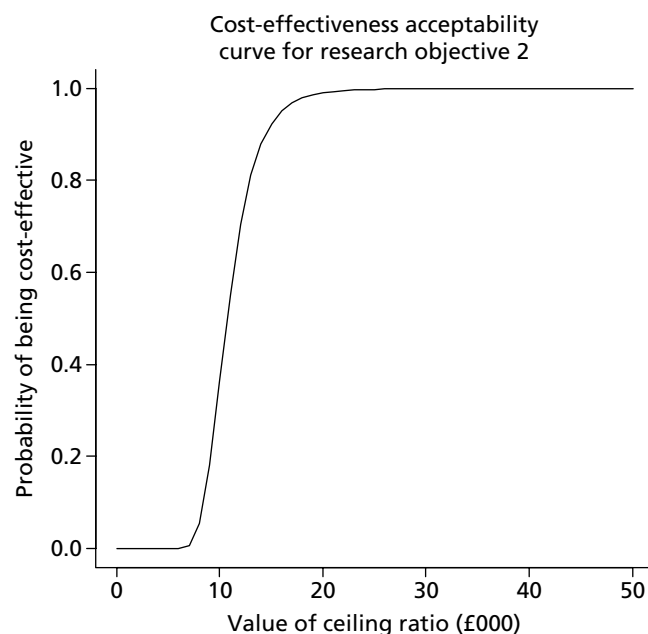


FIGURE 38 Probability that 'early' vs 'no or late' transfer is cost-effective at alternative levels of willingness to pay for a QALY gain.

Sensitivity analysis results for research objective 2

The sensitivity analysis shows that the base-case cost-effectiveness results are relatively robust to the alternative methodological standpoints considered; the INB is broadly similar across scenarios (Figure 39). The additional scenario considered for this objective was to limit the sample for the 'early' transfer group to those patients who were transferred within 8 hours of presentation. Tightening the criteria for 'early' transfer led to slightly higher incremental QALYs and increased the cost-effectiveness of 'early' transfer.

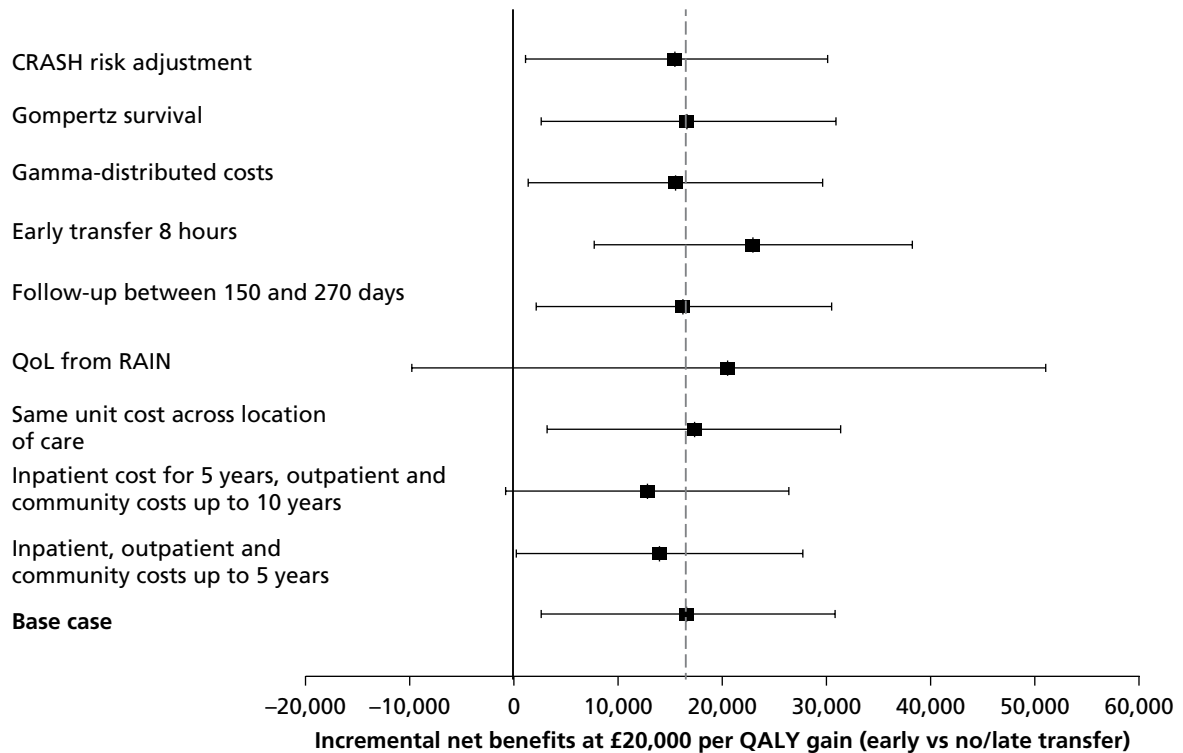


FIGURE 39 Sensitivity analyses reporting mean (95% CI) INB comparing care following TBI for 'early' vs 'no or late' transfer to a neuroscience centre. Vertical dashed line indicates incremental net benefits in the base case analysis. Solid vertical line indicates no difference in net monetary benefits between comparator groups.

Subgroup analysis results for research objective 2

The results for the subgroup analysis according to age group suggest that 'early' transfer has a very low probability of being cost-effective for patients aged >70 years (Figure 40).

The probability that 'early' transfer is cost-effective is lower for the subgroup of patients defined as without major extracranial injury. Here the probability that 'early' transfer is cost-effective is around 60% compared with 100% for the subgroup defined as having a major extracranial injury (Figure 41).

'Early' transfer appears most cost-effective for patients with severe TBI according to the baseline GCS score; the probability that 'early' transfer is relatively cost-effective is between 60% and 80% at ceiling ratios of between £20,000 and £30,000 per QALY (Figure 42).

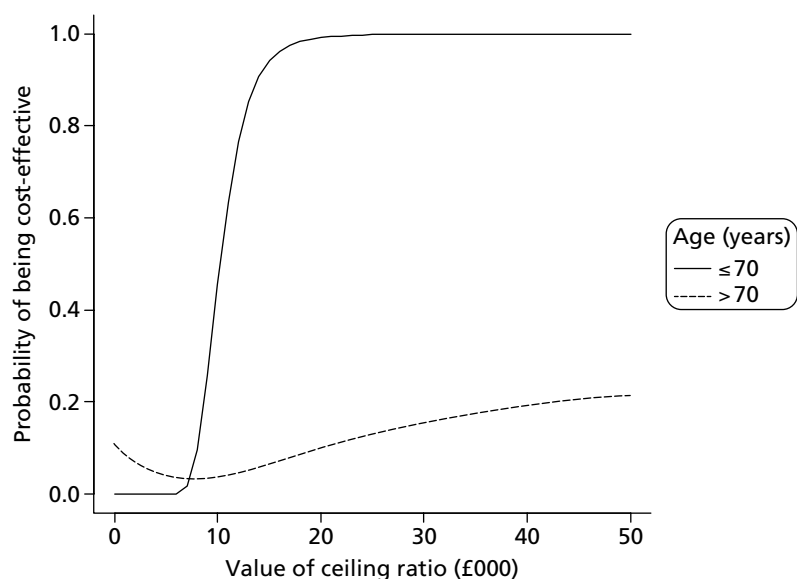


FIGURE 40 Probability that 'early' vs 'no or late' transfer is cost-effective, by age group, at alternative levels of willingness to pay for a QALY gain.

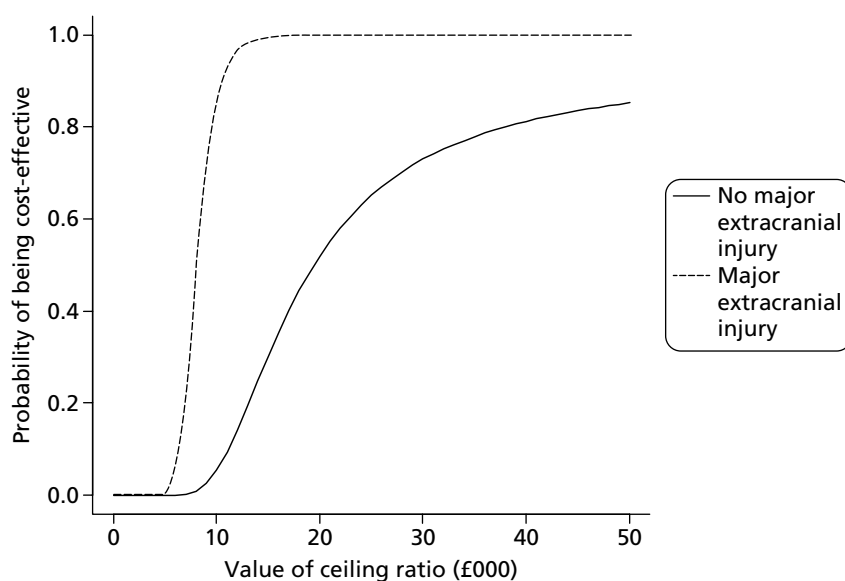


FIGURE 41 Probability that 'early' vs 'no or late' transfer is cost-effective, by presence or absence of major extracranial injury, at alternative levels of willingness to pay for a QALY gain.

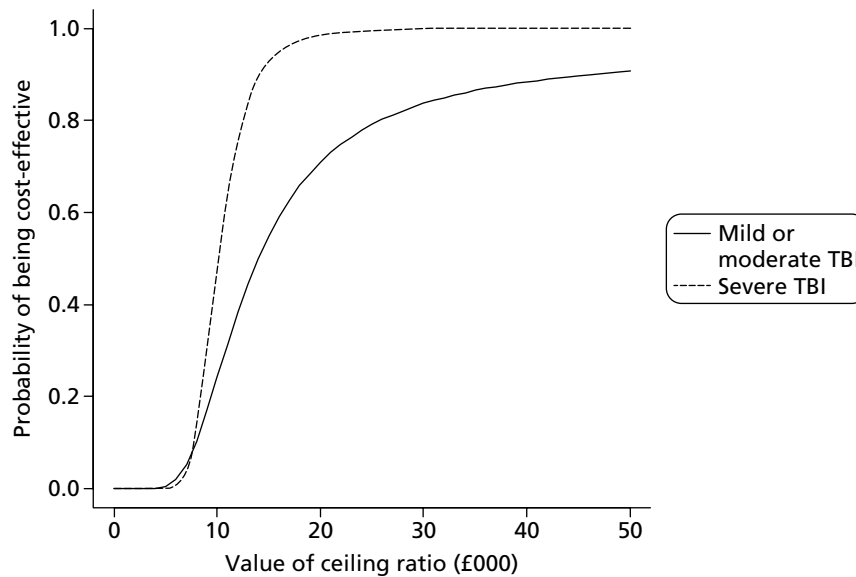


FIGURE 42 Probability that 'early' vs 'no or late' transfer is cost-effective, by baseline level of TBI severity, at alternative levels of willingness to pay for a QALY gain.

Discussion

Principal findings

This aspect of the study had two research objectives. The first of these was to compare the relative costs, consequences and cost-effectiveness of management in a dedicated neurocritical care unit compared with a combined neuro/general critical care unit for critically ill adult patients with acute TBI who present at, or are transferred to, a neuroscience centre. The second objective was to compare the relative costs, consequences and cost-effectiveness of 'early' (within 18 hours of hospital presentation) transfer compared with no transfer or 'late' (after 24 hours) transfer, for critically ill patients with acute TBI who initially present at a non-neuroscience centre and do not require surgery for evacuation of a mass lesion within 24 hours. The main findings are that, following case mix adjustment using the variables from the IMPACT Lab model,³⁵ dedicated neurocritical care units lead to higher mean QOL than combined units but considerable statistical uncertainty surrounds this result; and dedicated units are associated with additional costs. The cost-effectiveness results suggest that it is highly uncertain that dedicated neurocritical care units are more cost-effective than combined units; the probability that dedicated units are more cost-effective is around 60%. For patients presenting at non-neuroscience centres who do not require immediate neurosurgery, we find that, after risk adjustment, early transfer is associated with gains in survival, and improvements in mean QOL for survivors. Although early transfer is also associated with higher costs, these appear to be justified by the relatively large QALY gains, with an incremental cost per QALY of around £11,000. Hence, at the £20,000 per QALY threshold typically used by NICE, the probability that 'early' transfer is cost-effective is close to 100%. Although this finding is robust to all the alternative assumptions considered, the potential role for unobserved confounding must be recognised.

Meaning of the study and comparison with previous studies

This study extends the previous literature on the relative costs and consequences of alternative locations of neurocritical care.^{107–109} The finding that there is, on average, an improvement in risk-adjusted QOL if patients with acute TBI are managed in a dedicated neurocritical care unit rather than a combined neuro/general critical care unit has several possible explanations. First, a dedicated multidisciplinary team may provide more effective and immediate rehabilitation as part of acute care; they may also improve access to specialised neurorehabilitation after discharge from the unit, which can lead to improved outcomes.¹⁴⁵ Second, dedicated units may provide more aggressive monitoring and management, which have been suggested to reduce morbidity.¹⁶ Although concerns have also been raised that more invasive

approaches may increase mortality,¹¹⁶ the RAIN study did not find any differences in mortality at 6 months after TBI between patients managed in dedicated and combined units. A third explanation is that the differences in the mean QOL between the settings may simply reflect chance variation, and indeed the CIs include a difference of zero, and so the null hypothesis that there is no difference in QOL between the settings cannot be rejected. That said, we followed standard methods guidance for CEA, and the lifetime analysis incorporated the non-significant difference in the mean QOL observed at 6 months. We also made the conservative assumption that the gain in mean QOL for the dedicated neurocritical care units attenuated over time. Fourth, the improvement in average QOL for TBI patients managed in dedicated neurocritical care units rather than combined units could reflect unmeasured confounding between the settings. For this comparison, the baseline characteristics of the patients were similar between the groups. However, the mean improvement in QOL in favour of dedicated units is fairly small, and could be overturned if a factor associated with poor prognosis was somewhat more prevalent in the dedicated compared with combined units.

In this context, it is useful to consider the differences in patterns of care between specialist neurocritical care units and neuro/general critical care units that were perceived to exist at the study outset. Then, the published literature suggested there were between-unit differences in the ability to deliver protocol driven critical care according to expert guidelines.¹³ However, since then, the dissemination of perceived best practice (e.g. through NCCNet) may have reduced clinical practice variation among neuroscience centres. This may explain why any differences observed in costs and consequences according to dedicated compared with combined neuro/general critical care are small.

The finding that early transfer to a neuroscience centre for TBI patients appears cost-effective is driven by the gains in survival and QOL observed in the RAIN study at 6 months after hospital presentation. Previous work has found that there are benefits from early transfer for patients who have a space-occupying haematoma with worsening mass effect,¹¹⁵ but this study extends the evidence base to other critically ill patients with TBI. Previous research raised conflicting hypotheses, with some studies suggesting that, for non-surgical patients, early transfer and subsequently more aggressive management may lead to increase risks and costs that outweigh any gains,¹¹⁹ whereas other studies suggested that, delayed transfer may lead to worse outcomes.¹²⁰ In the RAIN study, only a small proportion (6%) of the 'no or late' transfer group had a delayed transfer. Hence, any detrimental effects from delayed transfer would be unlikely to explain the findings, and the main contrast is between an intention to transfer the TBI patient to a neuroscience centre compared with continuing management at a non-neuroscience centre.

The definition of an 'early' transfer is clearly arbitrary, and may differ across contexts. For the RAIN study it was judged important to define the time point at which an 'early' transfer was made according to what was broadly appropriate for the NHS context. Hence, in advance of any analysis, the RAIN Study Steering Group defined an 'early' transfer as being within 18 hours of hospital presentation. This pragmatic choice of cut-off time recognised that there may be several alternative care pathways that patients may take from initial hospital presentation to transfer to a neuroscience centre. The chosen cut-off time also recognised that even if an early decision to transfer is made, there may be local logistical barriers to an immediate transfer. Hence, an 18 hours time point was chosen to be conservative and included all admissions where there was 'an intention' to make a rapid transfer. A potential concern is that the relative cost-effectiveness of an 'early' transfer policy could be highly sensitive to the cut-off point, and indeed previous evidence from trauma networks encourages a 4-hour time window, but for neurosurgical interventions.¹⁰¹ Our sensitivity analysis suggested that applying an 8-hour rather than an 18 hours time window from hospital presentation, reduced the incremental cost per QALY for early transfer from £11,000 (base case) to £9000. Hence, the overall finding that 'early' transfer appears cost-effective is not sensitive to the choice of time threshold.

Our evaluation considered the relative costs and consequences of 'early' transfer according to alternative pre-defined subgroup analyses. The results suggest that 'early' transfer is relatively cost-effective, both for patients defined as having mild or moderate TBI (GCS score of 9–14) as well as for patients with severe TBI

(GCS score of 3–8) at admission. Patients aged >70 years have a higher odds ratio of death in the 'early' transfer group. For this subgroup the most cost-effective strategy appears to be to keep those patients presenting at a non-neuroscience centre within that setting. The effect of 'early' transfer on mortality appears to differ according to whether or not patients have a major extracranial injury. We observed large and significant gains from 'early' transfer in the subgroup of patients with major extracranial injury. However, for patients without a major extracranial injury, the improvements in mortality and QOL following 'early' transfer did not reach statistical significance, and we are, hence, unable to conclude that 'early' transfer of patients in this subgroup is cost-effective.

The relative gains from 'early' transfer in the subgroup with major extracranial injury are somewhat counterintuitive as it might be expected that the risks of physiological derangement associated with transfer would be greater in this subgroup. One possible explanation is that the presence of significant extracranial injury may represent a marker of a disease mechanism or injury type that predisposes patients to develop the pathophysiological derangements (such as severe intracranial hypertension) that most benefit from the specialist critical care available at a neuroscience centre. For example, high-speed RTAs may not only tend to cause more extracranial injury, but also may predispose to traumatic axonal injury and subdural haemorrhage, and enhance the benefits of specialist critical care. Another explanation is that the differential gains may reflect the broad definition of major extracranial injury adopted in the RAIN study. Specifically, patients who would not have met a more rigorous definition of major extracranial injury may have been misclassified as having significant extracranial injury. These patients may be at relatively low risk of death following transfer. This could have been coupled with the retention of unstable patients with truly significant extracranial injury in referring hospitals, which might be undetected by the RAIN study, as we had no metric of the severity of extracranial trauma. The net effect of such misclassification and inadequate severity characterisation may be to overstate the cost-effectiveness of early transfer in those defined as having major extracranial injury and understate the gains in the subgroup defined as not have major extracranial injury. A final explanation is that there may be residual confounding in the major extracranial injury stratum. This subgroup may have included patients who, according to unmeasured prognostic factors, were 'too unstable for transfer'. Further research would ideally record such potential confounders and use them as a basis for excluding such patients from the decision problem. That is, the population of interest should only include patient groups where there is equipoise as to the costs and benefits of 'early' transfer.

Strengths and weaknesses

Lifetime CEAs requires assumptions to be made about the long-term mortality, cost and QOL following alternative interventions – in this case, care locations. As the RAIN study was only designed to measure survival and QOL for all eligible patients up to 6 months, we carefully considered alternative ways of extrapolating from these data to the lifetime. There is no consensus from the literature on the size or the duration of the impact that an acute TBI has on mortality, QOL or costs. More specifically, estimates from the RAIN study provided the strongest basis for projecting the relative effects of alternative care locations on mortality, QOL and health and personal social service costs. Hence, in the base case, information from the RAIN study was used to support assumptions about the long-term prognosis for patients following a TBI, according to the location of critical care.

A potential issue raised by the results of the RAIN study is that few deaths were reported between 30 days and 1 year after hospital presentation; in general, the death rates reported were either similar to or lower than the age-/sex-matched general population. Rather, than just choosing the extrapolation approach that appeared to best fit the observed data, we considered which extrapolation approach would be most plausible according to the previous literature. Other studies have reported excess deaths for patients at 5–7 years following a TBI,^{146–149} whereas a more relevant study that included patients admitted to critical care following TBI observed only one death between 6 and 12 months out of over 400 survivors at 6 months.⁷³ In the base-case analysis we judged that the most reasonable extrapolation approach was to apply all-cause death rates from 6 months onwards. Then, to examine whether the results would be robust to an alternative approach we ran sensitivity analyses in which we applied the most plausible and

conservative of the parametric extrapolations (using the Gompertz function). This sensitivity analysis led to small differences in the ICER – for example, for research objective 2, the base-case ICER reduced marginally from £10,704 to £10,691. More, generally, the sensitivity analyses suggested that the findings did not appear to change substantively when alternative assumptions were made about the time period over which costs attributable to the TBI were applied, or whether the decrement in QOL observed at 6 months was maintained over the lifetime.

Although the RAIN study has added to the literature on alternative care pathways following TBI, it does have some limitations. First, the RAIN study only measured costs and outcomes for up to 6 months; however, the sensitivity analysis suggests that results appear robust to the choice of alternative assumptions made in extrapolating the data over the lifetime. Second, the study followed methodological guidance and took a health and personal social services perspective, and so excluded any broader societal costs, for example from productivity losses or ongoing costs of rehabilitation or nursing home care borne by the patient. Third, about half of patients eligible for follow-up at 6 months were missing data on health service use and QOL, and these data were not missing completely at random. We tackled this issue by using state-of-the-art approaches to handling missing data, in that we used multiple imputation models that respected the hierarchical structure of the data. That said, such approaches assume that the data are missing conditional on baseline factors and other end point and process measures that are observed, hence if missingness is driven by unobserved prognostic factors this could have led to biased estimates.

Finally, the major concern in any such non-randomised comparison is residual confounding. Although our sensitivity analysis that used variables from the CRASH risk prediction model suggested that the results were robust to the choice of risk adjustment method, unobserved confounders may explain the differences in costs and consequences between the comparator groups. Specifically, the comparison of observed baseline characteristics between the 'early' and 'no or late' transfer groups suggests that the patients transferred early were of much less severe case mix according to observed factors. This raises the concern that unobserved confounders associated with worse outcome may also be more prevalent in the 'no or late' transfer group. Further research is required to consider alternative approaches for handling the potential impact of unobserved confounders. Such approaches may include collecting data on additional baseline measures anticipated to be important, considering more flexible risk prediction and matching methods, formal sensitivity analyses that investigate whether the findings are robust to unobserved confounding, and alternative approaches as instrumental variable estimation that purport to handle unobserved confounding.

Summary

In summary, this evaluation finds that for critically ill patients with acute TBI who present at, or are transferred to, a neuroscience centre, management in a dedicated neurocritical care unit rather than a combined neuro/general critical care unit is associated with small gains in QALYs, at additional costs, but it remains highly uncertain whether dedicated units are more cost-effective. Overall, for adult patients with acute TBI who present at a non-neuroscience centre and do not require neurosurgery within 24 hours, 'early' transfer appears more cost-effective than 'no or late' transfer to a neuroscience centre, after risk adjustment. However, further research is required that considers alternative approaches for handling differences in baseline characteristics between settings. Such research could draw on the framework and data presented in the RAIN study to address alternative comparisons, for example contrasting management in high-volume settings with management in low-volume settings, or comparing settings with relatively high proportions of patients with TBI with those with relatively low proportions.

Chapter 7 Conclusions

Implications for health care

The risk prediction models evaluated in the RAIN study demonstrated sufficient statistical performance to support their use in research studies, for example as a basis for stratification in RCTs, but fell some way below the level that would be required to recommend their use to guide individual patient decision-making, particularly where this is likely to be of a life-or-death nature, for example withdrawal of life-sustaining therapy. The lack of calibration, particularly for models predicting unfavourable outcome at 6 months, also currently limits their utility as a tool for communication; however, once recalibrated or improved, and if used appropriately, there may be scope for the use of risk predictions at the individual patient level both to aid communication between health-care providers and in communicating risks to patients and their families.

The RAIN study provides the most robust evidence to date supporting the current NICE clinical guideline that all patients with severe TBI (GCS score of 3–8) would benefit from transfer to a neuroscience centre, regardless of their need for neurosurgery.¹¹ Indeed, the results of the RAIN study suggest that this guideline should potentially also extend to patients with mild or moderate TBI (GCS score of 9–14) requiring critical care. The only exception to this was in patients aged >70 years, for whom transfer was associated with a (non-significant) increased risk of death, and the most cost-effective strategy was management within the hospital at which they originally presented. However, if such a strategy is to be implemented then it will be necessary to review neurocritical care capacity and resourcing at neuroscience centres to ensure sufficient capacity is available to meet the additional workload this would entail.

Although the results of the RAIN study suggest that, within a neuroscience centre, management in a dedicated neurocritical care unit may be cost-effective compared with management in a combined neuro/general critical care unit, there was considerable statistical uncertainty and these results are not sufficiently strong to warrant any major reconfiguration of existing neurocritical care services.

In terms of public health implications, the high proportion of critical care admissions of patients with TBI associated with confirmed or suspected intoxication reported in the RAIN study, and subsequent substantial costs of care, reinforce the importance of public health messages and interventions to attempt to reduce this health-care burden.

Pre-hospital data reported in the RAIN study, particularly regarding neurological dysfunction, were often of poor quality; GCS score was documented for around three-quarters of patients, and pupil reactivity for only half of patients. Better systems are required to improve the routine documentation of pre-hospital data and ensure these form part of the permanent patient record.

Recommendations for future research

Recommendation 1: Further research should be undertaken to explore the potential to improve on the current risk prediction models for acute traumatic brain injury

Although the existing risk prediction models demonstrated acceptable discrimination for mortality at 6 months and, less so, for unfavourable outcome at 6 months, there appears to be considerable scope for further improvement. As a minimum, the risk prediction models for unfavourable outcome all require recalibration for use in a UK critical care setting. However, additional areas that may be explored, either within the RAIN study data set, by data linkage (e.g. with the TARN database), and/or by new prospective

data collection include: consideration of mechanism of injury; incorporation of pupil size in addition to reactivity; addressing the severity and/or site(s) of major extracranial injury; incorporating additional data on the physiological response to injury; and consideration of genetic factors in the host response to injury. Development of new risk prediction models may consider both classical statistical methods and machine learning approaches, such as artificial neural networks. The results of the RAIN study should be revisited in light of any improvements to risk modelling. A new risk prediction model may also be incorporated into a web-based prediction tool, as has been done for the CRASH and IMPACT models, to facilitate its use in practice.

Recommendation 2: Further research is required to consider alternative approaches for handling the potential impact of unobserved confounders on the RAIN study results

In addition to improving the risk prediction models used to underpin the non-randomised comparisons, alternative methodological approaches to complement risk adjustment include matching methods, such as propensity matching or GenMatch.¹⁵⁰ Such approaches would be complementary to the risk adjustment methods described, in that matching could be used to pre-process the RAIN study data before applying risk adjustment.¹⁵¹ To consider unobserved confounding, future research could also be undertaken using instrumental variable estimation¹⁵² and formal sensitivity analyses that investigate whether the findings are robust to unobserved confounding.¹⁵³

Recommendation 3: Options should be explored for continuing to follow up the RAIN study cohort to obtain data on long-term mortality, functional outcomes and quality of life

The RAIN study identified substantial gaps and discordance in the literature regarding the long-term outcomes of patients with acute TBI. The RAIN study database provides a large, representative cohort of critically ill adult patients following acute TBI. Continuing follow-up of the RAIN study cohort would provide much valuable information, both to strengthen the lifetime CEA and to address additional issues, such as accelerated late cognitive decline. However, this would require changes to the current research ethics and governance approvals for the RAIN study and, therefore, these should be addressed urgently.

Recommendation 4: Further research is required to better understand the alternative pathways of care for patients following acute TBI and the impact of these on costs and outcomes

The RAIN study addressed certain specific aspects of the alternative pathways of care for critically ill adult patients following acute TBI and many other aspects remain unexplored. The simple comparison of dedicated neurocritical care units compared with combined neuro/general critical care units may be expanded to model a volume–outcome relationship with the absolute number of patients with TBI admitted or a dose–response relationship with the proportion of admissions that are patients with TBI to any given neurocritical care unit (or neurosciences patients more generally), or to give consideration to variation across centres in the use of treatment protocols or particular interventions. Further analyses for patients presenting outside neuroscience centres may consider the effect of time to transfer on costs and outcomes – both for patients who require neurosurgery (for whom current guidelines often recommend transfer within 4 hours¹⁰¹) and those who do not. An alternative model of service delivery, not currently implemented in most regions of the UK, is bypass of local hospitals to transport patients with significant TBI directly to a neuroscience centre. A feasibility study for a cluster RCT on this intervention – the Head Injury Transportation Straight to Neurosurgery (HITS-NS) trial (www.hta.ac.uk/project/2223.asp) – is currently ongoing.

Recommendation 5: Further research should explore equity of access to post-critical care support for patients following acute traumatic brain injury

Improved access to specialist neurorehabilitation services has been identified as a potential driver of better outcomes reported from neuroscience centres.¹⁴⁵ However, provision of and access to such services varies and questionnaire responses in the RAIN study indicated much dissatisfaction with the continuity of care

and provision of rehabilitation and follow-up after discharge from critical care. Future research should identify the regional and local variation in provision of post-critical care support for patients following acute TBI and consider the impact of such provision on subsequent recovery.

Finally, the RAIN study should inform all future research studies in the neurocritical care of adult patients following acute TBI through provision of reliable data for sample size calculations and exploratory analyses, and informing the choice of risk adjustment methods and data set design.

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Appendix 1 Search strategy for updated systematic review of risk prediction models

Adapted from Perel *et al.*⁹

EMBASE (Ovid interface)

1. traumatic brain injury.mp. or exp traumatic brain injury / or exp *traumatic brain injury / or brain injur\$.ti. or exp craniocerebral trauma /
2. (brain\$ or coma\$ or conscious\$ or cranio\$ or skull\$).ti.
3. 1 and 2
4. case control study.mp. or (cohort study or cohort analysis).mp. or exp follow-up studies / or exp case control study / or follow-up studies.mp. or systematic review.mp. or trial.mp. or randomi\$.mp. or (prognos\$ or predict\$).mp.
5. 3 and 4
6. limit 5 to yr="2006 - 2009"

Appendix 2 Risk Adjustment In Neurocritical care study protocol version 1.4

RAIN

Risk Adjustment In
Neurocritical care

Prospective validation of risk prediction models for adult patients with acute traumatic brain injury to use to evaluate the optimum location and comparative costs of neurocritical care

STUDY PROTOCOL

Version 1.4

1 February 2011

Protocol reference number: ICNARC/02/04/09

REC reference: 09/MRE09/10

NIGB approval number: ECC 2-06(d)/2009

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PROJECT SUMMARY

NHS guidelines recommend that all patients with acute traumatic brain injury (TBI) should be treated within a specialist neuroscience centre. Despite these guidelines, many patients are not. Reasons for this may include initial location post-trauma, bed availability, and local variation partly due to the clinical assessment of the severity of the TBI and likely prognosis for the patient. Although the guidelines are based on the best available research evidence, this research is not sufficiently robust and is only partly based on data from the UK. For example, the question as to what level of severity of TBI warrants transfer (patients may be either not severe enough, or too severe, to warrant transfer) has not been fully addressed. An accurate risk prediction model, validated on a large number of NHS patients with TBI, could be used both to provide sufficient robust evidence to address this issue and to ensure standard clinical assessment of severity.

This project addresses these two objectives: to validate risk models for TBI and to compare the outcomes and costs of care for patients by location of definitive critical care. The project consists of four phases:

Phase I (months 1-4): A systematic review will be used to identify suitable risk models and the data required for their application.

Phase II (months 5-29): A prospective cohort study will be undertaken in neurocritical care units, general critical care units within a neuroscience centre, and general critical care units outside a neuroscience centre to collect data on consecutive adult patients admitted following TBI.

Phase III (months 25-32): The risk models will be validated in the study data, and the strengths and weaknesses of each model will be assessed. If required, the risk models will be recalibrated.

Phase IV (months 19-36): The cost-effectiveness of managing patients with TBI in different critical care settings will be evaluated in an economic model.

RESEARCH OBJECTIVES

The primary aims of this work are to validate risk prediction models for acute TBI in the setting of neurocritical care in the NHS, and to use these models to evaluate the optimum location and comparative costs of neurocritical care in the NHS.

Specific, detailed objectives to achieve these aims are:

1. To identify, from the literature, the existing risk prediction models for acute TBI that are most likely to be applicable to a neurocritical care setting, and identify a full list of variables required in order to be able to calculate these models.
2. To collect complete, valid and reliable data for the variables identified above for consecutive adult admissions with TBI to dedicated neurocritical care units within a neuroscience centre, general critical care units within a neuroscience centre and general critical care units outside a neuroscience centre within the NHS.
3. To undertake a prospective, external validation of existing models for adult patients with TBI admitted to critical care, to identify the strengths and weaknesses of each model, and, if possible, to identify the best model to use for risk adjustment in this setting.
4. To describe and compare adjusted outcomes for adult admissions with TBI from dedicated neurocritical care units within a neuroscience centre, general critical care units within a neuroscience centre and general critical care units outside a neuroscience centre within the NHS.
5. To compare the cost-effectiveness of care for patients with TBI between dedicated neurocritical care units within a neuroscience centre, general critical care units within a neuroscience centre and general critical care units outside a neuroscience centre within the NHS.
6. To make recommendations for policy and practice within the NHS.

BACKGROUND

Risk prediction in adult, general critical care

Risk prediction models have been in established use in adult, general critical care units for over 25 years, since the publication of the original Acute Physiology And Chronic Health Evaluation (APACHE) model in 1981.¹ In the UK, the first large-scale validation of a risk prediction model was the Intensive Care Society's APACHE II Study in Britain and Ireland (1987–1989).^{2;3} This study produced recalibrated coefficients for the APACHE II model, and led, in 1994, to the formation of the Intensive Care National Audit & Research Centre (ICNARC) and the Case Mix Programme, the national comparative audit of patient outcome in adult, general critical care units in England, Wales and Northern Ireland. ICNARC has continued to pioneer developments in risk prediction in the Case Mix Programme, most recently through the validation and recalibration of a number of general risk prediction models⁴ and subsequent development of a new model, the ICNARC model.⁵

Risk prediction in neurocritical care – why not use a general model?

Unlike adult, general critical care, no data are routinely collected in the NHS for risk-adjusted comparison of outcomes from neurocritical care. Consequently, four dedicated neurocritical care units currently participate in the Case Mix Programme. However, there are significant limitations to using models developed and validated for general critical care for patients receiving neurocritical care. Using a spectrum of measures for calibration and discrimination, risk prediction models, successfully developed and validated for adult admissions to general critical care units showed significant departure from perfect calibration in admissions with head injuries to adult, general and dedicated neurocritical care units.⁶ The inclusion and handling of variables of specific prognostic importance in TBI is often poor.⁶ For example, the APACHE II model assumes that any patient that is sedated for the entire first 24 hours in the critical care unit is deemed neurologically normal, which has previously led to suggestions that pre-sedation values of the Glasgow Coma Scale (GCS) should be used for these patients.⁷ The only general model to take any account of changes detected on computed tomography (CT) scan is the Mortality Prediction Model (MPM) II, and the inclusion of CT information in this model is limited to the presence of an intracranial mass effect. Furthermore, all risk prediction models for adult, general

critical care use an outcome of mortality at discharge from acute hospital, which is not considered adequate for neurocritical care where longer term (e.g. six-month) mortality and morbidity are more valid outcomes.⁸

Risk prediction in traumatic brain injury

A number of specific models for TBI exist, however a recent systematic review by the Cochrane Injuries Group found that most models are limited by being based on small samples of patients, having poor methodology, and rarely being validated on external populations.⁹ Of 102 models for TBI identified in the review, only two models by Hukkelhoven et al¹⁰ (one for mortality and one for unfavourable outcome at six months) met minimal criteria of being developed using appropriate methods on data from at least 500 patients in multiple centres, and validated in an external population. These models were based on 2,269 patients with moderate or severe TBI (GCS \leq 12) enrolled in two randomised controlled trials (RCTs), one in the United States and Canada and the other in Europe, Israel and Australia. The model for unfavourable outcome at six months was validated in an observational database of 796 patients with moderate or severe TBI in 55 European countries from the core data survey of the European Brain Injury Consortium (EBIC). The model for six-month mortality was validated in the EBIC data and also in an observational database of 746 patients with non-penetrating severe TBI (GCS \leq 8) in four US centres from the Trauma Coma Data Bank (TCDB).

The authors of the systematic review have also gone on to develop new models for 14-day mortality and unfavourable outcomes at six months aimed at addressing the shortcomings identified in their review.¹¹ Separate models were derived using only 'basic' (demographic and clinical) variables and incorporating additional CT variables, and different models were reported for high-income countries and for low- and middle-income countries. These models were based on 10,008 patients with TBI (GCS \leq 14) in the Corticosteroid Randomisation After Significant Head injury (CRASH) RCT.^{12;13} Of these, 2,482 patients were recruited from high-income countries, including 1,391 patients from 45 centres in the UK. The models were validated in the International Mission for Prognosis And Clinical Trial (IMPACT) database,^{14;15} a database combining data from 9,205 patients with moderate or severe TBI from eight RCTs and three observational studies (including the development and validation data

from the Hukkelhoven models). The authors acknowledge that “further prospective validation in independent cohorts is needed to strengthen the generalisability of the models.”

Further models for TBI have recently been developed using the IMPACT database and validated in CRASH data.¹⁶ Three models of increasing complexity were presented for both mortality and unfavourable outcome at 6 months. The ‘core’ model consists of weights for age, GCS motor score and pupil reactivity. The ‘extended’ model additionally incorporates hypoxia, hypotension, CT classification, traumatic subarachnoid haemorrhage and epidural haematoma. Finally, the ‘lab’ model also incorporates weights for glucose and haemoglobin.

While these recent developments in risk prediction models for TBI indicate potentially significant improvements over previously available models, these models still have limitations regarding their external validity (generalisability) for use in evaluating neurocritical care of patients with TBI in the NHS.¹⁷ All these models were developed using some or all data from RCTs. Even when trials are pragmatic, as was the case for the CRASH trial, using data from an RCT to develop a prognostic model may impact on generalisability through self-selection of centres to participate in the trial, selection of patients enrolled in the trial, and the potential for all patients enrolled in a trial (in both active and control arms) to receive a better standard of care than usual.¹⁸ Much of the data used in developing and validating these models is old. Only the CRASH database contains data from within the last 10 years, with the Hukkelhoven models based on data from the early 1990s, and the IMPACT data collected between 1984 and 1997. Models based on data from multiple sources are limited by differences in definitions of variables, timings of measurements, and inclusion criteria between the different data sources. The CRASH models for high-income countries are clearly of the most direct relevance to UK practice, as over half of all patients recruited to CRASH from high-income countries came from centres in the UK. However, in the CRASH trial as a whole, only 50% of patients were admitted to critical care.¹² This figure may have been higher within the UK but, nonetheless, applying these models to a critical care setting may introduce selection bias and invalidate the model’s accuracy. It is clear that all these models require further prospective validation, and potentially

recalibration, before they can be applied with confidence for research and audit in neurocritical care in the NHS.

Delivery of neurocritical care for traumatic brain injury in the NHS

In the NHS, adult patients with TBI are rarely managed by a single service; they are managed by a succession of services from first contact to definitive critical care, definitive critical care not always being provided in a dedicated neurocritical care unit. Despite guidelines recommending that all patients with severe TBI be treated within a neuroscience centre,¹⁹ many (particularly those without surgical lesions) are currently neither treated in nor transferred to one. A combination of geography, bed availability, local variation and clinical assessment of prognosis can often determine the location of definitive critical care for an adult patient with TBI. The Neurocritical Care Stakeholder Group, established to offer expert advice to Department of Health and Commissioners, indicated in their audit report that, within the NHS, only 67% of beds ring-fenced for neurocritical care were in dedicated neurocritical care units and that neurocritical care unit occupancy rates exceeded 90% (especially for Level 3 beds).²⁰ Most neurocritical care for adult patients with TBI was delivered either in dedicated neurocritical care units (42%) or in general critical care units within a neuroscience centre (35%). However, despite clear guidelines and the progressive regionalisation of neurosurgical care since 1948, 23% of patients with TBI were treated in general critical care units outside a neuroscience centre. Local critical care consultant opinion indicated at least 83% of these patients required transfer to a neuroscience centre. No data were available, or are routinely collected, within the NHS for risk-adjusted comparisons.

Where adult patients with TBI should be optimally treated is an important question for the NHS, both in terms of outcomes and costs. Belief and limited evidence has underpinned the establishment, and continuing expansion, of dedicated, neurocritical care facilities in the UK^{21;22} but no formal evaluation has been undertaken. Recent research has suggested benefit from managing severe head injury in specialist centres,²³ however this is acknowledged to be inconclusive due to lack of adjustment for all known confounders and the use of an unvalidated risk prediction model. It also does not address the issue of general versus specialist critical care units within neuroscience centres. Research is required to determine which location(s) for

neurocritical care are associated with improved outcomes for adult patients with TBI, particularly for those who do not require surgical intervention (external ventricular drain and/or craniotomy/craniectomy), a NICE recommendation for future research in their recently revised guideline.¹⁹ A key issue for policy-makers is whether the additional initial costs of more specialised care are justified by subsequent reductions in morbidity costs and/or improvements in patient outcomes. While conventional RCT methodology may be impractical in this setting, the presence of variation in the way services are organised and delivered can allow them to be compared using observational methods. This is only possible if a valid, reliable, appropriate and accurate risk prediction model exists.

At its inaugural meeting in February 2007, the newly formed Neurocritical Care Network (NCCNet), a network of units and staff providing neurocritical care to patients in both dedicated and general units, identified pursuing funding and establishing a risk prediction model to investigate and evaluate the location and outcomes of care for adult patients with TBI as their first, and top, priority. It was recognised that this aim could only be achieved through validation of an accurate risk prediction model for adult patients with TBI. The Society of British Neurological Surgeons, the Neuroanaesthesia Society of Great Britain and Ireland, the Intensive Care Society and the Association of British Neurologists, through the auspices of the Neurocritical Care Stakeholder Group, are all supportive of this.

STUDY DESIGN

The project will be divided into four phases, detailed below:

- Phase I: Identification of suitable models and definitions of dataset (objective 1; months 1–4)
- Phase II: Data collection and data validation (objective 2; months 5–29)
- Phase III: Validation of risk prediction models (objective 3; months 25–32)
- Phase IV: Evaluation of location of neurocritical care (objectives 4–6; months 19–36)

The flow of patients through the project is shown in Appendix 1.

Phase I: Identification of suitable models and definitions of dataset

The systematic review of prognostic models for TBI⁹ will be updated by applying the same search strategy as used by the Cochrane Injuries Group (Appendix 2) to identify any new publications since 2005 meeting the inclusion criteria. Experts in the field, including the CRASH and IMPACT groups, will be approached to identify additional work, published or ongoing, that may be of relevance. We already have established research links with individuals from both the CRASH and IMPACT investigators. The RAIN Steering Group will review the models identified from the published systematic review and updated searches to select the most appropriate models for validation in the neurocritical care setting. These are likely to include the CRASH models for high-income countries, and the Hukkelhoven and IMPACT models.

Once the models have been selected, a list of all data fields required to calculate the models will be extracted from the published descriptions of the models, together with definitions, where available, clarified with the model authors where necessary. Precise rules and definitions for the collection of these fields will be laid out in a data collection manual, and the technical requirements will be defined in a detailed dataset specification.

Phase II: Data collection and data validation

All 208 units participating in the Case Mix Programme and all critical care units in neuroscience centres (identified through NCCNet) will be invited to participate. For the units already participating in the Case Mix Programme, RAIN data collection will be piggybacked onto routine data collection. Neurocritical care units not participating may choose to join the Case Mix Programme, but this will not be a requirement of the study and RAIN data collection may be piggybacked onto routine data collection for the Department of Health mandated Critical Care Minimum Data Set (CCMDS).

Abstraction of prospective administrative and clinical data will be undertaken by data collectors trained to collect a dedicated core dataset for RAIN according to precise rules and definitions. Depending on local infrastructure, additional data will be collected either by web-based data entry or by modification of existing Case Mix Programme Version 3.0-compliant software to incorporate the additional fields required. As for Case Mix Programme data, all the additional data will undergo extensive validation, both locally and centrally, for completeness, illogicalities and inconsistencies.

Detailed data will be collected on consecutive patients with acute TBI (see: *Planned inclusion/exclusion criteria*). However, administrative and CCMDS data will be collected for all admissions to all participating units. Critical care data on TBI patients will be placed in the context of all TBI, including those not admitted to critical care, using data from the Trauma Audit & Research Network (TARN).

Data collected will cover administrative (e.g. NHS Number, dates and times) and socio-demographic factors and factors from pre-hospital, and the first and subsequent hospitals as well as factors at arrival to the definitive location for neurocritical care. Data items collected will include all those required to calculate the models selected from Phase I, including: mechanism, severity and timing of TBI and other injuries; CT scan classification (first/last prior to admission); components of and total GCS (pre-intubation/at admission); pupil reactions (first/worst); and physiological parameters (first/worst).

The experience from the CRASH trial suggests that adequate quality CT data can be obtained through reports generated at contributing centres, and this will be our

primary method by which imaging data will be recorded. However, we are aware that there have been concerns expressed in the past about the validity of such peripheral reporting in clinical trials. It is essential to know whether the data obtained from local reporting of CT images is adequate for accurate risk adjustment, since this will have significant implications on the practicability of using any particular predictive model. Data collectors will therefore be asked to record appropriate identifiers to allow us to access CT scans for review at a later date if required, and will be requested not to discard or destroy the films or digital imaging data for these patients until 5 years after entry into the study. We will obtain copies of the admission CT scans in a randomly selected sample of 10% of patients, weighted to include more patients from outside neuroscience centres, where patient throughput will be lower. Data collectors will be requested to send anonymised admission CT scans to Addenbrookes Hospital (Cambridge University Hospitals NHS Foundation Trust) using the Image Exchange Portal, where possible. These will be centrally viewed and assessed by Neurosciences Critical Care Consultants at Addenbrookes Hospital, and the reports generated will be compared to the corresponding submitted data to identify any systematic discrepancies. If significant discrepancies are identified, we will arrange systematic collection and central reporting of CT scans from all patients, subject to additional funding.

Data on six-month outcomes (see: *Proposed outcome measures*) will be collected centrally, using methods based on those employed in the CRASH and RESCUEicp RCTs. Prior to contacting patients, death registrations will be checked against the NHS Central Register using the 'list cleaning' service offered by the Medical Research Information Service to minimise any impact from contacting families of patients that have recently died. In addition, each patient's General Practitioner and, where available, neurocritical care follow-up service will be contacted to establish the last known status of the patient immediately prior to sending the questionnaire. Patients will be sent two questionnaires by post, which can be completed by the patient or by a relative, friend or carer. The first evaluates the Glasgow Outcome Scale (Extended) and EuroQol (EQ-5D) measures. Use of a postal questionnaire to collect the Glasgow Outcome Scale (Extended) has been found to have high reliability.²⁴ Recent consensus recommendations have suggested that patients with TBI should be followed up using generic as well as disease-specific measures of health-related quality of life.²⁵ The use

of EQ-5D will enable the calculation of quality-adjusted life years (QALYs) as the best global measure of cost-effectiveness. The second questionnaire examines which health services the patient has used since leaving hospital. This will be used to evaluate the costs for caring for patients. Strategies proven to improve response rates to postal questionnaires will be employed to ensure maximum possible response.²⁶ Non-respondents will be followed up with further postal questionnaires and finally by telephone interview, using a standardised telephone interview schedule. Using this approach, CRASH and RESCUEicp achieved 93% and 92% follow-up of head-injured patients at six months, respectively. In the minority of cases where the patient or their consultee does not respond, medical teams involved in the care of the patient, e.g., neurocritical care follow-up, will be contacted to determine the primary outcome measure for the study, whether the patient had a unfavourable or unfavourable outcome. As after a head injury patients can show dramatic personality changes and a variety of cognitive deficits, it is important that we have data covering these outcomes in order to determine why some patients make a better recovery than others.

Phase III: Validation of risk prediction models

The risk prediction models selected in Phase I will be calculated from the raw data collected in Phase II using standardised computer algorithms. Any ambiguities in the precise methods for each model will be clarified by contacting the model authors.

Models will be validated with measures of discrimination (the ability to separate survivors from non-survivors or those with favourable outcomes from those with unfavourable outcomes), calibration (the degree of agreement between the observed and predicted outcomes) and overall goodness-of-fit. If the calibration is poor, then the best model(s) will be recalibrated to provide revised coefficients specific to UK neurocritical care.

Assessment of loss to follow-up

Available data from the critical care and hospital stay will be used to compare the characteristics of responders and non-responders and to determine whether response varies by: age; severity of injury; physiological response to injury; organ monitoring

and support received in critical care; duration of stay in critical care and in hospital; destination following discharge from acute hospital; and predicted 6-month outcome.

Provided all variables associated with missing response are included in the risk model, complete case analysis of data with missing responses is statistically valid, under the assumption that data are missing at random given the observed covariates. We therefore do not propose using statistical methods for missing data such as multiple imputation unless: (1) the observed loss to follow up is considerably higher than anticipated; or (2) factors relating to processes of care (e.g. duration of critical care stay), and therefore excluded from the risk models, are found to be independent predictors of missing response.

Validation methods

Risk prediction models will be validated for discrimination, calibration and goodness-of-fit, based on methods used previously for the validation of risk prediction models for adult, general critical care^{4;5} and paediatric critical care,²⁷ and for evaluating general risk prediction models in patients with TBI.⁶

Discrimination will be assessed by the concordance (or *c* index),²⁸ equivalent to the area under the ROC curve.²⁹ The *c* index can be interpreted as the probability that a randomly selected patient with an unfavourable outcome will have a higher risk prediction than a randomly selected patient with a favourable outcome. The *c* index will be compared between different models (for the same outcome) using the non-parametric method of DeLong, DeLong and Clarke-Pearson.³⁰

Calibration will be assessed graphically by dividing the patients into ten groups at the deciles of the predicted risk and plotting the observed outcome against the expected outcome in these groups. The Hosmer-Lemeshow test will be used to test the hypothesis of perfect calibration,³¹ however we note that this test is highly sensitive to sample size³² and so a significant test result alone will not be taken to indicate 'poor' calibration. In addition, Cox's calibration regression will be used to relate the observed to the predicted outcomes.³³ Cox's calibration regression fits the model *true log odds* = $\alpha + \beta$ *predicted log odds* using logistic regression. If the model is perfectly calibrated, then $\alpha = 0$ and $\beta = 1$, i.e. *true log odds* = *predicted log odds*.

Overall model fit will be assessed with Brier's score,³⁴ the mean squared error between the observed and predicted outcomes.

Selection of optimum model(s)

The strengths and weaknesses of each model will be assessed, including consideration of factors such as the purpose(s) for which each model is suited, the choice of outcome variable, and the ease of data collection in addition to statistical performance.

Phase IV: Evaluation of location of neurocritical care

The existence of a validated risk prediction model for patients with TBI admitted to critical care will enable both non-randomised, observational research and audit in neurocritical care. The first research question that we aim to address using this model, forming part of this proposal, is:

“What is the clinical- and cost-effectiveness of managing of TBI in a dedicated neurocritical care unit within a neurosciences centre compared with a general critical care unit within a neurosciences centre or a general critical care unit not in a neurosciences centre?”

The cost analysis will take a health and personal social services perspective.³⁵ For each admission, each day during the hospital stay will be assigned to the appropriate healthcare resource group (HRG) using daily organ support data recorded for the CCMDS. For each admission, the costs per hospital bed-day for each HRG during critical care and for each bed-day for general medical care will be taken from the Payment by Results database using trust-specific unit costs.³⁶ These unit costs will be combined with each patient's resource use data to estimate the total cost of each initial hospital admission. Information will be collected on hospital readmissions and use of community health services post discharge at six-month follow-up. The study will report the total six-month hospital and community health service costs for each case. The analysis will compare mean costs across the groups recognising any differences in either the resource use or unit costs.

The effect of location of neurocritical care on six-month mortality and unfavourable outcomes will be evaluated using multilevel logistic regression models. Using a

multilevel model (MLM) enables adjustment for both patient-level factors, including the selected risk prediction model, and unit-level factors, such as the volume of cases, the size of the unit and, most importantly, the type (specialist or general) and location (neuroscience centre or not) of the unit.

The cost-effectiveness analysis will use the six-month EQ-5D, health services questionnaire and survival data to report six-month QALYs (risk adjusted). These endpoints will be valued at different levels of willingness to pay for a QALY gain to report risk-adjusted incremental net benefits of each location of neurocritical care. The cost and cost-effectiveness analysis will also use MLMs^{37;38} to report risk-adjusted incremental costs and cost-effectiveness according to the unit type and location. The bivariate cost-effectiveness models will recognise the correlation between costs and outcomes. The MLMs will also acknowledge the notoriously skewed nature of cost data by allowing the individual error terms to have non-normal distributions (e.g. gamma or log-normal). Finally, a cost-effectiveness model will extrapolate from the risk-adjusted estimates of six-month cost and outcomes to project risk-adjusted cost-effectiveness over the lifetime. An extensive sensitivity analysis will investigate whether the conclusions about the relative cost-effectiveness of care delivery are robust to assumptions made about model specification

Planned inclusion/exclusion criteria

All adult patients (aged 16 years or over) admitted to participating critical care units following TBI, and with a GCS<15 following resuscitation, will be identified by the treating clinicians. Confirmation reports will be sent to all units to ensure that every eligible admission is identified and, where possible, data will be validated against the Case Mix Programme database and CCMDS returns.

Any patient initially thought to have TBI, and entered into the RAIN database, but subsequently found to have a different cause for their neurological impairment (e.g. cerebrovascular accident) will be excluded from analyses.

When evaluating each risk prediction model, additional exclusion criteria will be applied to match the definitions of the population used to develop the model. For example, any model derived on only patients with severe head injury (GCS≤8) or

moderate to severe head injury ($GCS \leq 12$) would be validated on the equivalent population.

Planned interventions

None.

Proposed outcome measures

The primary outcomes will be mortality and unfavourable outcome, defined as death, vegetative state or severe disability on Glasgow Outcome Scale (Extended), at six months following admission to critical care. The duration of follow-up has been restricted to six months for the purpose of this study as this is the primary endpoint of the existing risk prediction models, and to limit costs, however discussions with service user representatives indicate that longer-term outcomes may be important. Further list cleaning against the NHS Central Register will enable ongoing follow-up of mortality beyond six months. Secondary outcome measures will include six-month and lifetime costs and cost-effectiveness.

Proposed sample size

We performed a simulation study to assess the power to detect a difference in the c index (area under the receiver operating characteristic, ROC, curve) between two different risk prediction models applied to the same population. Simulations were based on the following assumptions: the rate of unfavourable outcomes in the population will be 40% (based on the observed rate of unfavourable outcomes in high income countries in the CRASH trial,¹¹ and consistent with the results of a regional audit in East Anglia³⁹); statistical tests will be based on a two-sided p -value of $P=0.05$; we wish to be able to detect, with 80% power, a 10% relative difference in c index from the value of 0.83 observed for the CRASH model in the development sample.¹¹ A total of 17,500 datasets were simulated at different sample sizes using a binormal model⁴⁰ and the empirical power was assessed at each sample size as the proportion of datasets in which a statistically significant difference was detected (see Appendix 3).

Based on these simulations, a sample size of 3100 patients will be required for model validation. To allow for 8% loss to follow-up (based on the observed follow-up rates from CRASH and RESCUEicp), we will aim to recruit 3400 patients.

Using data from the Case Mix Programme Database, we anticipate the rate of admission of patients with TBI to be approximately 8 per unit per month for neurocritical care units, 6 per unit per month for general critical care units within a neuroscience centre, and 0.5 per unit per month for general critical care units outside a neuroscience centre. We will therefore aim to recruit at least 12 neurocritical care units, 13 general critical care units within neuroscience centres and 30 general critical care units outside neuroscience centres to complete recruitment within 18 months.

ORGANISATION

Study Steering Group

The Study Steering Group (SSG) responsibilities are to approve the study protocol and any amendments, to monitor and supervise the study towards its research objectives, to review relevant information from external sources, and to resolve problems identified by the Study Management Group. Face-to-face meetings will be held at regular intervals determined by need and not less than once a year, with routine business conducted by telephone, email and post. The SSG membership is shown below and terms of reference are given in Appendix 4. Representatives of the funder (NIHR HTA Programme) and the sponsor (ICNARC) will be invited to observe at SSG meetings.

Membership

<i>Prof Monty Mythen (Independent Chair)</i>	Director, Centre for Anaesthesia UCL
<i>Dr David Harrison (Chief Investigator)</i>	Statistician, Intensive Care National Audit & Research Centre (ICNARC)
<i>Dr Richard Grieve (Co-investigator)</i>	Lecturer in Health Economics, London School of Hygiene and Tropical Medicine
<i>Mr Peter Hutchinson (Co-investigator)</i>	Senior Surgical Scientist, Academic Neurosurgery Unit, University of Cambridge
<i>Dr Fiona Lecky (Co-investigator)</i>	Research Director, Trauma Audit and Research Network (TARN)
<i>Prof David Menon (Co-investigator)</i>	Professor of Anaesthesia, University of Cambridge
<i>Prof Kathy Rowan (Co-investigator)</i>	Director, ICNARC
<i>Dr Martin Smith (Co-investigator)</i>	Consultant in Neuroanaesthesia and Neurocritical care, The National Hospital for Neurology and Neurosurgery

<i>Dr Patrick Yeoman (Co-investigator)</i>	Consultant in Adult Critical Care, Queen's Medical Centre, Nottingham
<i>Mr Jonathan Hyam (Independent)</i>	Clinical Research Registrar in Neurosurgery, Nuffield Department of Surgery, Oxford
<i>Dr Ian Tweedie (Independent)</i>	Consultant Anaesthetist, The Walton Centre for Neurosurgery, Liverpool
<i>Miss Julie Bridgewater (Service User Representative)</i>	Headway UK, London
<i>Dr Gita Prabhu (Study Coordinator)</i>	RAIN Study Coordinator, ICNARC
<i>(Research Fellow)</i>	To be appointed

Study Management Group

The day-to-day running of the trial will be overseen by a Study Management Group consisting of the Chief Investigator and ICNARC-based Co-investigators, the Study Coordinator and the Research Fellow.

Data monitoring

As the study does not involve any change to usual care for patients, an independent Data Monitoring Committee (DMC) will not be required. The SSG will oversee those responsibilities usually delegated to a DMC and these have been incorporated into the terms of reference (Appendix 4).

Service user involvement

Through *Headway UK*, the national charity for people affected by brain injury, and their local Groups and Branches, a representative will be identified to take a full and active role in the SSG, promoting the patient's perspective. All involvement of service users in RAIN will follow the guidelines and recommendations for good practice from INVOLVE (<http://www.invo.org.uk>).

Research Governance

RAIN will be managed according to the Medical Research Council's Guidelines for Good Research Practice (http://www.mrc.ac.uk/pdf-good_research_practice.pdf), Guidelines for Good Clinical Practice in Clinical Trials (<http://www.mrc.ac.uk/pdf-ctg.pdf>) and Procedure for Inquiring into Allegations of Scientific Misconduct (http://www.mrc.ac.uk/pdf-mis_con.pdf). ICNARC has developed its own policies and procedures based on these MRC guidelines, which are adhered to for all research activities at ICNARC. In addition, ICNARC has contractual confidentiality agreements with all members of staff. Policies regarding alleged scientific misconduct and breach of confidentiality are reinforced by disciplinary procedures.

Ethical arrangements

Informed consent for inclusion in RAIN will be sought at the six-month follow-up. A patient information sheet and consent form will be included with the questionnaire. This will include contact details for the RAIN investigators, and the patient will be encouraged to contact the RAIN team if they have any questions. For patients unable to give their informed consent due to the nature of their head injury, the consent form may be completed by a consultee (as defined under the Mental Capacity Act 2005 and in compliance with the Adults with Incapacity (Scotland) Act 2000). Any patient, or the consultee, may withdraw their informed consent at any time without being required to give a reason. Applications to an NHS Research Ethics Committee and to the Patient Information Advisory Group (PIAG) under Section 251 of the NHS Act 2006 to hold patient identifiable data prior to consent are pending. The Case Mix Programme already holds PIAG approval to hold limited identifiable data (date of birth, sex, postcode, NHS number) – approval number PIAG 2-10(f)/2005.

Funding

Research costs for this study have been met by a grant from the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme (project reference 07/37/29). There are no NHS support costs or excess treatment costs associated with this research as there is no deviation from usual care.

Indemnity

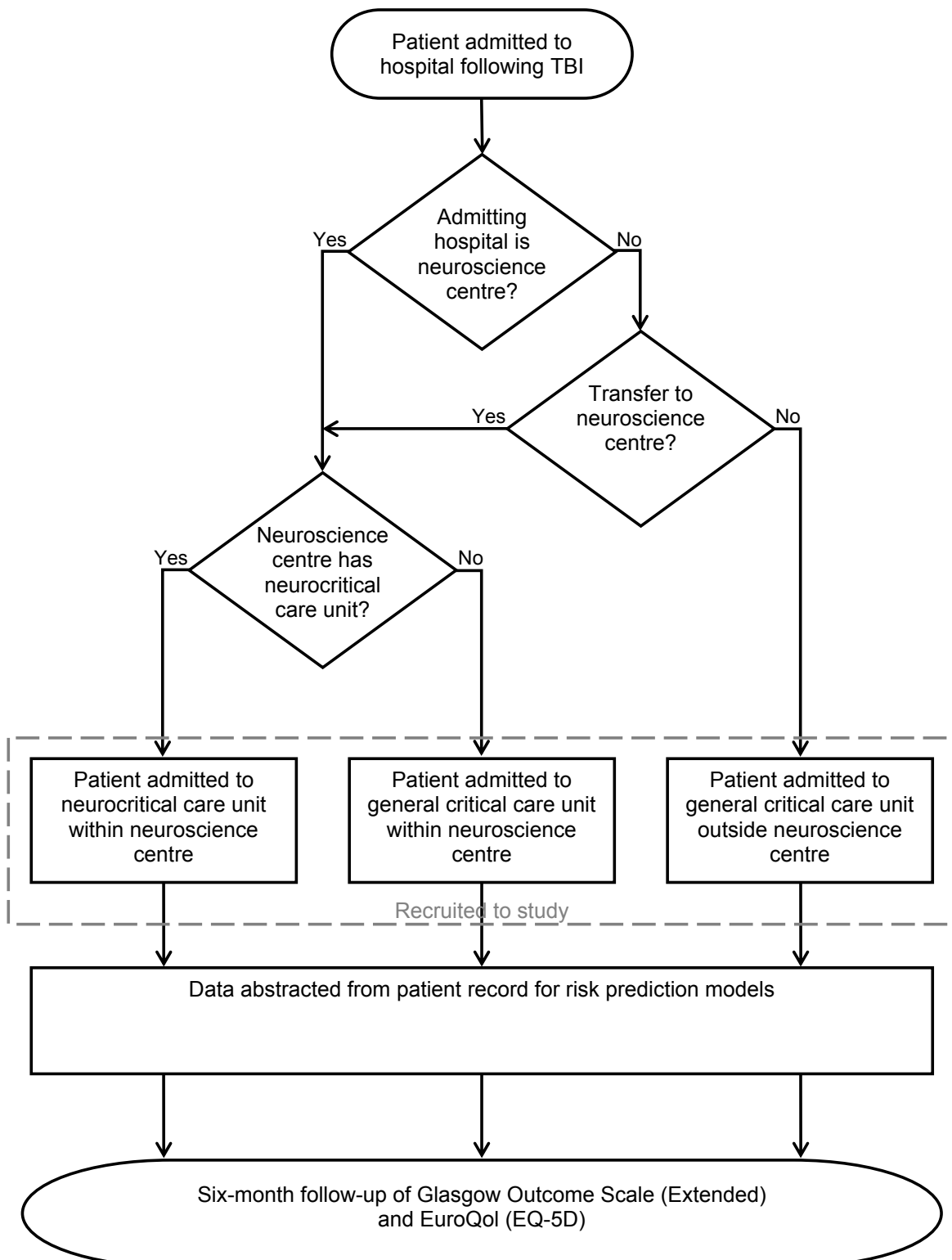
ICNARC holds professional liability insurance (certificate number A05305/0808, Markel International Insurance Co Ltd) to meet the potential legal liability of the sponsor for harm to participants arising from the management of the research. Indemnity to meet the potential legal liability of the sponsor and employers for harm to participants arising from the design of the research is provided by the NHS indemnity scheme. Indemnity to meet the potential legal liability of investigators/collaborators for harm to participants arising from the conduct of the research is provided by the NHS indemnity scheme or through professional indemnity.

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Appendix 1. Flow diagram



Appendix 2. Search strategy for prognostic models

Adapted from <http://www.biomedcentral.com/content/supplementary/1472-6947-6-38-S1.doc>

Medline (PUBMED version) 2006 onwards

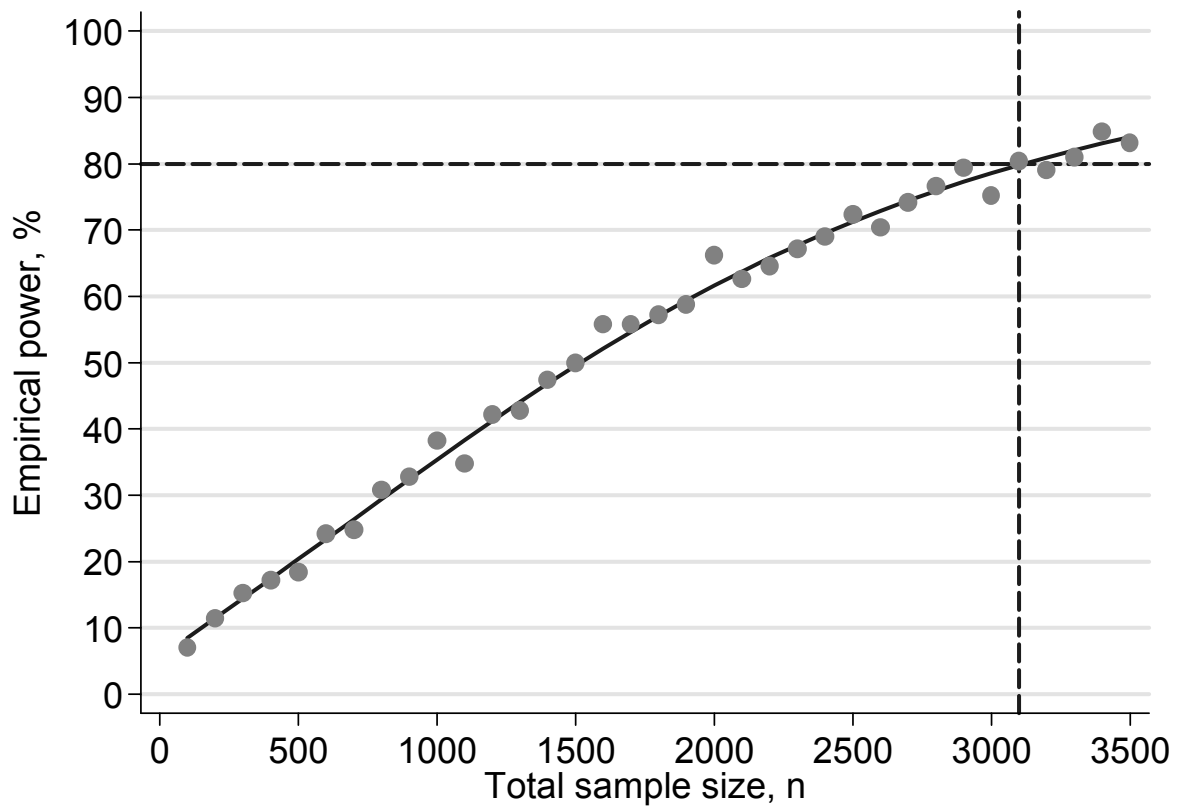
(("brain injuries"[MH] OR "craniocerebral trauma"[MH]) OR ("brain injuries"[TI] OR "traumatic brain injury"[TI] OR "brain trauma"[TI])) AND (brain[TI] OR brain*[TI] OR coma[TI] OR conscious*[TI] OR cranio*[TI] OR skull[TI]) AND ("Case-Control Studies"[MH] OR "Cohort Studies"[MH] OR "Follow-Up Studies"[MH] OR prognos*[TI] OR predict*[TI])

Embase (OVID version) 2006 onwards

1. traumatic brain injury.mp. or exp traumatic brain injury/ or exp *traumatic brain injury/ or brain injur\$.ti.
2. (brain or brain\$ or coma\$ or conscious\$ or cranio\$ or skull\$).ti.
3. 1 and 2
4. (prognos\$ or predict\$).mp.
5. 3 and 4
6. case control study.mp. or (cohort study or cohort analysis).mp. or exp follow up/ or exp case control study/ or follow up.mp. or systematic review.mp. or trial.mp. or randomi\$.mp.
7. 5 and 6

Appendix 3. Simulation study to assess sample size requirements

Empirical power to detect a difference in discrimination (c index 0.83 versus 0.80) in 17,500 simulated datasets at different sample sizes.



Appendix 4. Terms of Reference for the Study Steering Group

The role of the Study Steering Group (SSG) is to provide overall supervision for RAIN on behalf of the funder (HTA) and sponsor (ICNARC) and to ensure that the study is conducted to the rigorous standards set out in the MRC Guidelines for Good Clinical Practice. The day-to-day management of the study is the responsibility of the Investigators, and the Chief Investigator will set up a separate Study Management Group (SMG) to assist with this function.

- The SSG should approve the protocol and study documentation in a timely manner.
- In particular, the SSG should concentrate on progress of the study, adherence to the protocol, patient safety and consideration of new information of relevance to the research question.
- In the absence of a Data Monitoring Committee, the SSG should monitor the study data, and data emerging from other related studies, and consider whether there are any ethical or safety reasons why the study should not continue.
- The safety, rights and well being of the study participants are the most important consideration and should prevail over the interests of science and society.
- The SSG should provide advice, through its chair, to the Chief Investigator, the sponsor, and the funder, on all appropriate aspects of the study. Specifically, the SSG will:
 - Monitor recruitment rates and encourage the SMG to develop strategies to deal with any recruitment problems.
 - Monitor data completeness and comment on strategies from SMG to encourage satisfactory completion in the future.
 - Monitor follow-up rates and review strategies from SMG to deal with problems including sites that deviate from the protocol.
 - Approve any amendments to the protocol, where appropriate.
 - Approve any proposals by the SMG concerning any change to the design of the study.

Risk Adjustment In Neurocritical care Protocol Version 1.4

- Oversee the timely reporting of study results.
 - Approve and comment on the statistical analysis plan.
 - Approve and comment on the publication policy.
 - Approve and comment on the main study manuscript.
 - Approve and comment on any abstracts and presentations of results during the running of the study
 - Approve external or early internal requests for release of data or subsets of data.
- Membership of the SSG should be limited and include an independent Chair and at least two other independent members. The Investigators and the study staff are ex-officio.
 - Representatives of the sponsor and the HTA should be invited to all SSG meetings.
 - Responsibility for calling and organising the SSG meetings lies with the Chief Investigator. The SSG should meet at least annually, although there may be periods when more frequent meetings are necessary.
 - There may be occasions when the sponsor or the HTA will wish to organise and administer these meetings in exceptional circumstances.
 - The SSG will provide evidence to support any requests for extensions, including that all practicable steps have been taken to achieve targets.
 - The SSG will maintain confidentiality of all study information that is not already in the public domain.

Appendix 3 Risk Adjustment In Neurocritical care study data definitions



Data Collection Manual

Version 1.6

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General rules for data collection

Inclusion criteria

- all adult patients (aged 16 years or over) admitted to participating critical care units following acute TBI, and with a GCS<15 following resuscitation
- TBI is a brain injury resulting from mechanical trauma, whether or not a patient has a TBI is a clinical decision
- include both suspected and known TBI

Data

Data are collected on all consecutive admissions meeting the inclusion criteria. Data are collected for readmissions as for a new admission. Data are collected for the same time period for all admissions - there are no exclusions and no exceptions.

Data that are measured and/or recorded in any part of the permanent written or electronic patient record are acceptable, for example, data from charts, case notes or any medium that comprises the permanent patient record. This is based on the assumption that all clinically important information is documented. Such an assumption is the only realistic standardisation possible at this time.

In specifying and defining the dataset, judgements have had to be made. It is recognised that such judgements will not comply with all opinions. It should, be emphasised, however, that it is better to comply with rules and definitions which you deem incorrect than to substitute personal rules and/or definitions.

Missing data

If data are not available or are missing, then no value should be entered. It is not the aim of the RAIN Study to encourage unnecessary investigations.

Do not enter guesses or fabricated data. Where data are missing, these fields should be left blank. The value "0" must not be used to indicate missing numeric data.

Data collection time periods

▪ Patient:

- these fields specify patient details for six-month follow-up and data linkage to the Case Mix Programme, where relevant
-

▪ TBI pre-hospital:

- data are collected for the period prior to attendance at the first hospital for this TBI
-

▪ Source:

- data describing the route to the critical care unit are collected for the period from attendance at the first hospital for this TBI to admission to your unit
-

▪ TBI at hospital:

- data are collected for the period from attendance at the first hospital for this TBI to discharge from hospital/death
 - values required are those first recorded – first recorded is defined as within 12 hours of attendance at the first hospital for this TBI
-

▪ First CT:

- the results of the first CT scan performed after attendance at the first hospital for this TBI
-

▪ Outcome:

- data are collected for the period from admission to your unit to discharge from hospital/death
-

▪ GP:

- these fields specify information on the GP with whom this admission to your unit is registered

Additional information

[CMP: Text]

Field:	Additional information
--------	------------------------

Number of data items:	One
Options:	None

Definition for collection:

- any additional information considered relevant to this admission
 - text data entered in this field may provide extra information about data entered elsewhere for a specific field in the dataset or may provide extra information on the admission which is not collected as part of the dataset
 - entry of data in the text field is not compulsory
 - no identifiers (patient, nurse, doctor, unit, hospital) should be included in text data entered into this field
 - information entered in the text field may derive from any time period during data collection
 - space for comments is limited, please restrict comments to clarification of data entered and comments to facilitate data validation
-

Justification

Despite best intentions and endeavours, no dataset can be completely comprehensive and unequivocally objective, information provided in this field will enable the dataset to be improved over time

Basal cisterns

Field: Basal cisterns

Number of data items: One
Options: Absent
Compressed
Present

Definition for collection:

- specifies the appearance of the basal cisterns on the first CT scan following the TBI
 - first CT scan is defined as the first CT scan performed after attendance at the first hospital for this TBI
 - where there is more than one CT scan performed, the first CT scan must be used for data abstraction; if transferred, the first CT scan may be performed at a subsequent hospital
 - Absent indicates the basal cisterns are not visible on the first CT scan
 - Compressed indicates the basal cisterns appear compressed on the first CT scan
 - Present indicates the basal cisterns appear normal on the first CT scan
-

Justification

Required for risk prediction models

Brainstem pathology present

Field: Brainstem pathology present

Number of data items: One
Options: Yes
No

Definition for collection:

- specifies if a brainstem pathology was present on the first CT scan following the TBI
 - first CT scan is defined as the first CT scan performed after attendance at the first hospital for this TBI
 - where there is more than one CT scan performed, the first CT scan must be used for data abstraction; if transferred, the first CT scan may be performed at a subsequent hospital
 - Yes indicates brainstem pathology; this includes evidence of brainstem compression, contusion, haemorrhage or ischaemia
 - No indicates no brainstem pathology
-

Justification

Required for risk prediction models

Cardiovascular support days

Fields: Basic cardiovascular support days
Advanced cardiovascular support days

Number of data items: Two
Units of measurement: Calendar days

Definition for collection:

- specifies the number of calendar days during which the admission received any basic or advanced cardiovascular support whilst on your unit
- a calendar day is defined as any complete calendar day (00:00-23:59) or part thereof, e.g. a patient admitted on 1 January 2006 at 23:45 and discharged on 3 January 2006 at 00:10 would be recorded as having received three calendar days of care
- record 1, 2, 3 etc for one, two, three etc calendar days; record 998 for 998 or more calendar days; record 999 for support occurring but number of days not known
- Advanced Cardiovascular - indicated by one or more of the following:
 - admissions receiving multiple intravenous and/or rhythm controlling drugs (e.g. inotropes, nitrates etc.) (of which, at least one must be vasoactive) when used simultaneously to support or control arterial pressure, cardiac output or organ/tissue perfusion
 - admissions receiving critical care after resuscitation following cardiac arrest (not usually valid for longer than one calendar day after day of resuscitation)
 - admissions receiving continuous observation of cardiac output and other indices (e.g. with a pulmonary artery catheter, lithium dilution, pulse contour analyses, oesophageal doppler etc.)
 - admissions with an intra aortic balloon pump in place and other assist devices
 - admissions with a temporary cardiac pacemaker (valid each day while connected for therapeutic reasons to a functioning external pacemaker unit)
- Basic Cardiovascular - indicated by:
 - admissions with a CVP (central venous pressure) receiving monitoring or for central venous access to deliver titrated fluids to treat hypovolaemia
 - admissions with an arterial line receiving monitoring of arterial pressure and/or sampling of arterial blood
 - admissions receiving a single, intravenous, vasoactive drug to support or control arterial pressure, cardiac output or organ perfusion
 - admissions receiving single/multiple intravenous rhythm controlling drug(s) to control cardiac arrhythmias

- admissions receiving non-invasive measurement of cardiac output and other indices (e.g. with echocardiography, thoracic impedance etc.)
 - Note: If advanced and basic cardiovascular monitoring and support occur simultaneously, then only advanced cardiovascular monitoring and support should be recorded.
-

Justification

Required to describe organs supported

Cause of TBI

Field: Cause of TBI

Number of data items: One
Options: Road traffic accident
Fall
Assault
Other
Unknown

Definition for collection:

- specifies the documented cause of TBI
 - Road traffic accident is when the TBI is caused by any accident involving a vehicle (e.g. car, motorcycle, bike, etc.) to a driver, passenger, pedestrian etc.
 - Fall is when the TBI is caused by a fall from any height and includes tripping or slipping (e.g. on pavement etc.)
 - Assault is when the TBI is caused by a violent physical attack
 - Other is when the TBI cause is known but none of the above
 - Unknown is when the cause is not known
-

Justification

Required for description of TBI

Classification of surgery

Field: Classification of surgery

Number of data items: One
Options: e**M**ergency
Urgent
Scheduled
e**L**ective

Definition for collection:

- specifies whether the admission, whose Direct source was Theatre & recovery, was following emergency, urgent, scheduled or elective surgery
 - surgery is defined as undergoing all or part of a surgical procedure or anaesthesia for a surgical procedure in an operating theatre or an anaesthetic room
 - e**M**ergency surgery is defined as immediate surgery, where resuscitation (stabilisation and physiological optimisation) is simultaneous with surgical treatment and where surgery normally takes place within minutes of decision to operate
 - **U**rgent surgery is defined as surgery as soon as possible after resuscitation (stabilisation and physiological optimisation) and normally takes place within hours of decision to operate
 - **S**cheduled surgery is defined as early surgery but not immediately life-saving and normally takes place within days of decision to operate
 - e**L**ective surgery is defined as surgery at a time to suit both patient and surgeon and is booked in advance of routine admission to hospital
 - elective surgery initially postponed can subsequently become emergency, urgent or scheduled surgery
 - organ harvesting is not considered surgery
-

Justification

Required to describe admission with TBI

CMP Admission number (or SICCSAG key)

Field: CMP Admission number (or SICCSAG key)

Number of data items: One
Units of measurement: None

Definition for collection:

- unique number assigned to each admission to your unit
 - value should be automatically generated by your CMP software application as each admission record is created and should be inputted on the RAIN secure, web-based data entry system
 - use the SICCSAG key generated by your Wardwatcher software application in Scotland
 - admission to your unit is defined as the physical admission and the recording of that admission to a bed in your unit
-

Justification

Provides data linkage with CMP

Contact telephone number

Field: Contact telephone number

Number of data items: One

Definition for collection:

- specifies the contact telephone number, including area code for this admission to your unit
-

Justification

Required for the six-month follow-up of admission with TBI

Date of birth

Fields: Date of birth
 Date of birth estimated

Number of data items: Two
Units of measurement: Date dd/mm/yyyy
Options: Date of birth estimated – Yes or No

Definition for collection:

- specifies date of birth for this admission to your unit
 - if date of birth is unobtainable, then use judgement to estimate year of birth and record as 1 January of estimated year i.e. 01/01/yyyy
 - if 01/01/yyyy, then record whether date of birth is estimated or not
-

Justification

Required for risk prediction models

Date of discharge from critical care

[CMP: Date of ultimate discharge from ICU/HDU]

Field: Date of discharge from critical care

Number of data items: One
Units of measurement: Date dd/mm/yyyy

Definition for collection:

- specifies the latest documented date on which this admission was ultimately discharged from adult critical care, the critical care having been continuous since discharge from your unit
 - ultimate discharge is defined as the physical discharge and recording of that discharge from a bed in another critical care unit
 - a critical care unit is defined as an ICU or a combined ICU/HDU or an HDU
 - where more than one date of ultimate discharge from critical care is documented, the latest documented date is recorded
 - the date is not necessarily the date of discharge from the unit to which the admission was transferred from your unit
-

Justification

Required to describe admission with TBI

Date of discharge from your hospital

Field: Date of discharge from your hospital

Number of data items: One
Units of measurement: Date dd/mm/yyyy

Definition for collection:

- specifies the date of discharge of the admission from your hospital
 - date of discharge from your hospital is the latest documented date of the admission being physically within an acute in-patient bed in your hospital or the date of death in your hospital
 - discharge from your hospital is defined as the physical discharge and recording of that discharge from an acute in-patient bed in your hospital
 - where more than one date of discharge from your hospital is documented, the latest documented date is recorded
-

Justification

Required to describe admission with TBI

Date/Time of admission to your unit

Fields: Date of admission to your unit
 Time of admission to your unit

Number of data items: Two
Units of measurement: Date dd/mm/yyyy
 Time hh:mm

Definition for collection:

- specifies the date and time of admission to your unit
 - admission to your unit is defined as the physical admission and recording of that admission to a bed in your unit
 - date of admission to your unit is the earliest documented date of the admission being physically in a bed in your unit
 - time of admission to your unit may be the time first charted if not documented as earlier in the case notes (twenty-four hour clock)
 - where more than one date/time of admission to your unit is documented, the earliest documented date/time is recorded
-

Justification

Required to describe admission with TBI

Date/Time of original attendance at/admission to acute hospital

Field: Date of original attendance at/admission to acute hospital
Time of original attendance at/admission to acute hospital

Number of data items: Two
Units of measurement: Date dd/mm/yyyy
Time hh:mm

Definition for collection:

- specifies the earliest documented date and time on which this admission originally attended or was admitted to the first acute hospital for the current period of continuous in-patient treatment
 - an acute hospital is defined as any hospital providing a range of acute hospital services to diagnose, treat and care for seriously ill or injured patients; some acute hospitals may provide only specialist services while others will provide general services
 - attendance at acute hospital is defined as the physical attendance and recording of that attendance in another acute hospital, not your hospital i.e. not the hospital housing your unit
 - admission to acute hospital is defined as the physical admission and recording of that admission to an acute in-patient bed in another acute hospital, not your hospital i.e. not the hospital housing your unit
 - the date is not necessarily the date of attendance at/admission to the acute hospital from which the admission has been transferred to your unit
 - where more than one date of original attendance at/admission to at an acute hospital is documented, the earliest documented date is recorded
-

Justification

Required to describe admission with TBI

Date/Time of TBI

Fields: Date of TBI
 Date of TBI estimated
 Time of TBI
 Time of TBI estimated

Number of data items: Four
Units of measurement: Date dd/mm/yyyy
 Time hh:mm
Options: Date of TBI estimated – **Yes** or **No**
 Time of TBI estimated – **Yes** or **No**

Definition for collection:

- specifies the date and time of TBI
 - date of TBI is the documented date of TBI
 - time of TBI is the documented time of TBI
 - if the date and/or time of TBI is imprecise, then use judgement to estimate the date and/or time and record whether the date and/or time of TBI is estimated
-

Justification

Required for risk prediction models

Dependency prior to admission to acute hospital

Field: Dependency prior to admission to acute hospital

Number of data items: One
 Options: Able to live without assistance in daily activities
 miNor assistance with some daily activities
 maJor assistance with majority of/all daily activities
Total assistance with all daily activities

Definition for collection:

- specifies what the admission could do before the TBI
 - assess as best description for the dependency of this admission in the two weeks prior to admission to acute hospital and prior to the TBI, i.e. “usual” dependency
 - Able – receives no assistance with daily activities
 - miNor – receives some assistance with some daily activities
 - maJor – receives considerable assistance with majority of/all daily activities
 - Total – receives total assistance with all daily activities
 - assistance means personal assistance
 - daily activities include bathing, dressing, going to the toilet, moving in/out of bed/chair, continence and eating
 - it is recognised that these data are subjective, the important distinction is between total independence (able to live without assistance in daily activities), some level of dependence (minor/major limitations) and total dependence (total assistance with all daily activities) – the difference between minor or major assistance in daily activities is difficult to standardise and this lack of specificity is acknowledged
-

Justification

Required to describe admission with TBI

Dermatological support days

Field: Dermatological support days

Number of data items: One
 Units of measurement: Calendar days

Definition for collection:

- specifies the number of calendar days during which the admission received any dermatological support whilst on your unit
 - a calendar day is defined as any complete calendar day (00:00-23:59) or part thereof, e.g. a patient admitted on 1 January 2006 at 23:45 and discharged on 3 January 2006 at 00:10 would be recorded as having received three calendar days of care
 - record 1, 2, 3 etc for one, two, three etc calendar days; record 998 for 998 or more calendar days; record 999 for support occurring but number of days not known
 - Dermatological – indicated by one or more of the following:
 - admissions with major (e.g. greater than 30% body surface area affected) skin rashes, exfoliation or burns
 - admissions receiving complex dressings (e.g. major – greater than 30% body surface area affected – skin dressings, open abdomen, vacuum dressings or large – multiple limb or limb and head – trauma dressings)
-

Justification

Required to describe organs supported

Destination post-discharge

[CMP: Destination post-discharge from your hospital]

Field: Destination post-discharge

Number of data items: One
Options: other **A**cute hospital
n**O**n-acute hospital
Not in hospital

Definition for collection:

- specifies the destination to which the admission was directly transferred post-discharge from your hospital, the hospital housing your unit
- other **A**cute hospital, one that does not house your unit, is defined as another hospital (can be in the same or a different NHS Trust) that provides a range of acute hospital services to diagnose, treat and care for seriously ill or injured patients; some acute hospitals may provide only specialist services while others will provide general services
- n**O**n-acute hospital is defined as another hospital (can be in the same or a different NHS Trust) that provides a range of short or long-term non-acute services
- **N**ot in hospital is defined as discharge to a location that is no longer within a hospital

Justification

Required to describe admission with TBI

Diagnosis of TBI confirmed

Field: Diagnosis of TBI confirmed

Number of data items: One
Options: Yes
No

Definition for collection:

- specifies whether the admission had a TBI
 - TBI is defined as a brain injury resulting from mechanical trauma
-

Justification

Required for risk prediction models

Direct source

[CMP: Location (in)]

 Field: Direct source

 Number of data items: One
 Options:

- Ward
- oBstetrics area
- other interMediate care area
- Paediatric ICU/HDU
- level 3 bed in adult ICU or ICU/HDU
- level 2 bed in adult ICU or ICU/HDU
- adult HDU
- Theatre & recovery
- accident & Emergency
- Recovery only
- imaGing department
- Specialist treatment area
- Clinic
- Not in hospital

Definition for collection:

- specifies the direct source from which this admission was admitted directly to your unit
- Ward is a ward in the hospital
- oBstetrics area is a delivery suite, labour ward or obstetrics ward in the hospital
- other interMediate care area is a CCU or other area in the hospital where the level of care is greater than the normal ward but is not an ICU or combined ICU/HDU or HDU (use text box to specify where)
- Paediatric ICU/HDU is a paediatric ICU or combined ICU/HDU or HDU in the hospital
- level 3 bed in adult ICU or ICU/HDU is a level 3 bed in either an adult ICU or a combined ICU/HDU in the hospital
- level 2 bed in adult ICU or ICU/HDU is a level 2 bed in either an adult ICU or a combined ICU/HDU in the hospital
- adult HDU is an adult HDU or equivalent step-up/step-down unit in the hospital, where the Critical Care Minimum Data Set (CCMDS) is collected
- Theatre and recovery is a theatre in the hospital, the admission having undergone all or part of a surgical procedure or anaesthesia for a surgical procedure
- accident & Emergency is an accident & emergency department in the hospital

- **R**ecovery only is a recovery room used as a temporary critical care facility
 - **i**ma**G**ing department is an X-ray, CT, MRI, PET or other department in the hospital dedicated to providing diagnostic imaging or interventional radiology
 - **S**pecialist treatment area includes endoscopy and catheter suites in the hospital
 - **C**linic is defined as an out-patient or other clinic in the hospital
 - **N**ot in hospital is defined as not in hospital
-

Justification

Required to describe admission with TBI

Discharge location[CMP: Hospital housing location (out)]

Field: Discharge location

Number of data items: One
Options: Same hospital
other Acute hospital
non-acute hospital

Definition for collection:

- specifies the hospital housing the destination to which this admission was discharged from your unit
 - Same hospital is defined as the hospital that houses your unit
 - other Acute hospital, one that does not house your unit, is defined as another hospital (can be in the same or a different NHS Trust) that provides a range of acute hospital services to diagnose, treat and care for seriously ill or injured patients; some acute hospitals may provide only specialist services while others will provide general services
 - non-acute hospital is defined as another hospital (can be in the same or a different NHS Trust) that provides a range of short or long-term non-acute services
-

Justification

Required to describe admission with TBI

Discharged to

[CMP: Location (out)]

 Field: Discharged to

 Number of data items: One
 Options: **W**ard
 o**B**stetrics area
 other inter**M**ediate care area
 Recovery only
 Paediatric ICU/HDU
 level 3 bed in adult **I**CU or ICU/HDU
 level 2 bed in adult ICU or ICU/**H**DU
 adult **H**DU
 Not in hospital

Definition for collection:

- specifies the destination to which this admission was discharged from your unit
 - **W**ard is a ward in the hospital
 - o**B**stetrics area is a delivery suite, labour ward or obstetrics ward in the hospital
 - other inter**M**ediate care area is a CCU or other area where the level of care is greater than the normal ward but is not an ICU or combined ICU/HDU or HDU (use text box to specify where)
 - **R**ecovery only is a recovery room used as a temporary critical care facility
 - **P**aediatric ICU/HDU is a paediatric ICU or ICU/HDU or HDU in the hospital
 - level 3 bed in adult **I**CU or ICU/HDU is a level 3 bed in either an adult ICU or a combined ICU/HDU in the hospital
 - level 2 bed in adult ICU or ICU/**H**DU is a level 2 bed in either an adult ICU or a combined ICU/HDU in the hospital
 - adult **H**DU is an adult HDU or equivalent step-up/step-down unit in the hospital, where the Critical Care Minimum Data Set (CCMDS) is collected
 - **N**ot in hospital is defined as discharge to a location that is no longer within a hospital
-

Justification

Required to describe admission with TBI

Evacuation of haematoma

Fields: Evacuation of haematoma
Evacuation of haematoma date
Evacuation of haematoma time

Number of data items: Three
Units of measurement: Date dd/mm/yyyy
Time hh:mm
Options: Evacuation of haematoma – Yes or No

Definition for collection:

- specifies if there was surgical evacuation of any haematoma after the first CT scan
 - first CT scan is defined as the first CT scan performed after attendance at the first hospital for this TBI
 - Yes indicates surgical evacuation of a haematoma after the first CT scan
 - No indicates no surgical evacuation of a haematoma after the first CT scan
 - evacuation of haematoma date is the documented date the surgery commenced
 - evacuation of haematoma time is the documented time the surgery commenced
-

Justification

Required for risk prediction models

Expected outcome at six months

Field: Expected outcome at six months

Number of data items: One
 Options: Good recovery
Moderate disability
Severe disability
Persistent vegetative state
Death

Definition for collection:

- specifies the expected outcome of the admission six months following the TBI
 - expected outcome should be determined at unit discharge by the consultant responsible for care at the point of discharge
 - assess as best description for the expected outcome for this admission six months following the TBI (i.e. the predicted recovery)
 - Good recovery – expected resumption of normal life or expected resumption of normal life despite minor deficits
 - Moderate disability – expected disabled but independent (i.e. might work in a sheltered setting etc.)
 - Severe disability – expected conscious but disabled, dependent for daily support
 - Persistent vegetative state – expected minimal responsiveness
 - Death – expected non-survival
-

Justification

Required to describe admission with TBI

Fall height

Field: Fall height

Number of data items: One
Options: Less than or equal to two metres
Greater than two metres
Unknown height

Definition for collection:

- specifies height from which admission fell and includes tripping or slipping (e.g. on pavement etc.) and falling from a building, a high wall or bridge
 - where fall was Less than or equal to two metres; the height may be documented as explicit text allowing assessment of the height of fall
 - where fall was Greater than two metres; the height may be documented as explicit text allowing assessment of the height of fall
 - Unknown is when fall height not known
-

Justification

Required for description of TBI

First CT scan

Fields: First CT scan available
 First CT scan date
 First CT scan time
 First CT scan Radiology Number

Number of data items: Four
 Units of measurement: Date dd/mm/yyyy
 Time hh:mm
 Options: First CT scan available – Yes or No

Definition for collection:

- specifies the availability, date, time and Radiology Number of the first CT scan following the TBI
 - first CT scan is defined as the first CT scan performed after attendance at the first hospital for this TBI
 - where there is more than one CT scan performed, the first CT scan must be used for data abstraction; if transferred, the first CT scan may be performed at a subsequent hospital
 - if the first CT scan is available then indicate Yes, if not available then indicate No
 - first CT scan date is the documented date of the first CT scan
 - first CT scan time is the documented time of the first CT scan
 - first CT scan Radiology Number is the documented Radiology Number of the first CT scan
-

Justification

Required for risk prediction models

First CT scan assessed by/on

Fields: First CT scan assessed by – specialty
 First CT scan assessed by – grade
 Date first CT scan assessed

Number of data items: Three
 Units of measurement: Date dd/mm/yyyy
 Options: First CT scan assessed by – specialty – **C**ritical care,
Neurocritical care, **E**mergency medicine, **A**naesthesia,
 Ne**U**roanaesthesia, **R**adiology, neur**O**radiology, **S**urgery or
 neurosur**G**ery
 First CT scan assessed by – grade – **C**onsultant,
Specialist registrar or **O**ther clinician

Definition for collection:

- specifies who assessed the first CT scan, following the TBI, for the RAIN Study and when this CT scan was assessed
 - first CT scan is defined as the first CT scan performed after attendance at the first hospital for this TBI
 - where there is more than one CT scan performed, the first CT scan must be used for data abstraction; if transferred, the first CT scan may be performed at a subsequent hospital
 - first CT scan assessed by – specialty, specifies the area of expertise of the clinician that provided the data to input for the CT results for this admission
 - first CT scan assessed by – grade, specifies the grade of the clinician that provided the data to input for the CT results for this admission
 - date first CT scan assessed provides the date on which the clinician that provided the data to input for the CT results for this admission
-

Justification

Required for risk prediction models

First CT scan result

Field: First CT scan result

Number of data items: One
Options: Abnormal
Normal

Definition for collection:

- specifies whether the first CT scan result following the TBI was normal or abnormal
 - first CT scan is defined as the first CT scan performed after attendance at the first hospital for this TBI
 - where there is more than one CT scan performed, the first CT scan must be used for data abstraction; if transferred, the first CT scan may be performed at a subsequent hospital
 - Abnormal indicates the first CT scan result showed one or more abnormalities
 - Normal indicates the first CT scan result showed no abnormality
-

Justification

Acts as a filter field for CT findings

First recorded at hospital activated partial thromboplastin time (APTT) (ratio)

Fields: First recorded at hospital APTT (ratio)
or
First recorded at hospital APTT missing

Number of data items: Two
Units of measurement: Ratio
Options: First recorded at hospital APTT missing – Yes or No

Definition for collection:

- specifies the first APTT from blood sampled within 12 hours of attendance at the first hospital for this TBI
 - the APTT must be documented
 - the first APTT may not be measured and recorded at the first hospital and, if transferred, may be measured and recorded at a subsequent hospital within 12 hours of attendance at first hospital for this TBI
 - laboratory results only - laboratory results are defined as results of tests performed either in the departments of Clinical Chemistry or Haematology or in the near-patient testing/point of care testing laboratories with formal quality control programmes in operation
 - record the APTT as a ratio
 - if no blood was sampled for APTT measurement within 12 hours of being at or in the first hospital, then record APTT as missing
-

Justification

Required for risk prediction models

First recorded at hospital activated partial thromboplastin time (APTT) (seconds)

Fields: First recorded at hospital APTT (seconds)
 First recorded at hospital APTT (seconds)
 or
 First recorded at hospital APTT missing

Number of data items: Three
 Units of measurement: Seconds
 Options: First recorded at hospital APTT missing – Yes or No

Definition for collection:

- specifies the first APTT from blood sampled within 12 hours of attendance at the first hospital for this TBI
 - the APTT must be documented
 - the first APTT may not be measured and recorded at the first hospital and, if transferred, may be measured and recorded at a subsequent hospital within 12 hours of attendance at first hospital for this TBI
 - laboratory results only - laboratory results are defined as results of tests performed either in the departments of Clinical Chemistry or Haematology or in the near-patient testing/point of care testing laboratories with formal quality control programmes in operation
 - record the APTT in seconds and the control time in seconds
 - if no blood was sampled for APTT measurement within 12 hours of being at or in the first hospital, then record APTT as missing
-

Justification

Required for risk prediction models

First recorded at hospital arterial blood gas

Fields: First recorded at hospital PaO₂
 Associated FiO₂
 Associated PaCO₂
 Associated pH/H⁺
 First at hospital arterial blood gas missing

Number of data items: Five
 Units of measurement: PaO₂ kPa or mmHg
 FiO₂ fraction
 PaCO₂ kPa or mmHg
 pH/H⁺ pH or nmol l⁻¹

Options: First at hospital arterial blood gas missing – Yes or No

Definition for collection:

- specifies the first arterial blood gas values measured and recorded within 12 hours of attendance at the first hospital for this TBI
 - the arterial blood gas values must be documented
 - the first arterial blood gas values may not be measured and recorded at the first hospital and, if transferred, may be measured and recorded at a subsequent hospital within 12 hours of attendance at first hospital for this TBI
 - all values assessed and recorded from same arterial blood gas
 - if no arterial blood gas values are measured and recorded, then record arterial blood gas as missing
 - see Appendix: Table of FiO₂ approximations for non-intubated admissions receiving oxygen treatment
-

Justification

Required for risk prediction models

First recorded at hospital Glasgow Coma Score (GCS)

Fields: First recorded at hospital GCS recorded?
 First recorded at hospital total GCS
 Associated eye component
 Associated motor component
 Associated verbal component
 Was this the last pre-sedation GCS?

Number of data items: Six
 Units of measurement: None
 Options: First recorded at hospital GCS recorded? – Yes or No
 Was this the last pre-sedation GCS? – Yes or No

Definition for collection:

- specifies the first pre-sedation GCS assessed and recorded within 12 hours of attendance at the first hospital for this TBI
 - the first GCS may not be assessed and recorded at the first hospital and, if transferred, may be assessed and recorded at, or en route to (i.e. on the transfer form), a subsequent hospital within 12 hours of attendance at first hospital for this TBI
 - if GCS assessed and recorded within 12 hours of attendance at the first hospital then indicate Yes, if not, then indicate No
 - all values assessed and recorded from the same assessment of the first total GCS following attendance at first hospital
 - only GCS assessed when the admission is free from the effects of sedative and/or paralysing or neuromuscular blocking agents are valid
 - the determination as to whether an admission is free from the effects of sedative and/or paralysing or neuromuscular blocking agents is left to clinical judgement, as this is the only realistic standardisation for collection of these data at this time
 - admissions with self-sedation through deliberate or accidental overdose/poisoning should have a GCS assessed as seen
 - the GCS may be either documented as a score (for example, as numbers) or as explicit text allowing precise assignment of the score (e.g. “fully alert and orientated” equals 15).
 - see Appendix: How to assess the Glasgow Coma Score (GCS)
 - indicate whether this was the most recent or last pre-sedation GCS recorded (i.e. is there another pre-sedation GCS recorded since this value?)
-

Justification

Required for risk prediction models

First recorded at hospital haemoglobin

Fields: First recorded at hospital haemoglobin
or
First recorded at hospital haemoglobin missing

Number of data items: Two
Units of measurement: g dl⁻¹
Options: First recorded at hospital haemoglobin missing – **Y**es or **N**o

Definition for collection:

- specifies the first haemoglobin value from blood sampled within 12 hours of attendance at the first hospital for this TBI
 - the haemoglobin value must be documented
 - the first haemoglobin value may not be measured and recorded at the first hospital and, if transferred, may be measured and recorded at a subsequent hospital within 12 hours of attendance at first hospital for this TBI
 - laboratory results only - laboratory results are defined as results of tests performed either in the departments of Clinical Chemistry or Haematology or in near-patient testing/point-of-care testing laboratories with formal quality control programmes in operation
 - if no blood was sampled for haemoglobin measurement within 12 hours of being at or in the first hospital, then record haemoglobin values as missing
-

Justification

Required for risk prediction models

First recorded at hospital heart rate

Field: First recorded at hospital heart rate

Number of data items: One
Units of measurement: beats min⁻¹

Definition for collection:

- specifies the first heart (ventricular) rate measured and recorded within 12 hours of attendance at the first hospital for this TBI
 - the first heart (ventricular) rate may not be measured and recorded at the first hospital and, if transferred, may be measured and recorded at, or en route to (i.e. on the transfer form), a subsequent hospital within 12 hours of attendance at first hospital for this TBI
 - where no heart rate was detectable or measurable, then the value zero should be recorded
-

Justification

Required for risk prediction models

First recorded at hospital oxygen saturation

Fields: First recorded at hospital oxygen saturation

Number of data items: One
Units of measurement: %

Definition for collection:

- specifies the first oxygen saturation measured and recorded within 12 hours of attendance at the first hospital for this TBI
 - the first oxygen saturation may not be measured and recorded at the first hospital and, if transferred, may be measured and recorded at, or en route to (i.e. on the transfer form), a subsequent hospital within 12 hours of attendance at first hospital for this TBI
 - oxygen saturation is normally recorded with pulse oximeter
-

Justification

Required for risk prediction models

First recorded at hospital platelet count

Fields: First recorded at hospital platelet count
or
First recorded at hospital platelet count missing

Number of data items: Two
Units of measurement: $\times 10^9 \text{ l}^{-1}$
Options: First recorded at hospital platelet count missing – Yes or No

Definition for collection:

- specifies the first platelet count from blood sampled within 12 hours of attendance at the first hospital for this TBI
 - the platelet count must be documented
 - the first platelet count may not be measured and recorded at the first hospital and, if transferred, may be measured and recorded at a subsequent hospital within 12 hours of attendance at first hospital for this TBI
 - laboratory results only - laboratory results are defined as results of tests performed either in the departments of Clinical Chemistry or Haematology or in the near-patient testing/point of care testing laboratories with formal quality control programmes in operation
 - if no blood was sampled for platelet count measurement within 12 hours of being at or in the first hospital, then record platelet count as missing
-

Justification

Required for risk prediction models

First recorded at hospital prothrombin time (PT) (ratio)

Fields: First recorded at hospital PT (ratio)
or
First recorded at hospital PT missing

Number of data items: Two
Units of measurement: Ratio
Options: First recorded at hospital PT missing – Yes or No

Definition for collection:

- specifies the first PT from blood sampled within 12 hours of attendance at the first hospital for this TBI
 - the PT must be documented
 - the first PT may not be measured and recorded at the first hospital and, if transferred, may be measured and recorded at a subsequent hospital within 12 hours of attendance at first hospital for this TBI
 - laboratory results only - laboratory results are defined as results of tests performed either in the departments of Clinical Chemistry or Haematology or in the near-patient testing/point of care testing laboratories with formal quality control programmes in operation
 - record first PT as a ratio
 - the INR (International Normalised Ratio) may be entered for the PT ratio
 - if no blood was sampled for PT measurement within 12 hours of being at or in the first hospital, then record PT as missing
-

Justification

Required for risk prediction models

First recorded at hospital prothrombin time (PT) (seconds)

Fields: First recorded at hospital PT (seconds)
 First recorded at hospital PT control time (seconds)
 or
 First recorded at hospital PT missing

Number of data items: Three
 Units of measurement: Seconds
 Options: First recorded at hospital PT missing – **Y**es or **N**o

Definition for collection:

- specifies the first PT from blood sampled within 12 hours of attendance at the first hospital for this TBI
 - the PT must be documented
 - the first PT may not be measured and recorded at the first hospital and, if transferred, may be measured and recorded at a subsequent hospital within 12 hours of attendance at first hospital for this TBI
 - laboratory results only - laboratory results are defined as results of tests performed either in the departments of Clinical Chemistry or Haematology or in the near-patient testing/point of care testing laboratories with formal quality control programmes in operation
 - record first PT in seconds and the control time in seconds
 - if no blood was sampled for PT measurement within 12 hours of being at or in the first hospital, then record PT as missing
-

Justification

Required for risk prediction models

First recorded at hospital pupil reactivity and size of pupils

Field: First recorded at hospital pupil reactivity and/or size recorded?
 First recorded at hospital pupil reactivity (left eye)
 First recorded at hospital size of pupils (left eye)
 First recorded at hospital pupil reactivity (right eye)
 First recorded at hospital size of pupils (right eye)

Number of data items: Five
 Units of measurements: mm
 Options: First recorded at hospital pupil reactivity and/or size recorded?
 – **Yes** – both, yes – **R**eactivity, yes – **S**ize or **N**o
 First recorded at hospital pupil reactivity – **R**eactive, **U**nreactive or **u**Nable to assess
 First recorded at hospital size of pupils – **1** mm, **2** mm, **3** mm, **4** mm, **5** mm, **6** mm or greater than or equal to **7** mm

Definition for collection:

- specifies the first pupil reactivity and size of pupils assessed and recorded, for both eyes, within 12 hours of attendance at the first hospital for this TBI
 - the first pupil reactivity and size of pupils may not be assessed and recorded at the first hospital and, if transferred, may be assessed and recorded at, or en route to (i.e. on the transfer form), a subsequent hospital within 12 hours of attendance at first hospital for this TBI
 - if pupil reactivity and size were assessed and recorded within 12 hours of attendance at the first hospital for this TBI then indicate **Yes** - both, if neither recorded then indicate **No**, if reactivity was assessed but not size then record yes – **R**eactivity, if size was measured but not reactivity then record yes - **S**ize
 - **R**eactive is defined as pupillary contraction to strong direct light, **U**nreactive is defined as no pupillary contraction to strong direct light
 - **u**Nable to assess is where pupils cannot be inspected (e.g. eyes are closed due to facial injury or swelling, etc)
 - pupils are recorded regardless of whether admission is ventilated or sedated
 - chronically altered pupils from previous disease should be recorded as unable to assess
 - only assess pupil reactivity and size when an admission is free from iatrogenic drug effects (e.g. drops given for dilation)
 - size of pupils is the diameter of the right and left pupil in mm; if pupils are equal to or more than 7 mm then record as greater than or equal to **7** mm
-

Justification

Required for risk prediction models

First recorded at hospital serum glucose

Fields: First recorded at hospital serum glucose
or
First recorded at hospital serum glucose missing

Number of data items: Two
Units of measurement: mmol l⁻¹
Options: First recorded at hospital serum glucose missing – Yes or No

Definition for collection:

- specifies the first serum glucose value from blood sampled within 12 hours of attendance at the first hospital for this TBI
 - the serum glucose value must be documented
 - the first serum glucose value may not be measured and recorded at the first hospital and, if transferred, may be measured and recorded at a subsequent hospital within 12 hours of attendance at first hospital for this TBI
 - laboratory results only - laboratory results are defined as results of tests performed either in the departments of Clinical Chemistry or Haematology or in the near-patient testing/point of care testing laboratories with formal quality control programmes in operation
 - serum glucose values can be taken from the blood gas analyser
 - if no blood was sampled for serum glucose measurement within 12 hours of being at or in the first hospital, then record serum glucose as missing
-

Justification

Required for risk prediction models

First recorded at hospital temperature

Fields: First recorded at hospital temperature
First recorded at hospital temperature site

Number of data items: Two
Units of measurement: °C
Options: First recorded at hospital temperature site – **C**entral or **N**on-central

Definition for collection:

- specifies the first temperature measured and recorded within 12 hours of attendance at the first hospital for this TBI
 - the first temperature may not be measured and recorded at the first hospital and, if transferred, may be measured and recorded at, or en route to (i.e. on the transfer form), a subsequent hospital within 12 hours of attendance at first hospital for this TBI
 - central are preferred to non-central temperatures, so if first temperature measured and recorded is non-central value, then use subsequent central if measured and recorded within one hour
 - central sites include tympanic membrane, nasopharyngeal, oesophageal, rectal, pulmonary artery and bladder; all other sites are considered to be non-central
 - temperature values are included irrespective of whether the value was artificially manipulated through treatment such as central cooling
 - temperature values measured and recorded for the purpose of estimating perfusion e.g. toe or ear lobe, are not to be included
 - first recorded at hospital temperature site specifies whether site at which temperature was taken is **C**entral or **N**on-central
-

Justification

Required for risk prediction models

Gastrointestinal support days

Field: Gastrointestinal support days

Number of data items: One
Units of measurement: Calendar days

Definition for collection:

- specifies the number of calendar days during which the admission received any gastrointestinal support whilst on your unit
 - a calendar day is defined as any complete calendar day (00:00-23:59) or part thereof, e.g. a patient admitted on 1 January 2006 at 23:45 and discharged on 3 January 2006 at 00:10 would be recorded as having received three calendar days of care
 - record 1, 2, 3 etc for one, two, three etc calendar days; record 998 for 998 or more calendar days; record 999 for support occurring but number of days not known
 - Gastrointestinal – indicated by the following:
 - admissions receiving parenteral or enteral nutrition (i.e. any method of feeding other than normal oral intake)
-

Justification

Required to describe organs supported

GP Practice name

Fields: GP Practice name

Number of data items: One

Definition for collection:

- specifies the name of the GP practice to which this admission to your unit is registered
 - if the GP practice name is unobtainable, then leave field blank
-

Justification

Required for the six-month follow-up of admission with TBI

GP Practice postcode

Field: GP Practice postcode

Number of data items: One

Definition for collection:

- specifies the postcode of the GP practice to which this admission to your unit is registered
 - if outcode (first half of postcode) is obtainable, then record this
 - if postcode is unobtainable, then record UNKNOWN
-

Justification

Required for the six-month follow-up of admission with TBI

GP's initial(s)

Field: GP's initial(s)

Number of data items: One

Definition for collection:

- specifies the initial(s) of the GP to whom this admission to your unit is registered
 - if the initial(s) of the GP are not available, then please leave the field blank
-

Justification

Required for the six-month follow-up of admission with TBI

GP's surname

Field: GP's surname

Number of data items: One

Definition for collection:

- specifies the surname (family name) of the GP to whom this admission to your unit is registered
-

Justification

Required for the six-month follow-up of admission with TBI

Has the patient been recruited into any other research study

Field: Has the patient been recruited into any other research study?

Number of data items: Four
Options: RESCUEicp – **Y**es or **N**o
Eurotherm3235 – **Y**es or **N**o
STITCH – **Y**es or **N**o
Other – **Y**es or **N**o

Definition for collection:

- specifies if the admission has been recruited into another research study or studies that involve(s) a six-month follow-up or multiple follow-ups
 - if the admission has been recruited into a research study that involves a six-month follow-up or multiple follow-ups that has not been listed (e.g. Balti-2 etc.), then select Other and enter the name of the research study in the Additional information text box
 - participation in another study does not prevent recruitment into RAIN, as RAIN is entirely observational and does not affect treatment
-

Justification

To ensure that follow up is streamlined so that patients are not contacted more often than is necessary

High/mixed density lesion greater than one millilitre present

Field: High/mixed density lesion greater than one millilitre present

Number of data items: One
Options: Yes
No

Definition for collection:

- specifies if there is a high/mixed density lesion greater than one millilitre on the first CT scan following the TBI
 - first CT scan is defined as the first CT scan performed after attendance at the first hospital for this TBI
 - where there is more than one CT scan performed, the first CT scan must be used for data abstraction; if transferred, the first CT scan may be performed at a subsequent hospital
 - Yes indicates there is a high/mixed density lesion of greater than one millilitre
 - No indicates there is no high/mixed density lesion of greater than one millilitre
-

Justification

Required for risk prediction models

Hospital number

Field: Hospital number

Number of data items: One

Definition for collection:

- unique number assigned by your hospital to each NHS hospital admission/patient
-

Justification

Provides a unique identifier that can be used to identify the patient on other hospital systems

Intoxication at time of TBI

Field: Intoxication at time of TBI

Number of data items: One
Options: Yes
Suspected
No

Definition for collection:

- specifies whether admission was intoxicated (e.g. with drugs, alcohol etc.) at the time of TBI
 - Yes where evidence of intoxication recorded
 - Suspected where evidence indicates the admission may have been intoxicated (e.g., found outside pub, smells of alcohol etc.)
 - No where no evidence of intoxication recorded
-

Justification

Required for description of TBI

Last pre-sedation Glasgow Coma Score (GCS)

Fields: Last pre-sedation total GCS
 Associated eye component
 Associated motor component
 Associated verbal component
 Location of last pre-sedation GCS

Number of data items: Five
 Units of measurement: None
 Options: Location – Accident & **E**mergency, **W**ard, **C**ritical care, **A**cute
 Assessment unit or **N**ot in hospital

Definition for collection:

- specifies the last pre-sedation GCS assessed and recorded following admission to hospital or last GCS prior to or at admission to your unit, if never sedated
- all values assessed and recorded from the same assessment of the last pre-sedation total GCS following admission to hospital
- only GCS assessed when the admission is free from the effects of sedative and/or paralysing or neuromuscular blocking agents are valid
- the determination as to whether an admission is free from the effects of sedative and/or paralysing or neuromuscular blocking agents is left to clinical judgement, as this is the only realistic standardisation for collection of these data at this time
- admissions with self-sedation through deliberate or accidental overdose/poisoning should have a GCS assessed as seen
- the GCS may be either documented as a score (for example, as numbers) or as explicit text allowing precise assignment of the score (e.g. “fully alert and orientated” equals 15).
- see Appendix: How to assess the Glasgow Coma Score (GCS)
- location of last pre-sedation GCS specifies where the last pre-sedation GCS was recorded
- Accident & **E**mergency is the Accident and Emergency department
- **W**ard is any ward in the hospital
- **C**ritical care includes the intensive care unit, high dependency unit or equivalent step-up/down unit in the hospital and a recovery room used as a temporary critical care facility
- **A**cute assessment Unit includes a medical or surgical admissions/assessment unit, or clinical decision unit in the hospital

- **N**ot in hospital includes when the patient is being transferred (e.g. in an ambulance etc.)
 - if the admission had the GCS recorded in specialist treatment area (e.g. endoscopy, catheter suites), imaging area (e.g. X-ray, CT, MRI or PET) or other transient locations, record the previous location from which the admission was sent from (A&E, Ward, Critical care or Acute assessment unit)
-

Justification

Required for risk prediction models

Lesion(s) present

Field: Lesion(s) present

Number of data items: One
 Options: Yes
 No

Definition for collection:

- specifies if lesions(s) are present on the first CT scan following the TBI
 - first CT scan is defined as the first CT scan performed after attendance at the first hospital for this TBI
 - where there is more than one CT scan performed, the first CT scan must be used for data abstraction; if transferred, the first CT scan may be performed at a subsequent hospital
 - a lesion is defined as a high density or mixed density abnormality which may be within or outside the brain; it includes abnormalities referred to as haematoma, intracerebral haemorrhage, contusion, or shearing injuries
 - Yes indicates one or more lesions
 - No indicates no lesions
-

Justification

Acts as a filter field for CT findings

Level of care at discharge[CMP: Level of care received at discharge from your unit]

Field: Level of care at discharge

Number of data items: One
 Options: Level 3
 Level 2
 Level 1
 Level 0

Definition for collection:

- level of care refers to the type of care received by the admission immediately prior to discharge from your unit
- location of an admission does not determine level of care
- Level 3 – indicated by one or more of the following:
 - admissions receiving advanced respiratory monitoring and support due to an acute illness
 - admissions receiving monitoring and support for two or more organ system dysfunctions (excluding gastrointestinal support) due to an acute illness
 - admissions solely receiving basic respiratory monitoring and support and basic cardiovascular monitoring and support due to an acute illness only meet Level 2
- Level 2 – indicated by one or more of the following:
 - admissions receiving monitoring and support for one organ system dysfunction (excluding gastrointestinal support) due to an acute illness
 - admissions solely receiving advanced respiratory monitoring and support due to an acute illness meet Level 3
 - admissions solely receiving basic respiratory and basic cardiovascular monitoring and support due to an acute illness meet Level 2
 - admissions receiving pre-surgical optimisation including invasive monitoring and treatment to improve organ system function
 - admissions receiving extended post-surgical care either because of the procedure and/or the condition of the admission
 - admissions stepping down to Level 2 from Level 3 care
- Level 1 – indicated by one or more of the following:
 - admission recently discharged from a higher level of care
 - admissions receiving a greater degree of observation, monitoring, intervention(s), clinical input or advice than Level 0 care

- admissions receiving critical care outreach service support fulfilling the medium-score group, or higher, as defined by NICE Guidelines 50
 - Level 0 – indicated by the following:
 - admissions in hospital and receiving normal ward care
-

Justification

Required to describe admission with TBI

Levels of care

Fields: Level 3 days
 Level 2 days
 Level 1 days
 Level 0 days

Number of data items: Four
 Units of measurement: Calendar days

Definition for collection:

- a calendar day is defined as any complete calendar day (00:00-23:59) or part thereof e.g. a patient admitted on 1 January 2006 at 23:45 and discharged on 3 January 2006 at 00:10 would be recorded as having received three calendar days of care
- specifies the total number of calendar days during which the admission received care at a specific level of care whilst on your unit
- record 1, 2, 3 etc for one, two, three etc calendar days; record 998 for 998 or more calendar days; record 999 for support occurring but number of days not known
- the highest level of care within a calendar day is recorded such that if an admission changes from level 2 care to level 3 care, or vice versa, during a calendar day, then the level of care recorded is level 3 e.g. a complete calendar day on which an admission receives 30 minutes of level 3 care and 23 hours, 30 minutes of level 2 care is recorded as one calendar day of level 3 care
- location of an admission does not determine level of care
- Level 3 – indicated by one or more of the following:
 - admissions receiving advanced respiratory monitoring and support due to an acute illness
 - admissions receiving monitoring and support for two or more organ system dysfunctions (excluding gastrointestinal support) due to an acute illness
 - admissions solely receiving basic respiratory monitoring and support and basic cardiovascular monitoring and support due to an acute illness only meet Level 2
- Level 2 – indicated by one or more of the following:
 - admissions receiving monitoring and support for one organ system dysfunction (excluding gastrointestinal support) due to an acute illness
 - admissions solely receiving advanced respiratory monitoring and support due to an acute illness meet Level 3
 - admissions solely receiving basic respiratory and basic cardiovascular monitoring and support due to an acute illness meet Level 2

- admissions receiving pre-surgical optimisation including invasive monitoring and treatment to improve organ system function
 - admissions receiving extended post-surgical care either because of the procedure and/or the condition of the admission
 - admissions stepping down to Level 2 from Level 3 care
 - Level 1 – indicated by one or more of the following:
 - admission recently discharged from a higher level of care
 - admissions receiving a greater degree of observation, monitoring, intervention(s), clinical input or advice than Level 0 care
 - admissions receiving critical care outreach service support fulfilling the medium-score group, or higher, as defined by NICE Guidelines 50
 - Level 0 – indicated by the following:
 - admissions in hospital and receiving normal ward care
-

Justification

Required to describe admission with TBI

Liver support days

Field: Liver support days

Number of data items: One
 Units of measurement: Calendar days

Definition for collection:

- specifies the number of calendar days during which the admission received liver support whilst on your unit
 - a calendar day is defined as any complete calendar day (00:00-23:59) or part thereof e.g. a patient admitted on 1 January 2006 at 23:45 and discharged on 3 January 2006 at 00:10 would be recorded as having received three calendar days of care
 - record 1, 2, 3 etc for one, two, three etc calendar days; record 998 for 998 or more calendar days; record 999 for support occurring but number of days not known
 - Liver – indicated by the following:
 - admissions receiving management of coagulopathy (including liver purification and detoxification techniques) for acute on chronic hepatocellular failure, for portal hypertension, or for primary acute hepatocellular failure admissions being considered for transplantation
-

Justification

Required to describe organs supported

Major extracranial injury

Field: Major extracranial injury

Number of data items: One
Options: Present
Absent

Definition for collection:

- specifies whether major extracranial injury or injuries exist
 - major injury is defined as an injury that would require hospital admission in its own right
 - extracranial injury is defined as injury to any part of the body (excludes skull, but includes face, limbs, torso etc.)
 - major extracranial injuries may have been diagnosed pre-hospital or within 12 hours of attendance at first hospital for this TBI admission
 - Present when major extracranial injury or injuries are recorded
 - Absent when major extracranial injury or injuries are not recorded
-

Justification

Required for risk prediction models

Midline shift present

Field: Midline shift present

Number of data items: One
Options: Yes – greater than five millimetres
No – less than or equal to five millimetres

Definition for collection:

- specifies if a midline shift of the brain is present on the first CT scan following the TBI
 - first CT scan is defined as the first CT scan performed after attendance at the first hospital for this TBI
 - where there is more than one CT scan performed, the first CT scan must be used for data abstraction; if transferred, the first CT scan may be performed at a subsequent hospital
 - Yes indicates a midline shift of greater than five millimetres is present i.e. when the degree of displacement of the midline is more than 5 millimetres
 - No indicates a midline shift of less than or equal to five millimetres is present i.e. when the degree of displacement of midline is from 0-5 millimetres
 - see Appendix: How to measure the midline shift
-

Justification

Required for risk prediction models

Neurological support days

Field: Neurological support days

Number of data items: One
Units of measurement: Calendar days

Definition for collection:

- specifies the number of calendar days during which the admission received any neurological support whilst on your unit
 - a calendar day is defined as any complete calendar day (00:00-23:59) or part thereof e.g. a patient admitted on 1 January 2006 at 23:45 and discharged on 3 January 2006 at 00:10 would be recorded as having received three calendar days of care
 - record 1, 2, 3 etc. for one, two, three etc. calendar days; record 998 for 998 or more calendar days; record 999 for support occurring but number of days not known
 - Neurological – indicated by one or more of the following:
 - admissions with central nervous system depression sufficient to prejudice their airway and protective reflexes, except central nervous system depression caused by sedation prescribed to facilitate mechanical ventilation; or, except poisoning (e.g. deliberate or accidental self-administered overdose, alcohol, drugs etc.)
 - admissions receiving invasive neurological monitoring or treatment (e.g. ICP (intracranial pressure), jugular bulb sampling, external ventricular drain etc.)
 - admissions receiving continuous intravenous medication to control seizures and/or for continuous cerebral monitoring
 - admissions receiving therapeutic hypothermia using cooling protocols or devices
-

Justification

Required to describe organs supported

NHS number (or CHI number)

Field: NHS number (or CHI number)

Number of data items: One

Definition for collection:

- unique number assigned by the NHS as a numeric ten digit code to each NHS patient
 - use the Community Health Index (CHI) number in Scotland
-

Justification

Required to record the patient journey across hospitals allowing us to investigate transfers

One or more small petechial haemorrhages less than or equal to one millilitre present

Field: One or more small petechial haemorrhages less than or equal to one millilitre present

Number of data items: One
Options: Yes
No

Definition for collection:

- specifies if there are one or more small petechial haemorrhages less than or equal to one millilitre present on the first CT scan following the TBI
 - first CT scan is defined as the first CT scan performed after attendance at the first hospital for this TBI
 - where there is more than one CT scan performed, the first CT scan must be used for data abstraction; if transferred, the first CT scan may be performed at a subsequent hospital
 - small petechial haemorrhages includes small petechial haemorrhages at gray-white matter junction, hemispheric white matter, corpus callosum or brainstem
 - Yes indicates there are one or more small petechial haemorrhages less than or equal to one millilitre present
 - No indicates there are no small petechial haemorrhages present
-

Justification

Required for risk prediction models

Patient's full name

Fields: Patient's first name
 Patient's surname

Number of data items: Two

Definition for collection:

- specifies the first name and surname (family name) of this admission to your unit
-

Justification

Required for the six-month follow-up of admission with TBI

Patient's house number or name

Fields: Patient's house number or name

Number of data items: One

Definition for collection:

- specifies the normal residential house number/name for this admission to your unit
 - for visitors to area, use normal residential address for admission's permanent place of residence
 - if address is unobtainable, then leave field blank
-

Justification

Required for the six-month follow-up of admission with TBI

Patient's postcode

Field: Patient's postcode

Number of data items: One

Definition for collection:

- specifies the normal residential postcode for this admission to your unit
 - for visitors to area, use normal residential postcode for admission's permanent place of residence in United Kingdom
 - if admission is not a resident of the United Kingdom and Ireland, then use the drop-down list of countries
 - if outcode (first half of postcode) is obtainable, then record this
 - if postcode is unobtainable, then record UNKNOWN
-

Justification

Required for the six-month follow-up of admission with TBI

Patient's title

Field: Patient's title

Number of data items: One

Definition for collection:

- specifies the title (Mr, Mrs, Ms etc) of this admission to your unit
-

Justification

Required for the six-month follow-up of admission with TBI

Pre-hospital AVPU

Fields: Pre-hospital AVPU recorded?
Pre-hospital AVPU

Number of data items: Two
Options: Pre-hospital AVPU recorded? – Yes or No
Pre-hospital AVPU – Alert, Voice, Pain or Unresponsive

Definition for collection:

- specifies the last AVPU assessed and recorded prior to attendance at first hospital for this TBI
 - if AVPU assessed and recorded prior to attendance at first hospital for this TBI, then indicate Yes, if not, then indicate No
 - Alert indicates that the admission was fully awake (although may be confused or disorientated etc.), spontaneously opened eyes, responded to voice and had bodily motor function
 - Voice indicates that the admission made a response when spoken to, this may be a verbal response (speech, a groan etc.) or movement of a limb
 - Pain indicates that the admission made a response to a painful stimulus (e.g. limb withdrawal from the painful stimulus etc.)
 - Unresponsive indicates that the admission did not give any eye, voice or motor response when spoken to or to a painful stimulus, i.e. unconscious
-

Justification

Required for risk prediction models

Pre-hospital blood pressure

Fields: Pre-hospital blood pressure recorded?
 Pre-hospital systolic blood pressure
 Pre-hospital paired diastolic blood pressure
 Pre-hospital hypotension strongly suspected?

Number of data items: Four
 Units of measurement: mmHg
 Options: Pre-hospital blood pressure recorded? – Yes or No
 Hypotension strongly suspected? – Yes or No

Definition for collection:

- specifies the first blood pressure measured and recorded and whether the admission was hypotensive prior to attendance at the first hospital for this TBI
 - if pre-hospital blood pressure was measured and recorded prior to attendance at the first hospital for this TBI, then indicate Yes, if not, then indicate No
 - if pre-hospital blood pressure values recorded, then record first systolic blood pressure measured and recorded (i.e. prior to attendance at the first hospital for this TBI) plus paired diastolic blood pressure (i.e. values from same measurement)
 - blood pressure values are included irrespective of the measurement method used
 - where blood pressure values are not detectable or measurable, the value zero should be recorded
 - if only the systolic blood pressure value was measured and recorded (i.e. paired diastolic is missing), then enter this value
 - if pre-hospital hypotension strongly suspected, then indicate Yes, if not, then indicate No
 - hypotension strongly suspected specifies that admission had poor peripheral perfusion, a major haemorrhage (or other injuries likely to have caused a major bleed, such as a serious fracture to the pelvis or major long bones), increased lactate levels, admission appeared to be in shock, or if admission was recorded as "blood pressure low" etc but actual numbers were not recorded
-

Justification

Required for risk prediction models

Pre-hospital Glasgow Coma Score (GCS)

Fields: Pre-hospital GCS recorded?
 Pre-hospital total GCS
 Associated eye component
 Associated motor component
 Associated verbal component
 Was this the last pre-sedation GCS?

Number of data items: Six
 Units of measurement: None
 Options: Pre-hospital GCS recorded? – Yes or No
 Was this the last pre-sedation GCS? – Yes or No

Definition for collection:

- specifies the last pre-sedation GCS assessed and recorded prior to attendance at first hospital for this TBI
 - if GCS assessed and recorded prior to attendance at first hospital for this TBI, then indicate Yes, if not, then indicate No
 - all values assessed and recorded from the same assessment of the last total GCS prior to attendance at first hospital
 - only GCS assessed when the admission is free from the effects of sedative and/or paralysing or neuromuscular blocking agents are valid
 - the determination as to whether an admission is free from the effects of sedative and/or paralysing or neuromuscular blocking agents is left to clinical judgement, as this is the only realistic standardisation for collection of these data at this time
 - admissions with self-sedation through deliberate or accidental overdose/poisoning should have a GCS assessed as seen
 - the GCS may be either documented as a score (for example, as numbers) or as explicit text allowing precise assignment of the score (e.g. “fully alert and orientated” equals 15)
 - if only the total GCS prior to admission to first hospital was recorded (i.e. the associated components are missing), then enter this value
 - see Appendix: How to assess the Glasgow Coma Score (GCS)
 - indicate whether this was the most recent or last pre-sedation GCS recorded (i.e. is there another pre-sedation GCS recorded since this value?)
-

Justification

Required for risk prediction models

Pre-hospital oxygen saturation

Fields: Pre-hospital oxygen saturation recorded?
Pre-hospital oxygen saturation
Pre-hospital hypoxia strongly suspected?

Number of data items: Three
Units of measurement: %
Options: Pre-hospital oxygen saturation recorded? – Yes or No
Pre-hospital hypoxia strongly suspected? – Yes or No

Definition for collection:

- specifies the first oxygen saturation measured and recorded and whether the admission was hypoxic prior to attendance at the first hospital for this TBI
 - if pre-hospital oxygen saturation measured and recorded prior to attendance at the first hospital for this TBI, then indicate Yes, if not then indicate No
 - if pre-hospital oxygen saturation measured and recorded, then record the first oxygen saturation measured and recorded (i.e. prior to attendance at the first hospital for this TBI)
 - oxygen saturation is normally recorded with pulse oximeter
 - if pre-hospital hypoxia strongly suspected, then indicate Yes, if not, then indicate No
 - pre-hospital hypoxia strongly suspected specifies that admission was recorded as, for example, cyanosed, had a blocked airway, had aspirated gastrointestinal contents, had clinical evidence of tension pneumothorax etc.
-

Justification

Required for risk prediction models

Pre-hospital pupil reactivity and size of pupils

Field: Pre-hospital pupil reactivity and/or size recorded?
 Pre-hospital pupil reactivity (left eye)
 Pre-hospital size of pupils (left eye)
 Pre-hospital pupil reactivity (right eye)
 Pre-hospital size of pupils (right eye)

Number of data items: Five
 Units of measurement: mm
 Options: Pre-hospital pupil reactivity and/or size recorded?
 – **Yes** – both, yes – **R**ectivity, yes – **S**ize or **N**o
 Pre-hospital pupil reactivity – **R**eactive, **U**nreactive or
uNable to assess
 Pre-hospital size of pupils – **1** mm, **2** mm, **3** mm, **4** mm, **5** mm,
6 mm or greater than or equal to **7** mm

Definition for collection:

- specifies first pupil reactivity and size of pupils assessed and recorded, for both eyes, prior to attendance at the first hospital for this TBI
 - if pupil reactivity and size were assessed and recorded prior to attendance at the first hospital for this TBI then indicate **Yes** - both, if neither recorded then indicate **No**, if reactivity was assessed but not size then record yes – **R**ectivity, if size was measured but not reactivity then record yes - **S**ize
 - **R**eactive is defined as pupillary contraction to strong direct light, **U**nreactive is defined as no pupillary contraction to strong direct light
 - **u**Nable to assess is defined where pupils cannot be inspected (e.g. eyes are closed due to facial injury or swelling, etc)
 - pupils are recorded regardless of whether admission is ventilated or sedated
 - chronically altered pupils from previous disease should be recorded as unable to assess
 - only assess pupil reactivity and size when an admission is free from iatrogenic drug effects (e.g. drops given for dilation)
 - size of pupils is the diameter of the right and left pupil in mm; if pupils are equal to or more than 7 mm then record as greater than or equal to **7** mm
-

Justification

Required for risk prediction models

Previous RAIN Study Admission number

Field: Previous RAIN Study Admission number

Number of data items: One
Units of measurement: None

Definition for collection:

- specifies the previous RAIN Study Admission number for this admission
 - if the admission was previously admitted to your unit and entered on the RAIN secure, web-based data entry system, then enter the RAIN Study Admission number for this admission
 - admission to your unit is defined as the physical admission and the recording of that admission to a bed in your unit
-

Justification

Acts as a filter field for all RAIN Study screens

Prior source[CMP: Prior location (in)]

Field: Prior source

Number of data items: One
Options: **W**ard
o**B**stetrics area
other inter**M**ediate care area
Paediatric ICU/HDU
level 3 bed in adult **I**CU or ICU/HDU
level 2 bed in adult ICU or ICU/**H**DU
adult **H****D****U**
Not in hospital

Definition for collection:

- specifies the non-transient prior source for admissions where the Direct source is transient (i.e. theatre & recovery, accident & emergency, recovery only, imaging department, specialist treatment area, clinic)
 - **W**ard is a ward in the hospital
 - **o****B**stetrics area is a delivery suite, labour ward or obstetrics ward in the hospital
 - other inter**M**ediate care area is a CCU or other area in the hospital where the level of care is greater than the normal ward but is not an ICU or combined ICU/HDU or HDU (use text box to specify where)
 - **P**aediatric ICU/HDU is a paediatric ICU or combined ICU/HDU or HDU in the hospital
 - level 3 bed in adult **I**CU or ICU/HDU is a level 3 bed in either an adult ICU or a combined ICU/HDU in the hospital
 - level 2 bed in adult ICU or ICU/**H**DU is a level 2 bed in either an adult ICU or a combined ICU/HDU in the hospital
 - adult **H****D****U** is an adult HDU or equivalent step-up/step-down unit in the hospital, where the Critical Care Minimum Data Set (CCMDS) is collected
 - **N**ot in hospital is defined as not in hospital
-

Justification

Required to describe admission with TBI

Prior source location[CMP: Hospital housing non-transient location (in)]

Field: Prior source location

Number of data items: One
Options: Same hospital
other Acute hospital
nOn-acute hospital

Definition for collection:

- specifies the hospital housing the non-transient (Ward, Obstetrics area, Level 3 bed in adult ICU or ICU/HDU, Adult HDU etc) prior source for admission where the Direct source is transient
 - Same hospital is defined as the hospital that houses your unit
 - other Acute hospital, one that does not house your unit, is defined as another hospital (can be in the same or a different NHS Trust) that provides a range of acute hospital services to diagnose, treat and care for seriously ill or injured patients; some acute hospitals may provide only specialist services while others will provide general services
 - nOn-acute hospital is defined as another hospital (can be in the same or a different NHS Trust) that provides a range of short or long-term non-acute services
-

Justification

Required to describe admission with TBI

Pupil reactivity and size of pupils on admission to your unit

Field: Pupil reactivity and/or size on admission to your unit recorded?
 Admission pupil reactivity (left eye)
 Admission size of pupils (left eye)
 Admission pupil reactivity (right eye)
 Admission size of pupils (right eye)

Number of data items: Five
 Units of measurements: mm
 Options: Pupil reactivity and/or size on admission to your unit recorded?
 – **Yes** – both, yes – **Reactivity**, yes – **Size** or **No**
 Pupil reactivity on admission to your unit – **Reactive**, **Unreactive**
 or **uNable** to assess
 Admission size of pupils – **1** mm, **2** mm, **3** mm, **4** mm, **5** mm,
6 mm or greater than or equal to **7** mm

Definition for collection:

- specifies pupil reactivity and size of pupils assessed and recorded, for both eyes, following admission to your unit
 - if pupil reactivity and size were measured and assessed following admission to your unit then indicate **Yes** - both, if neither recorded then indicate **No**, if reactivity was assessed but not size then record yes – **Reactivity**, if size was measured but not reactivity then record yes - **Size**
 - **Reactive** is defined as pupillary contraction to strong direct light, **Unreactive** is defined as no pupillary contraction to strong direct light
 - **uNable** to assess is defined where pupils cannot be inspected (e.g. eyes are closed due to facial injury or swelling, etc)
 - pupil reactivity and size of pupils must be measured and recorded within one hour of admission to your unit
 - if pupil reactivity and size is measured and recorded more than once within one hour of admission to your unit, then enter the values closest to the time of admission
 - pupils are recorded regardless of whether admission is ventilated or sedated
 - chronically altered pupils from previous disease should be recorded as unable to assess
 - only assess pupil reactivity and size when an admission is free from iatrogenic drug effects (e.g. drops given for dilation)
 - size of pupils is the diameter of the right and left pupil in mm; if pupils are equal to or more than 7 mm then record as greater than or equal to **7** mm
-

Justification

Required for risk prediction models

RAIN Study Admission number

Field: RAIN Study Admission number

Number of data items: One
Units of measurement: None

Definition for collection:

- unique number assigned to each admission to your unit with TBI
 - value will be automatically generated by secure, web-based data entry system as each admission record is created
 - admission to your unit is defined as the physical admission and the recording of that admission to a bed in your unit
-

Justification

Provides a unique confidential identifier for each admission with TBI to each unit participating in the RAIN Study

RAIN Study Centre number

Field: RAIN Study Centre number

Number of data items: One

Definition for collection:

- unique unit identifier supplied by ICNARC to each unit participating in the RAIN Study
 - value will be automatically generated by secure web-based data entry system
-

Justification

Provides a unique, confidential identifier for each unit participating in the RAIN Study

Registered GP Practice Code

Field: Registered GP Practice Code

Number of data items: One

Definition for collection:

- specifies the Registered GP Practice Code of the GP to whom this admission to your unit is registered
 - this consists of a letter followed by five numerals
 - if there is no Registered GP Practice Code leave the field blank
-

Justification

Required for the six-month follow-up of admission with TBI

Renal support days

Field: Renal support days

Number of data items: One
Units of measurement: Calendar days

Definition for collection:

- specifies the number of calendar days during which the admission received renal support whilst on your unit
 - a calendar day is defined as any complete calendar day (00:00-23:59) or part thereof e.g. a patient admitted on 1 January 2006 at 23:45 and discharged on 3 January 2006 at 00:10 would be recorded as having received three calendar days of care
 - record 1, 2, 3 etc for one, two, three etc calendar days; record 998 for 998 or more calendar days; record 999 for support occurring but number of days not known
 - Renal - indicated by the following:
 - admissions receiving acute renal replacement therapy (e.g. haemodialysis, haemofiltration etc.)
 - admissions receiving renal replacement therapy for chronic renal failure where other acute organ support is received
 - last day of renal support is the date and time of completion of final renal replacement treatment
-

Justification

Required to describe organs supported

Residence post-discharge

[CMP: Residence post-discharge from acute hospital]

Field: Residence post-discharge

Number of data items: One
 Options: **h**o**M**e
 n**U**rning home or equivalent
 health-related institution – **S**hort-term rehabilitation
 health-related institution – **L**ong-term rehabilitation
 other **H**ealth-related institution
 n**O**n-health-related institution
Residential place of work/education
 hos**P**ice or equivalent
No fixed address/abode or temporary abode

Definition for collection:

- specifies the admission's permanent/semi-permanent place of residence post-discharge from acute hospital
- **h**o**M**e includes owner occupied and rented property, sheltered housing, safe housing, warden-controlled housing, mobile homes, houseboats, bed and breakfast (if not on holiday and on a semi-permanent basis) etc.
- n**U**rning home or equivalent is an establishment providing nursing or personal care services to the older or infirm or chronically-ill population
- health-related institution – **S**hort-term rehabilitation includes a short-term care facility where rehabilitation (active promotion of recovery) care is focused on restoring and optimizing the admission's functional independence and health for a defined period with a view to subsequent discharge to a permanent/semi-permanent place of residence
- health-related institution – **L**ong-term rehabilitation includes a long-term care facility where rehabilitation (active promotion of recovery) care is intertwined with maintenance (active prevention of deterioration) and other care (support for disabilities) focused on stabilising the admission's functional independence and health for an undefined period and with only the possibility of subsequent discharge to a permanent/semi-permanent place of residence
- other **H**ealth-related institution includes any other health-related institution (not short-term or long-term rehabilitation) from which there is no possibility of subsequent discharge to a permanent/ semi-permanent place of residence (e.g. institution for chronically sick etc.)
- n**O**n-health-related institution includes prison, correctional facility, children's home etc.
- **R**esidential place of work/education includes barracks, oil rig, lighthouse, monastery, trawler, embassy, cruise ship, boarding school, university etc.

- hospice or equivalent is an establishment providing medical care and support services to terminally-ill persons
 - **N**o fixed address/abode or temporary abode includes homeless or in hostels, bed and breakfast (if not on holiday and on a temporary basis)
-

Justification

Required to describe admission with TBI

Residence prior to admission to acute hospital

Field: Residence prior to admission to acute hospital

Number of data items: One
 Options: **h**o**M**e
nU**r**sing home or equivalent
Hhealth-related institution
no**N**on-health-related institution
Residential place of work/education
hosP**i**ce or equivalent
No fixed address/abode or temporary abode

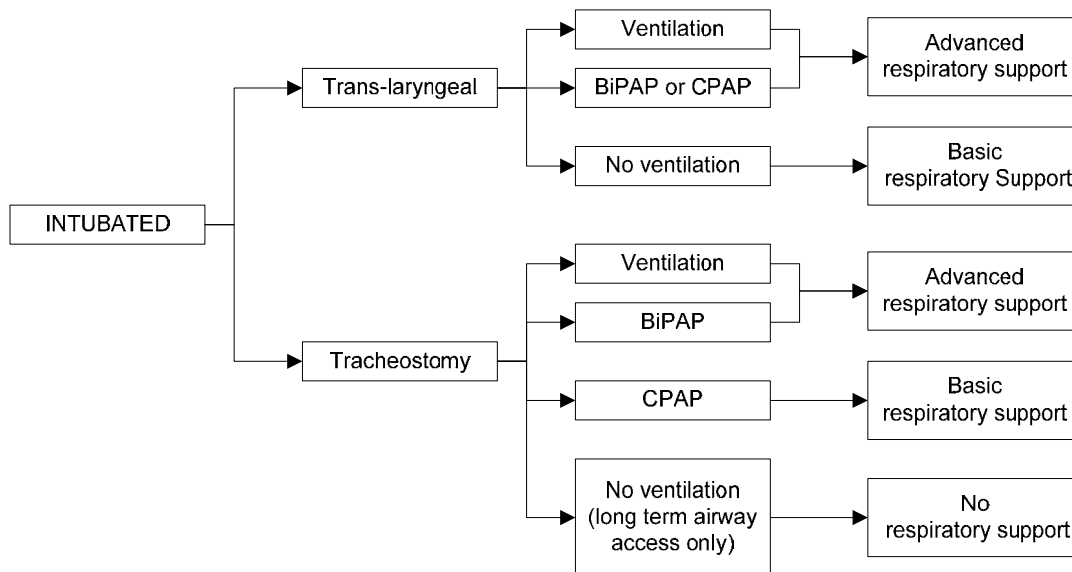
Definition for collection:

- specifies admission's permanent/semi-permanent place of residence prior to admission to acute hospital
 - for transient locations e.g. on holiday, in the pub, on the tennis court, in a car park, in a hotel (medical tourist), outside etc. use admission's permanent/semi-permanent place of residence
 - **h**o**M**e includes owner occupied and rented property, sheltered housing, safe housing, warden-controlled housing, mobile homes, houseboats, bed and breakfast (if not on holiday and on a semi-permanent basis) etc.
 - **n**U**r**sing home or equivalent is an establishment providing nursing or personal care services to the older or infirm or chronically-ill population
 - **H**health-related institution includes psychiatric hospital, hospital or institution for chronically sick etc.
 - **n**o**N**on-health-related institution includes prison, correctional facility, children's home etc.
 - **R**esidential place of work/education includes barracks, oil rig, lighthouse, monastery, trawler, embassy, cruise ship, boarding school, university etc.
 - **hos**P**i**ce or equivalent is an establishment providing medical care and support services to terminally-ill persons
 - **N**o fixed address/abode or temporary abode includes homeless or in hostels, bed and breakfast (if not on holiday and on a temporary basis)
-

Justification

Required to describe admission with TBI

- admissions recently (i.e. within 24 hours) extubated after a period (i.e. more than 24 hours) of mechanical ventilation via an endotracheal tube
 - admissions receiving mask/hood CPAP or mask/hood BiPAP or non-invasive ventilation
 - admissions receiving CPAP via a tracheostomy
 - admissions intubated to protect their airway but receiving no ventilatory support and who are otherwise stable.
- Note: If advanced and basic respiratory monitoring and support occur simultaneously, then only advanced respiratory monitoring and support should be recorded.
 - The following diagram may aid categorisation to advanced or basic respiratory support



Justification

Required to describe organs supported

Road traffic accident details

Field: Road traffic accident details

Number of data items: One
Options: Vehicle occupant
Motorcyclist
Cyclist
Pedestrian
Other

Definition for collection:

- specifies road traffic accident details
 - Vehicle occupant includes driver or passenger in vehicle
 - Motorcyclist includes driver or passenger on motorcycle or sidecar (e.g. motorised two-wheeled vehicle) etc.
 - Cyclist includes cyclist or passenger on pedal bike
 - Pedestrian includes someone on foot
 - Other is where road traffic accident details do not fit into above categories
-

Justification

Required to describe admission with TBI

Sex

Field: Sex

Number of data items: One
Options: **F**emale
Male

Definition for collection:

- specifies the genotypical (i.e. sex they were born as) sex of the admission
-

Justification

Required to describe admission with TBI

Site(s) of major extracranial injury

Fields: Spine
 Limb
 Head and neck
 Chest
 Pelvis
 Abdomen

Number of data items: Six
 Options: Present
 Absent

Definition for collection:

- specifies site(s) of major extracranial injury or injuries
 - major injury is defined as an injury that would require hospital admission in its own right
 - extracranial injury is defined as injury to any part of the body (excludes skull, but includes face, limbs, torso etc)
 - spine specifies injury to nerve tissue in spinal canal and/or damage to the spinal vertebrae
 - limb specifies injury to arms (including hands) or legs (including feet)
 - head and neck specifies extracranial injury to scalp, face or neck
 - chest specifies injury to area between the neck and diaphragm (heart and lungs area)
 - pelvis specifies injury to skeletal structure that joins spine and lower limbs
 - abdomen specifies injury to lower torso (excluding pelvis)
-

Justification

Required for risk prediction models

Source location[CMP: Hospital housing non-transient location (in) or Hospital housing transient location (in)]

Field: Source location

Number of data items: One
Options: Same hospital
other Acute hospital
nOn-acute hospital

Definition for collection:

- specifies the hospital housing the Direct source from which this admission was admitted to your unit
 - Same hospital is defined as the hospital that houses your unit
 - other Acute hospital, one that does not house your unit, is defined as another hospital (can be in the same or a different NHS Trust) that provides a range of acute hospital services to diagnose, treat and care for seriously ill or injured patients; some acute hospitals may provide only specialist services while others will provide general services
 - nOn-acute hospital is defined as another hospital (can be in the same or a different NHS Trust) that provides a range of short or long-term non-acute services
-

Justification

Required to describe admission with TBI

Spinal cord injury present

Fields: Spinal cord injury present

Number of data items: One
Options: Yes
No

Definition for collection:

- specifies if there was a spinal cord injury consistent with major neurological deficit
 - Yes indicates injury to the nerve tissue in spinal canal consistent with major neurological deficit
 - **N**o indicates no injury to the nerve tissue in spinal canal or any injury that is not consistent with major neurological deficit
-

Justification

Required to describe admission with TBI

Status at discharge from your hospital

Field: Status at discharge from your hospital

Number of data items: One
Options: Alive
Dead

Definition for collection:

- specifies the status of the admission at discharge from the hospital housing your unit
-

Justification

Required for risk prediction models

Status at discharge from your unit

Field: Status at discharge from your unit

Number of data items: One
Options: Alive
Dead

Definition for collection:

- specifies the status of the admission at discharge from your unit
 - Dead includes admissions who leave your unit to become heartbeating organ donors
-

Justification

Required for risk prediction models

Third ventricle

Field: Third ventricle

Number of data items: One
Options: Obliterated
Present

Definition for collection:

- specifies the appearance of the third ventricle on the first CT scan following the TBI
 - first CT scan is defined as the first CT scan performed after attendance at the first hospital for this TBI
 - where there is more than one CT scan performed, the first CT scan must be used for data abstraction; if transferred, the first CT scan may be performed at a subsequent hospital
 - Obliterated indicates the third ventricle is not present
 - Present indicates the third ventricle appears normal on the first CT scan
-

Justification

Required for risk prediction models

Traumatic subarachnoid haemorrhage present

Field: Traumatic subarachnoid haemorrhage present

Number of data items: One
Options: Yes
No

Definition for collection:

- specifies if a traumatic subarachnoid haemorrhage was present on the first CT scan following the TBI
 - first CT scan is defined as the first CT scan performed after attendance at the first hospital for this TBI
 - where there is more than one CT scan performed, the first CT scan must be used for data abstraction; if transferred, the first CT scan may be performed at a subsequent hospital
 - traumatic subarachnoid haemorrhage is defined as a collection of blood between the arachnoid and pia mater either over the convexity or in the basal cisterns
 - Yes indicates there is a traumatic subarachnoid haemorrhage
 - **N**o indicates no traumatic subarachnoid haemorrhage
 - if there is uncertainty on whether subarachnoid haemorrhage is caused by the TBI, then record as Yes
-

Justification

Required for risk prediction model

Type of high/mixed density lesion(s) present

Field: Extradural haematoma(s) present
 Subdural haematoma(s) present
 Intracerebral haematoma(s) haemorrhage(s) or contusion(s)
 present
 Posterior fossa haematoma(s) present
 Main mass lesion

Number of data items: Five
 Options: Type of high/mixed density lesion(s) present – **Y**es or **N**o
 Main mass lesion – **E**xtradural, **S**ubdural, **I**ntracerebral or
 Posterior fossa haematoma

Definition for collection:

- specifies the type(s) of haematoma(s) present on the first CT scan following the TBI
 - first CT scan is defined as the first CT scan performed after attendance at the first hospital for this TBI
 - where there is more than one CT scan performed, the first CT scan must be used for data abstraction; if transferred, the first CT scan may be performed at a subsequent hospital
 - extradural haematoma (or epidural haematoma or extradural haemorrhage) is defined as an accumulation of blood between the skull and dura mater
 - subdural haematoma (or subdural haemorrhage) is defined as a collection of blood between the dura and the arachnoid mater
 - intracerebral haematoma (or intracerebral haemorrhage or contusion) is defined as bleeding within the cerebral hemispheres
 - posterior fossa haematoma is defined as a collection of blood in the intracranial cavity in posterior fossa
 - main mass lesion indicates which is the main (largest volume) mass lesion
-

Justification

Required for risk prediction models

Type of TBI

Field: Type of TBI

Number of data items: One
Options: **P**enetrating
Non-penetrating

Definition for collection:

- specifies type of TBI
 - **P**enetrating head injury is defined as when an object/projectile penetrates the skull; the skull may have a fracture, but if an object has not penetrated the skull it is classed as non-penetrating
 - **N**on-penetrating head injury is when an object/projectile does not penetrate the skull and includes closed head injury; the skull may have a fracture, but if an object has not penetrated the skull it is classed as non-penetrating
-

Justification

Required for risk prediction models

Type of unit (in)[CMP: Type of adult ICU/HDU (in)]

Field: Type of unit (in)

Number of data items: One
 Options: General
Cardiac
Thoracic
Liver
Spinal injury
Burns & plastic
Renal
Neurosciences
Medical
surgical
Obstetric

Definition for collection:

- specifies the type of adult ICU or combined ICU/HDU or HDU from which the admission was transferred prior to admission to your unit
 - specifies the principal clinical service or predominant patient population
 - for mixed units use either General or the predominant specialty
-

Justification

Required to describe admission with TBI

Type of unit (out)[CMP: Type of adult ICU/HDU (out)]

Field: Type of unit (out)

Number of data items: One
Options: **G**eneral
Cardiac
Thoracic
Liver
Spinal injury
Burns & plastic
Renal
Neurosciences
Medical
sUrgical
Obstetric

Definition for collection:

- specifies the type of adult ICU or combined ICU/HDU or HDU to which the admission was transferred post-discharge from your unit
 - specifies the principal clinical service or predominant patient population
 - for mixed units use either **G**eneral or the predominant specialty
-

Justification

Required to describe admission with TBI

Ultimate date of discharge

[CMP: Date of ultimate discharge from hospital]

Field: Ultimate date of discharge

Number of data items: One
Units of measurement: Date dd/mm/yyyy

Definition for collection:

- specifies the latest documented date of the admission being physically within an acute in-patient bed in an acute hospital, or the date of death
 - ultimate discharge from hospital is defined as the physical discharge and recording of that discharge from an acute in-patient bed in an acute hospital
 - an acute hospital is defined as any hospital providing a range of acute hospital services to diagnose, treat and care for seriously ill or injured patients; some acute hospitals may provide only specialist services while others will provide general services
 - where more than one date of discharge from hospital is documented, the latest documented date is recorded
 - this is not necessarily the date of discharge from the acute hospital to which the admission was directly transferred
-

Justification

Required to describe admission with TBI

Ultimate status at discharge

[CMP: Status at ultimate discharge from hospital]

Field: Ultimate status at discharge

Number of data items: One
Options: Alive
Dead

Definition for collection:

- specifies the status at ultimate discharge from acute hospital
 - the hospital is another acute hospital, not the hospital housing your unit
-

Justification

Required for the risk prediction models

Ultimate status at discharge from critical care

[CMP: Status at ultimate discharge from ICU/HDU]

Field: Ultimate status at discharge from critical care

Number of data items: One
Options: Alive
Dead

Definition for collection:

- specifies the status of the admission on ultimate discharge from adult critical care, the ultimate discharge is defined as the physical discharge and recording of that discharge from a bed in another critical care unit
 - critical care unit is defined as an ICU or a combined ICU/HDU or an HDU
-

Justification

Required for risk prediction models

Unit in your critical care transfer group (in)[CMP: Adult ICU/HDU within your critical care transfer group (in)]

Field: Unit in your critical care transfer group (in)

Number of data items: One
Options: Yes
No

Definition for collection:

- specifies whether the critical care unit (adult ICU or combined ICU/HDU or HDU) is part of your critical care transfer group
 - a critical care transfer group is defined as the group, recommended by “Comprehensive Critical Care” and supported by “Quality Critical Care”, specified and developed to reduce the number of long distance transfers that take place and to ensure that transfers are contained within the critical care network or, by special agreement, between hospitals at the borders of adjacent networks
-

Justification

Required to describe admission with TBI

Unit in your critical care transfer group (out)[CMP: Adult ICU/HDU within your critical care transfer group (out)]

Field: Unit within your critical care transfer group (out)

Number of data items: One
Options: Yes
No

Definition for collection:

- specifies whether the critical care unit (adult ICU or combined ICU/HDU or HDU) is part of your critical care transfer group
 - a critical care transfer group is defined as the group, recommended by “Comprehensive Critical Care” and supported by “Quality Critical Care”, specified and developed to reduce the number of long distance transfers that take place and to ensure that transfers are contained within the critical care network or, by special agreement, between hospitals at the borders of adjacent networks
-

Justification

Required to describe admission with TBI

Volume of largest high/mixed density lesion

Field: Volume of largest high/mixed density lesion

Number of data items: One
 Options: **G**reater than 25 millilitres
Less than or equal to 25 millilitres

Definition for collection:

- specifies if the volume of the largest high/mixed density lesion, present on the first CT scan following the TBI, is greater than 25 millilitres
- first CT scan is defined as the first CT scan performed after attendance at the first hospital for this TBI
- where there is more than one CT scan performed, the first CT scan must be used for data abstraction; if transferred, the first CT scan may be performed at a subsequent hospital
- **G**reater than 25 millilitres specifies that the volume of the largest high/mixed density lesion is greater than 25 millilitres
- **L**ess than or equal to 25 millilitres specifies that the volume of the largest high/mixed density lesion is less than or equal to 25 millilitres
- volume of lesion is estimated by using the formula:

$$\text{Volume (ml)} = (\text{length} \times \text{breadth} \times \text{height}) \text{ divided by } 2$$

All measurements are in cm, in relation to the scale displayed on each CT image. Any blood in contiguity with the lesion is considered part of it and included in the measurement

- length is measured on the CT slice where the lesion is largest
 - breadth is the measurement of the lesion at right angles to the length, *measured on the same slice as the length*
 - height is calculated by multiplying the CT slice thickness by the number of CT slices on which the lesion is visible
-

Justification

Required for risk prediction models

Appendix: Table of FiO₂ approximations

Conversion table for FiO₂ when measured on nasal cannula or mask (see references overleaf):

Values given represent an estimation of the likely overall FiO₂ in the airway, not just the concentration in the mask, assuming a relatively normal respiratory pattern.

Nasal cannula l min ⁻¹	FiO ₂	Face mask		Face mask with reservoir bag		"Venturi" type face mask e.g. Ventimask		Aerosol face mask O ₂ 15 l min ⁻¹ via nebulizer	
		l min ⁻¹	FiO ₂	l min ⁻¹	FiO ₂	Set %	FiO ₂	Set %	FiO ₂
1	0.22	2*	0.25	6	0.60	24	0.24	35	0.28
2	0.25	3*	0.27	7	0.70	28	0.28	40	0.30
3	0.27	4	0.30	8	0.80	35	0.35	70	0.50
4	0.30	5	0.35	9	0.85	40	0.40	100	0.60
5	0.35	6	0.40	10+	0.90	60	0.50		
		7	0.45						
		8+	0.50						

* we acknowledge that there is some fresh evidence that fresh gas flows less than 4 l min⁻¹ are not recommended because of the risk of CO₂ retention.

References

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Appendix: How to assess the Glasgow Coma Score (GCS)

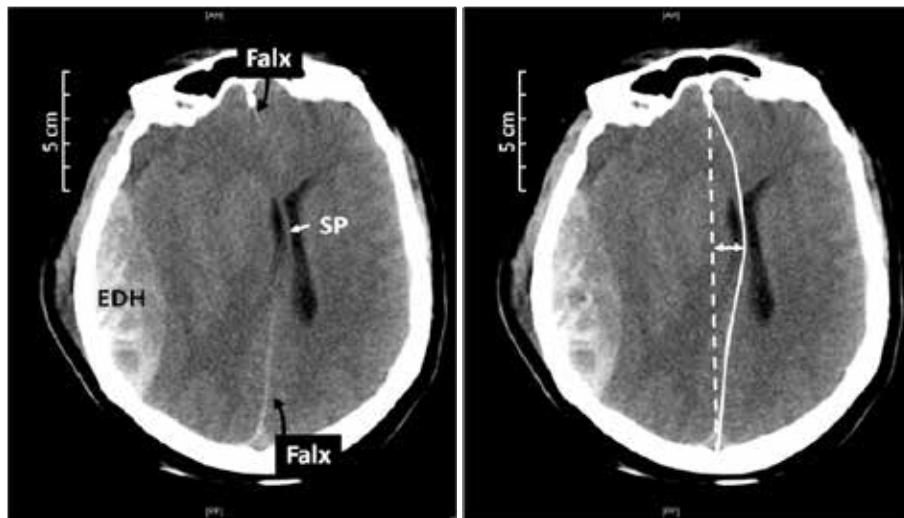
The GCS is assessed for adults¹ as follows:

The best eye opening response:	GCS
Spontaneous	4
To verbal command	3
To pain	2
No response	1
The best motor response:	
Obeys verbal command	6
Localises pain	5
Flexion withdrawal	4
Flexion-abnormal/decorticate rigidity	3
Extension/decerebrate rigidity	2
No response	1
The best verbal response:	
Oriented and converses	5
Disoriented and converses	4
Inappropriate words	3
Incomprehensible sounds (not words)	2
No response	1
If an admission is intubated, use clinical judgement to score verbal response as follows:	
Appears oriented and able to converse	5
Responsive but ability to converse questionable	3
Generally unresponsive	1

Reference

- 1 Knaus WA et al. Data Dictionary for Introduction to Data Collection, The APACHE II System: A severity of disease classification system

Appendix: How to measure the midline shift



Stage 1: Identifying anatomical landmarks (left image)

1. Choose a slice on which the septum pellucidum is clearly seen between the two lateral ventricles.
2. Identify the attachment of the falx cerebri to the front and back of the skull.
3. In some cases the falx will split at the back to encase the superior sagittal sinus (as in picture on left).
4. If the falx does split, the posterior midline is between the two leaves of the falx (as above).
5. Identify the septum pellucidum (between the lateral ventricles).

Stage 2: Drawing the midline (right image)

6. Draw a line between the point of attachment of the falx to the front and back of the skull.
7. This is the midline (the dashed line on the image on the right).
8. In some instances, the falx may not be seen clearly – if this is the case, draw the midline between the bony prominences that represent the points of attachment of the falx on the inside of the skull (the frontal crest and internal occipital crest).

Stage 3: Measuring midline shift (right image)

9. Check by eye on more than one CT slice and choose the one where midline shift is most pronounced.
10. Measure the lateral (horizontal) displacement of the septum pellucidum from the midline *at the point where such lateral displacement is maximal* (on the image on the right, the distorted midline is identified by the dotted line, which goes through the septum pellucidum).
11. Measurement on image archiving systems (e.g. PACS) can be done by drawing the midline using the scale/ruler tool, and then drawing a second line (as in the image above) to measure midline shift – the software will give you a measurement automatically.
12. Where the measurement is being done on CT film, calibrate the midline shift against the CT scale bar which will be there on every CT image (as above).
13. Report the midline shift in millimetre

Appendix 4 Risk Adjustment In Neurocritical care study data collection form and data set flow

RAIN

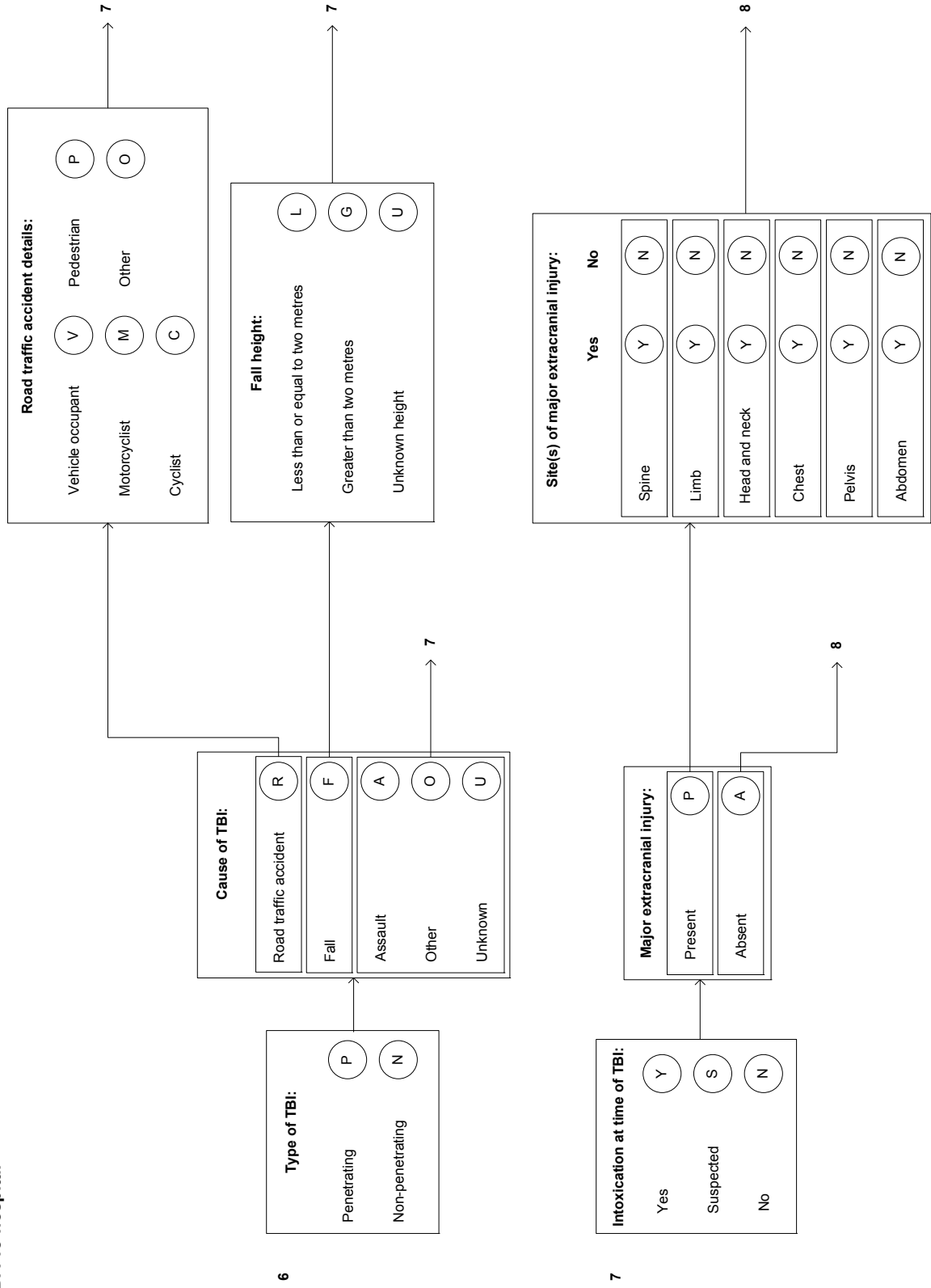
Risk Adjustment In
Neurocritical care

Data Collection Form **(Version 1.4)**

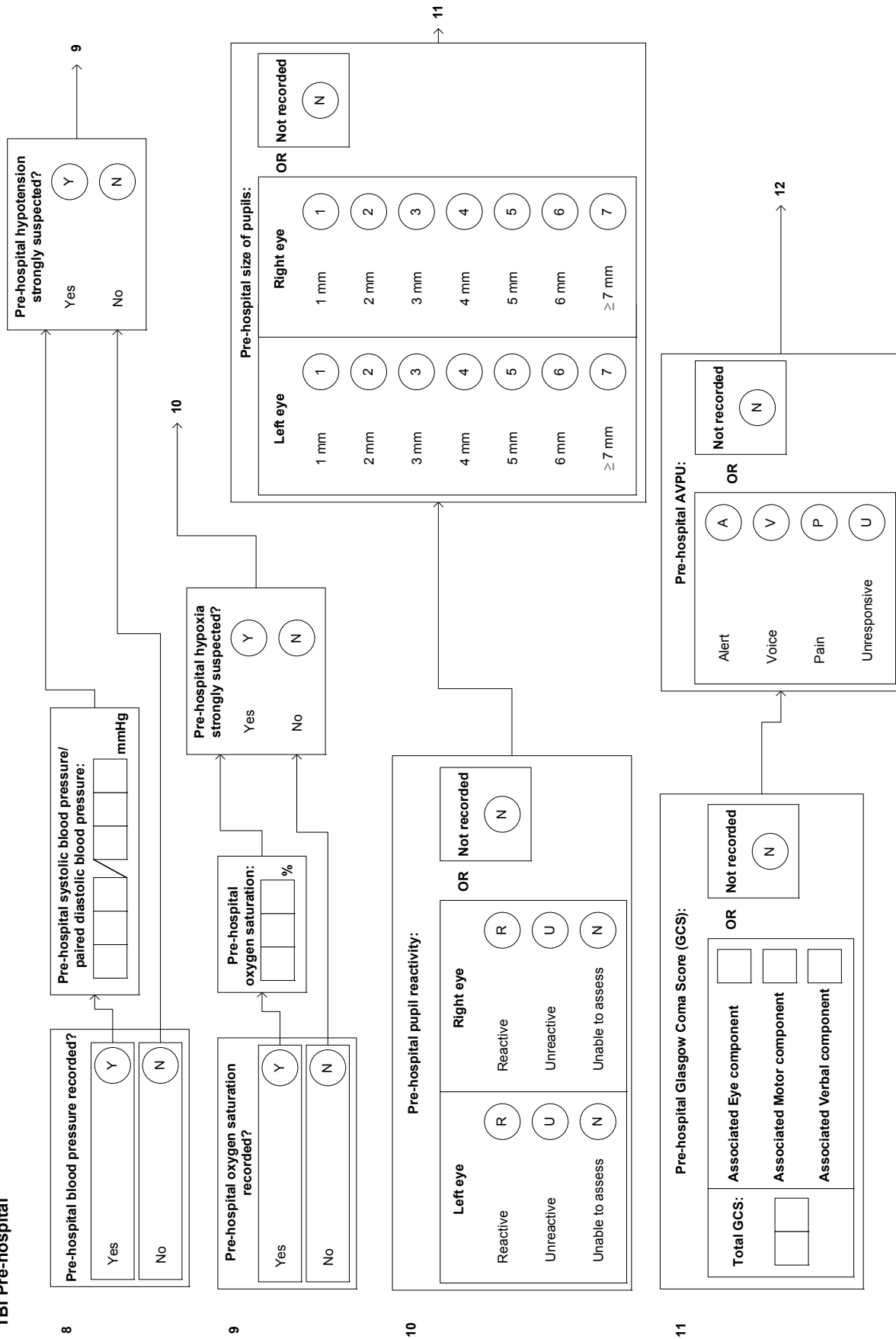
Non-Case Mix Programme (Non-CMP) Units

ICNARC © 2010

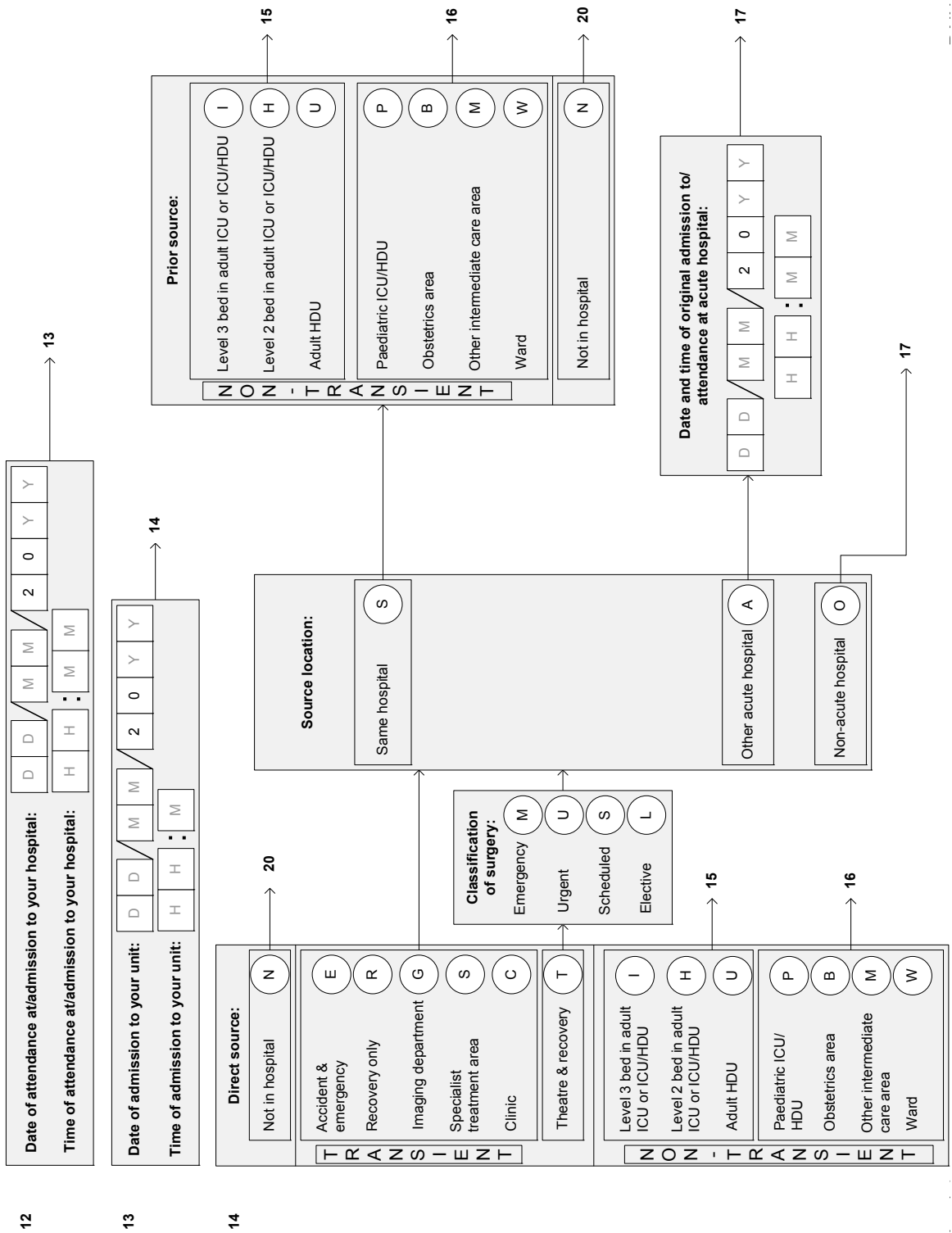
TBI Pre-hospital



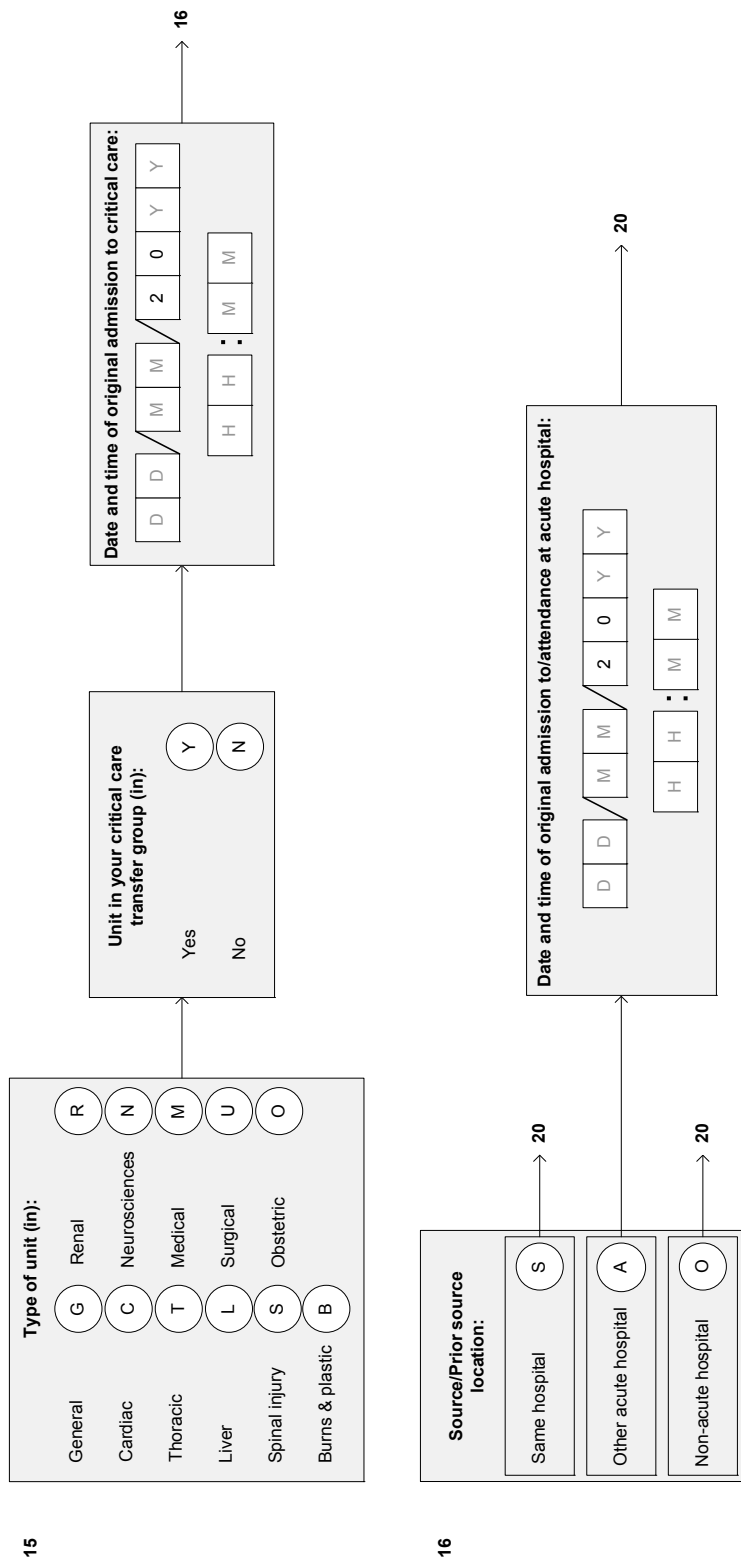
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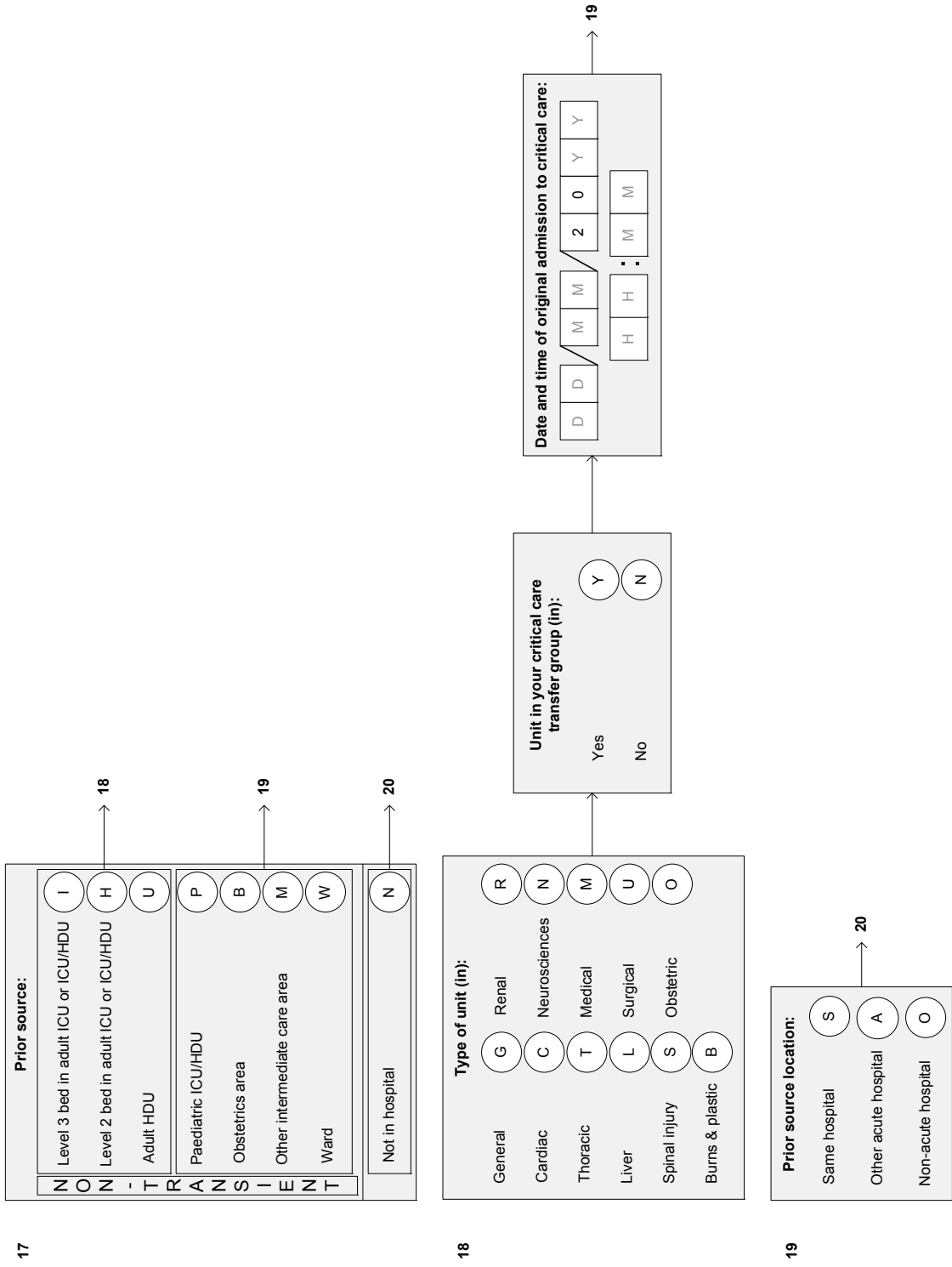
Source



Source



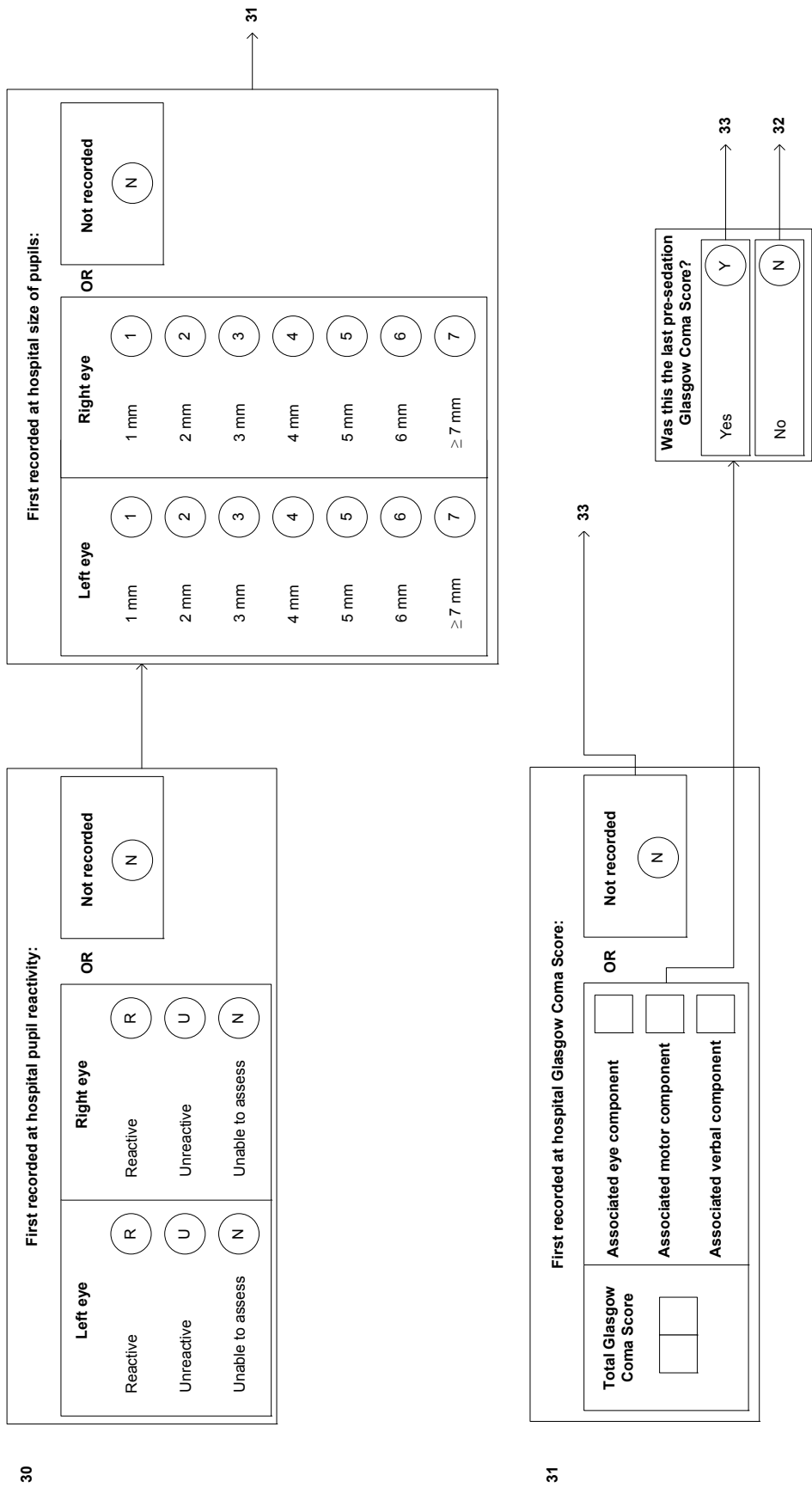
Source



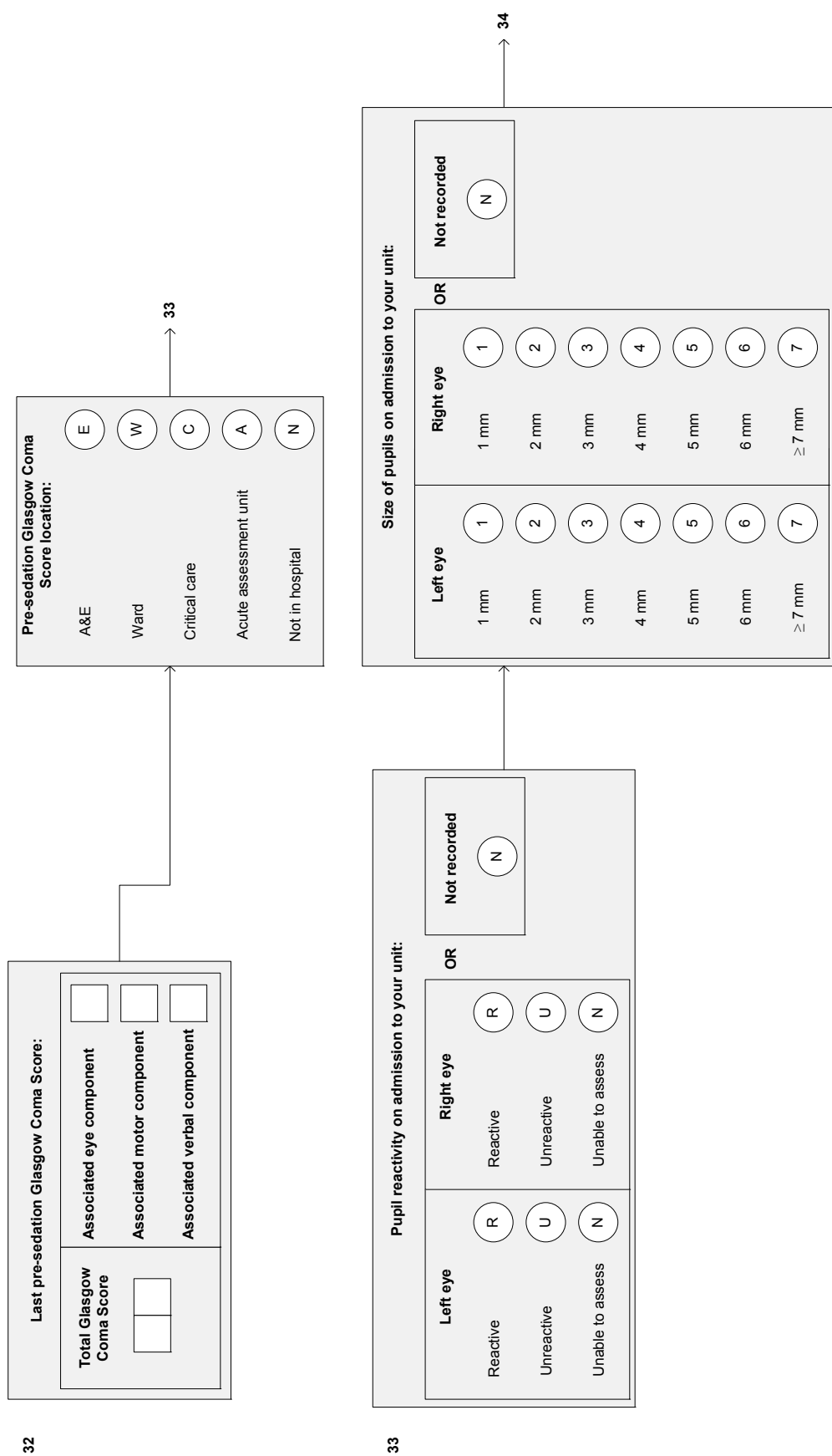
TBI at hospital

20	First recorded at hospital temperature:	<input type="text"/> . <input type="text"/> °C	Site: <input type="radio"/> Central <input type="radio"/> Non-central	→ 21																			
21	First recorded at hospital blood pressure:	<input type="text"/> / <input type="text"/> mmHg		→ 22																			
22	First recorded at hospital heart rate:	<input type="text"/> bpm		→ 23																			
23	First recorded at hospital oxygen saturation:	<input type="text"/> %		→ 24																			
24	First recorded at hospital arterial blood gas:	<table border="1"> <tr> <td>PaO₂</td> <td><input type="text"/> . <input type="text"/> kPa</td> <td>AND</td> <td>PaCO₂</td> <td><input type="text"/> . <input type="text"/> kPa</td> </tr> <tr> <td>OR</td> <td><input type="text"/> . <input type="text"/> mmHg</td> <td>AND</td> <td>OR</td> <td><input type="text"/> . <input type="text"/> mmHg</td> </tr> <tr> <td>FIO₂</td> <td><input type="text"/> . <input type="text"/></td> <td></td> <td>pH/H⁺</td> <td><input type="text"/> . <input type="text"/> pH</td> </tr> <tr> <td></td> <td></td> <td></td> <td>OR</td> <td><input type="text"/> . <input type="text"/> mmol l⁻¹</td> </tr> </table>	PaO ₂	<input type="text"/> . <input type="text"/> kPa	AND	PaCO ₂	<input type="text"/> . <input type="text"/> kPa	OR	<input type="text"/> . <input type="text"/> mmHg	AND	OR	<input type="text"/> . <input type="text"/> mmHg	FIO ₂	<input type="text"/> . <input type="text"/>		pH/H ⁺	<input type="text"/> . <input type="text"/> pH				OR	<input type="text"/> . <input type="text"/> mmol l ⁻¹	→ 25
PaO ₂	<input type="text"/> . <input type="text"/> kPa	AND	PaCO ₂	<input type="text"/> . <input type="text"/> kPa																			
OR	<input type="text"/> . <input type="text"/> mmHg	AND	OR	<input type="text"/> . <input type="text"/> mmHg																			
FIO ₂	<input type="text"/> . <input type="text"/>		pH/H ⁺	<input type="text"/> . <input type="text"/> pH																			
			OR	<input type="text"/> . <input type="text"/> mmol l ⁻¹																			
25	First recorded at hospital haemoglobin:	<input type="text"/> . <input type="text"/> g dl ⁻¹	<input type="radio"/> Missing	→ 26																			
26	First recorded at hospital platelet count:	<input type="text"/> . <input type="text"/> x 10 ⁹ l ⁻¹	<input type="radio"/> Missing	→ 27																			
27	First recorded at hospital serum glucose:	<input type="text"/> . <input type="text"/> mmol l ⁻¹	<input type="radio"/> Missing	→ 28																			
28	First recorded at hospital prothrombin time (PT):	<table border="1"> <tr> <td>Ratio</td> <td><input type="text"/> . <input type="text"/></td> <td>OR</td> <td>Time</td> <td><input type="text"/> s</td> </tr> <tr> <td></td> <td></td> <td>AND</td> <td>Control time</td> <td><input type="text"/> s</td> </tr> </table>	Ratio	<input type="text"/> . <input type="text"/>	OR	Time	<input type="text"/> s			AND	Control time	<input type="text"/> s	→ 29										
Ratio	<input type="text"/> . <input type="text"/>	OR	Time	<input type="text"/> s																			
		AND	Control time	<input type="text"/> s																			
29	First recorded at hospital activated partial thromboplastin time (APTT):	<table border="1"> <tr> <td>Ratio</td> <td><input type="text"/> . <input type="text"/></td> <td>OR</td> <td>Time</td> <td><input type="text"/> s</td> </tr> <tr> <td></td> <td></td> <td>AND</td> <td>Control time</td> <td><input type="text"/> s</td> </tr> </table>	Ratio	<input type="text"/> . <input type="text"/>	OR	Time	<input type="text"/> s			AND	Control time	<input type="text"/> s	→ 30										
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		AND	Control time	<input type="text"/> s																			

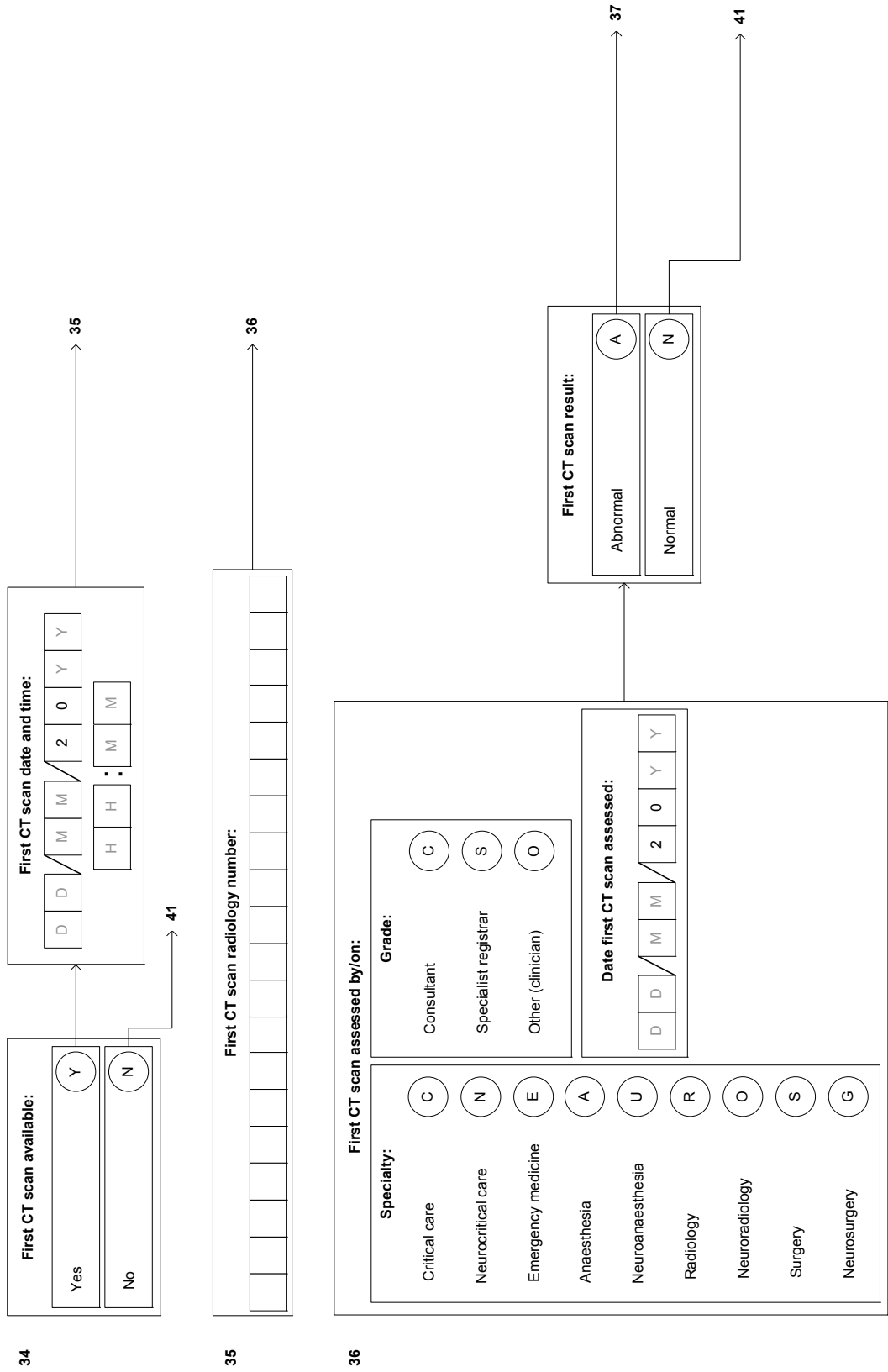
TBI at hospital



TBI at hospital



First CT



First CT (findings)

37

Traumatic subarachnoid haemorrhage present: Yes Y N

Brainstem pathology present: Yes Y N

Basal cisterns: Absent A C P

Third ventricle: Obliterated O P

→ 38

38

Midline shift present: Yes – greater than 5 mm Y N
No – less than or equal to 5 mm

Lesion(s) present: Yes Y N

One or more small petechial haemorrhage(s) ≤ 1 ml present: Yes Y N

High/mixed density lesion(s) > 1 ml present: Yes Y N

→ 39

→ 41

39

Type of high/mixed density lesion(s) present: Yes No

Extradural haematoma(s) present	<input type="radio"/> Y <input type="radio"/> N	<input type="radio"/> N
Subdural haematoma(s) present	<input type="radio"/> Y <input type="radio"/> N	<input type="radio"/> N
Intracerebral haematoma(s), haemorrhage(s) or contusion(s) present	<input type="radio"/> Y <input type="radio"/> N	<input type="radio"/> N
Posterior fossa haematoma(s) present	<input type="radio"/> Y <input type="radio"/> N	<input type="radio"/> N

Main mass lesion: E S I P

→ 40

40

Evacuation of haematoma: Yes Y N

Date and time of evacuation of haematoma:

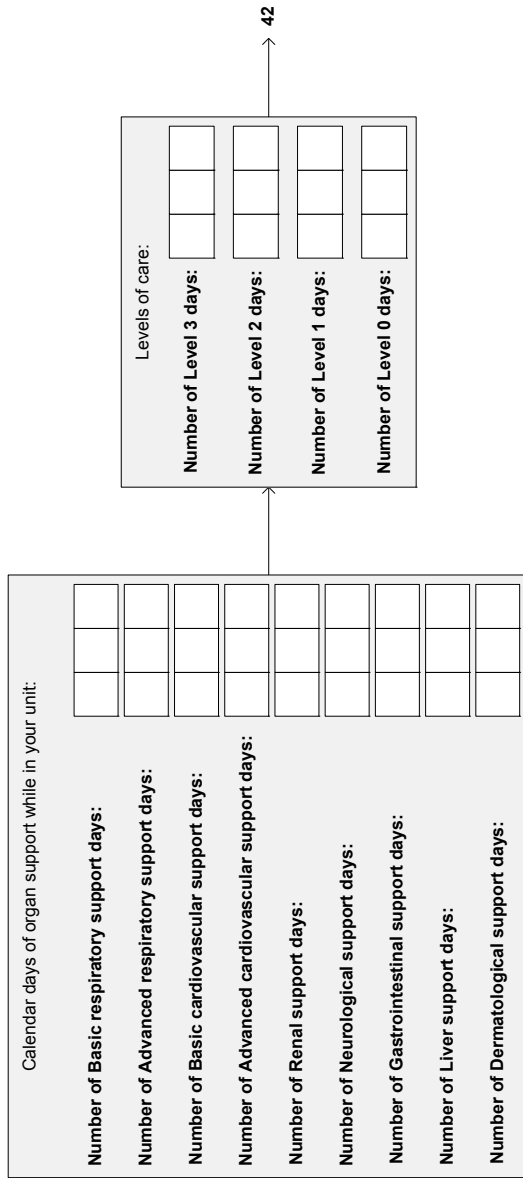
D	D	M	M	2	0	Y	Y
H	H	M	M	:	M	M	

Volume of largest high/mixed density lesion: Greater than 25 ml G L
Less than or equal to 25 ml

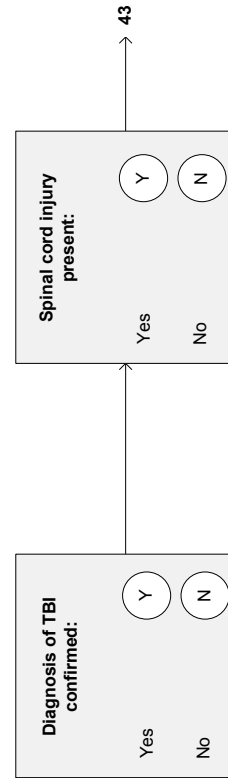
→ 41

Outcome

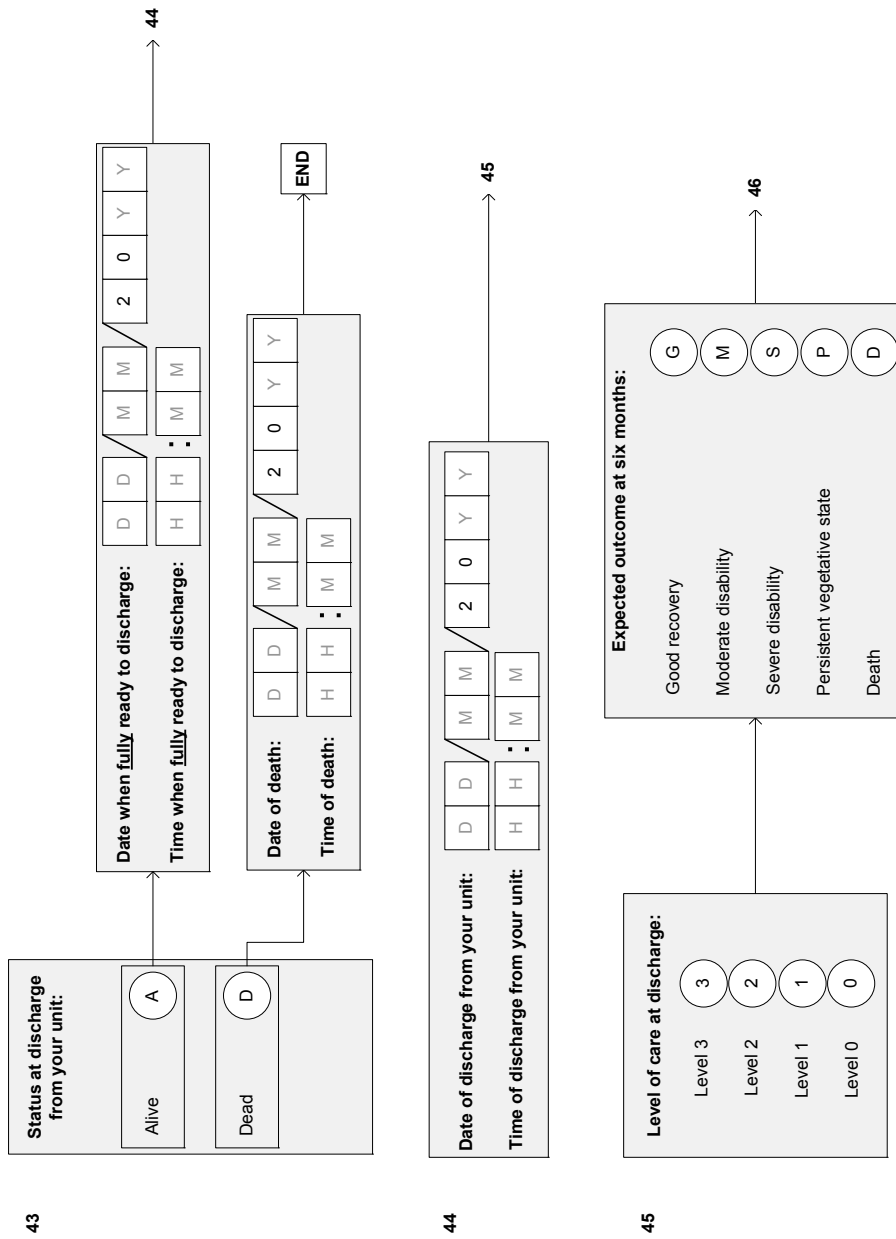
41



42

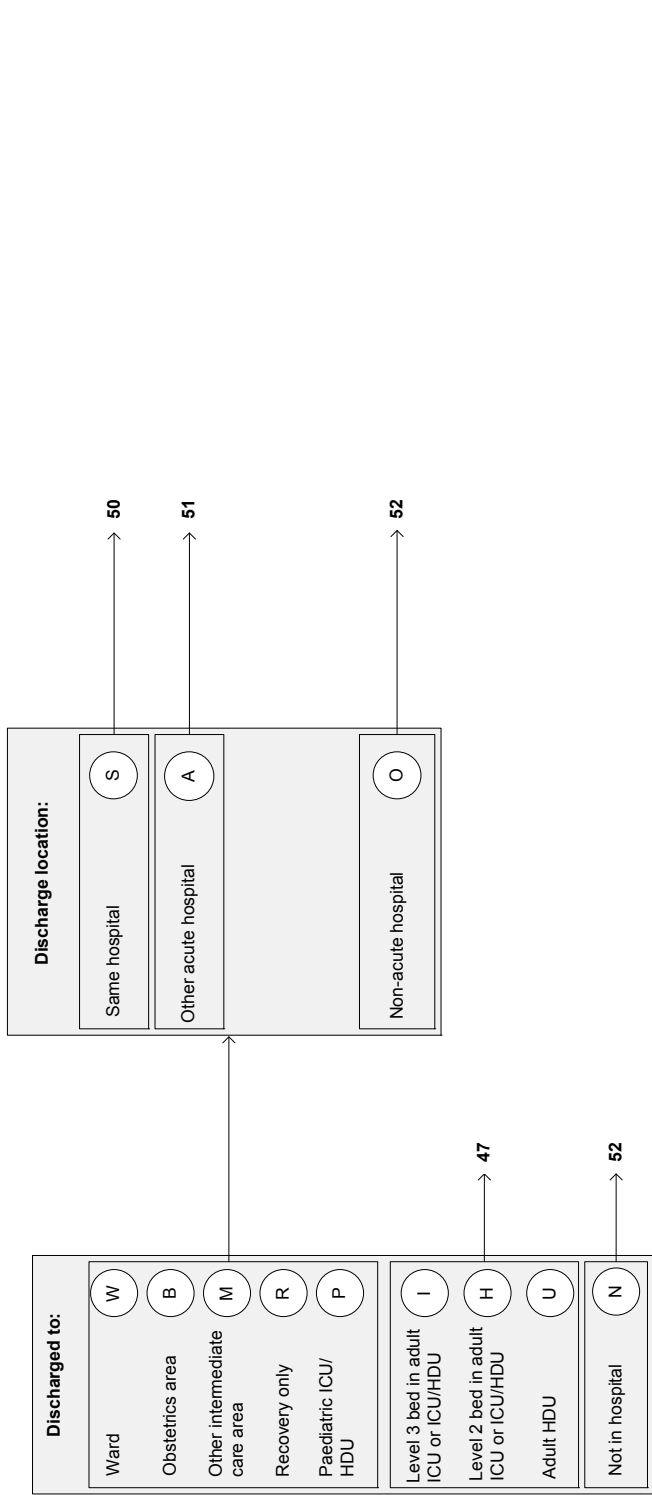


Outcome

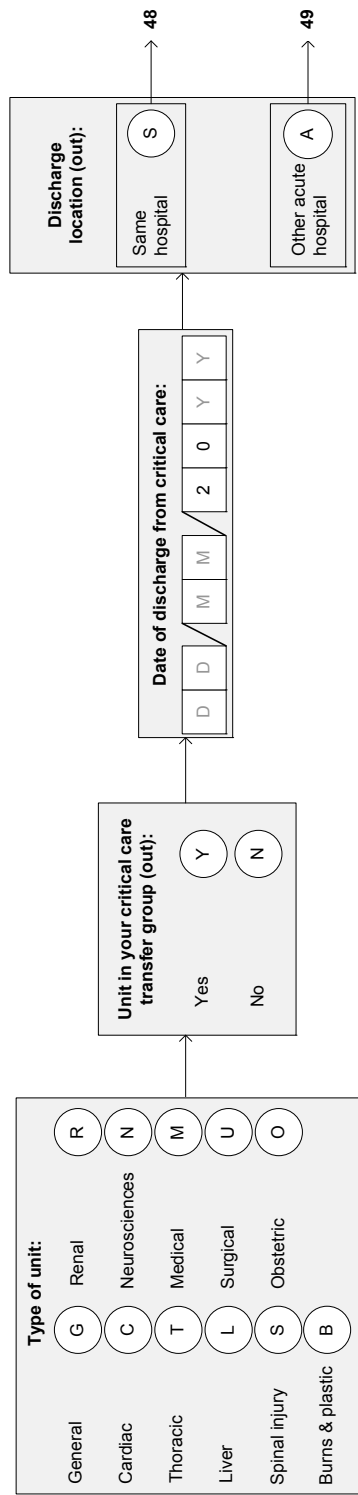


Outcome

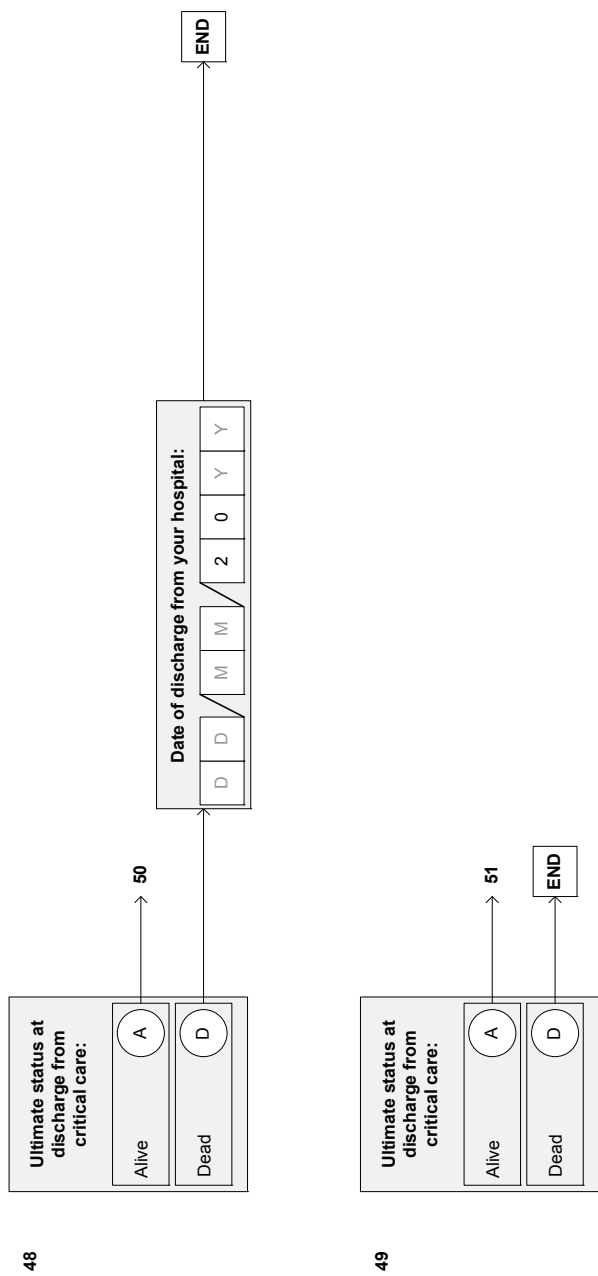
46

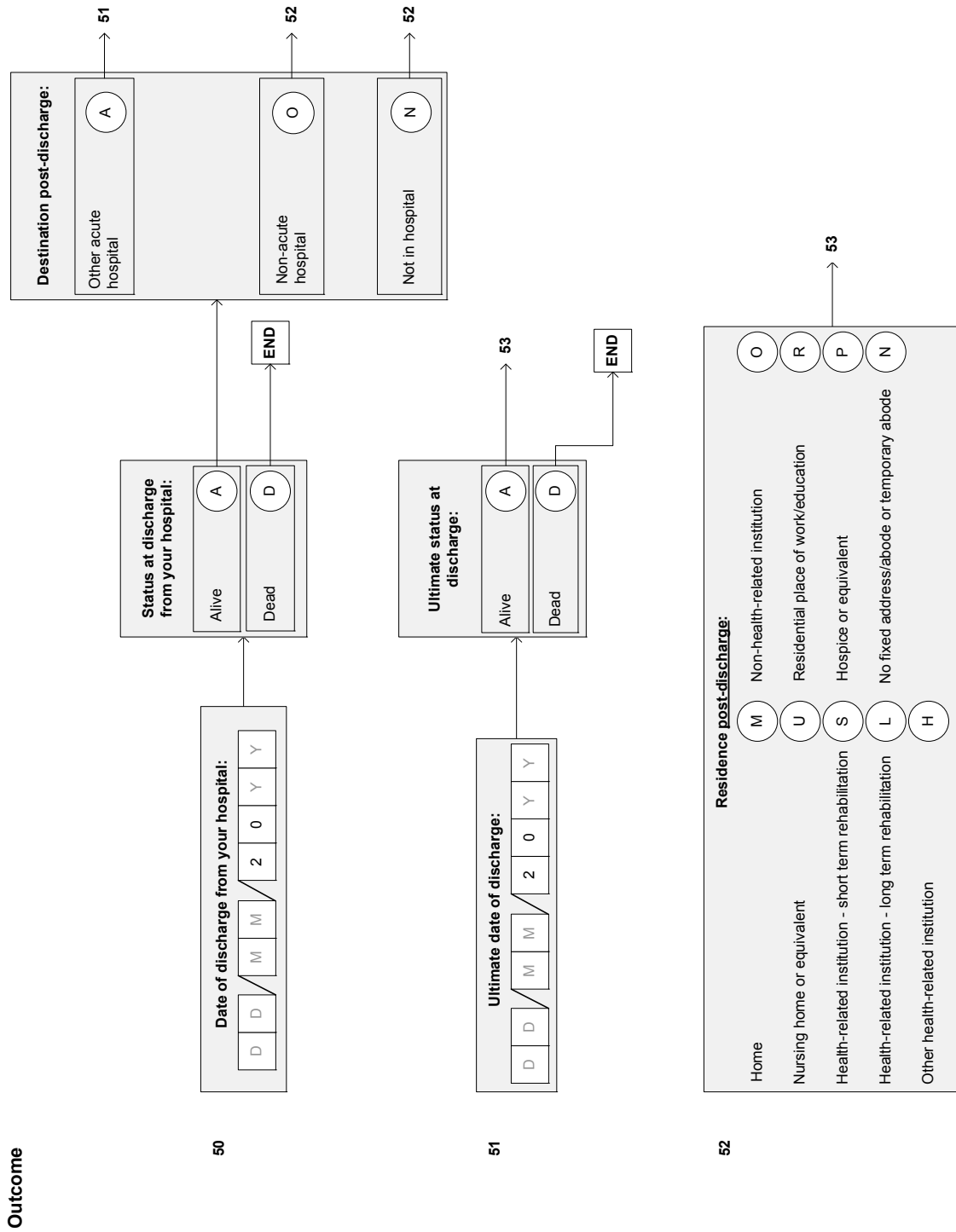


47



Outcome





GP

53

GP's initials:

GP's surname:

54

Registered GP Practice Code:

AND/OR

GP Practice name:

GP Practice address:

GP Practice postcode:

END

RAIN

Risk Adjustment In
Neurocritical care

Flows

Version 1.4

Non Case Mix Programme (Non-CMP) Units

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Flows

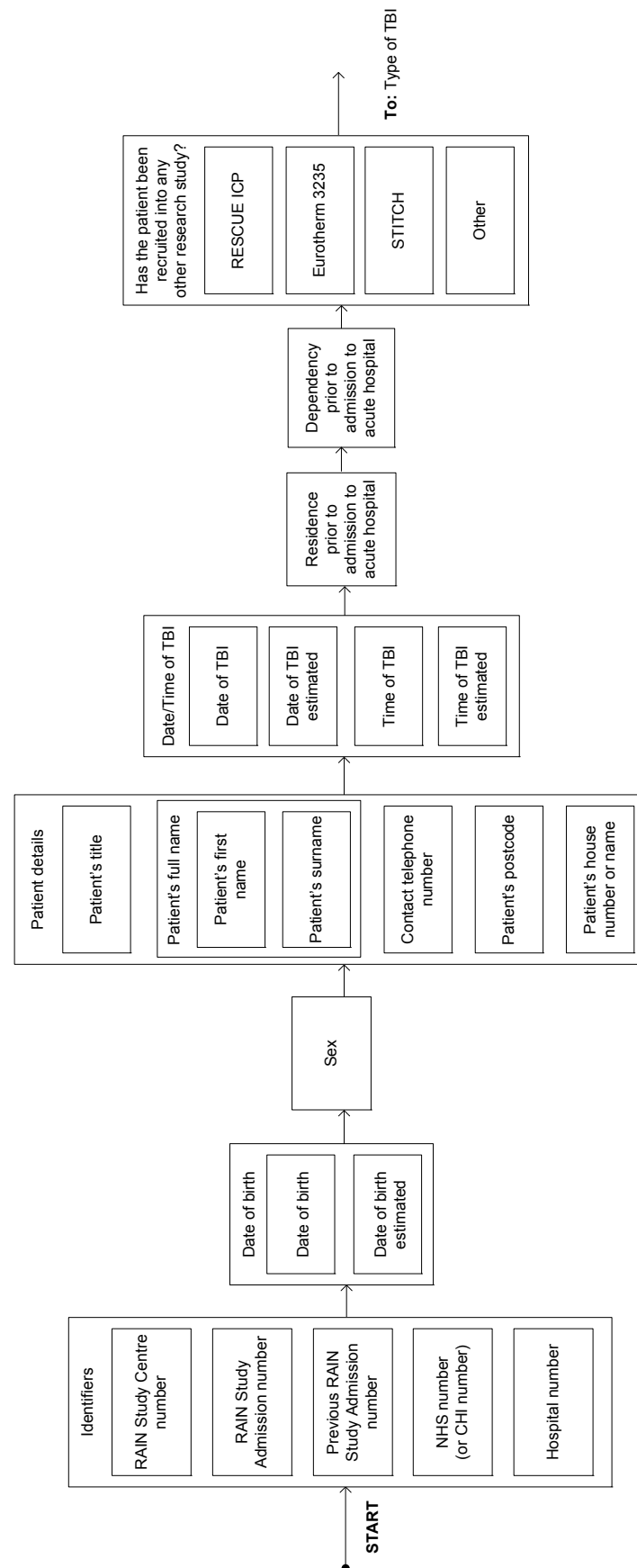
Order

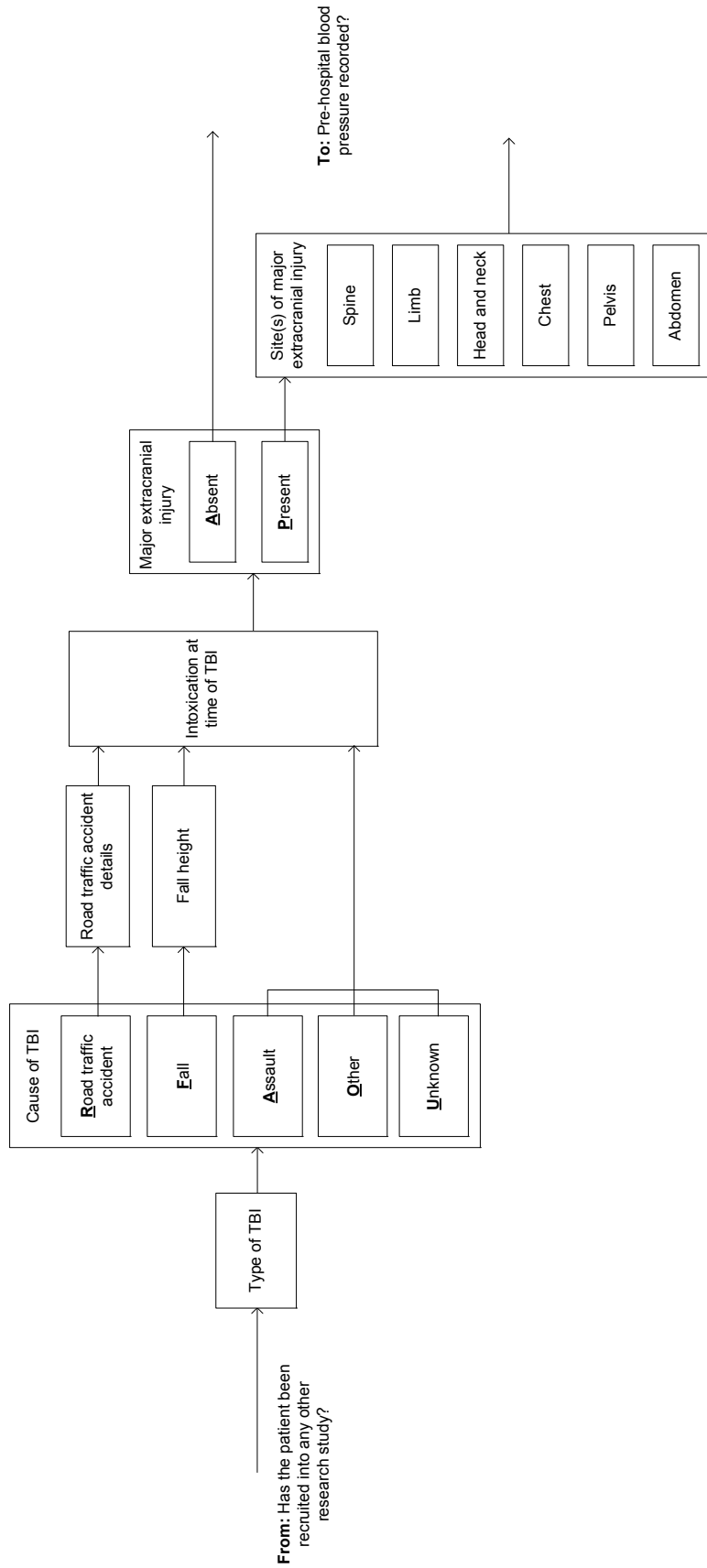
- the RAIN Dataset Specification (RAINDS) Version 1.4 contains the following sections, which appear in this order in the flows:
 - Patient
 - TBI pre-hospital
 - Source
 - TBI at hospital
 - CT
 - Outcome
 - GP

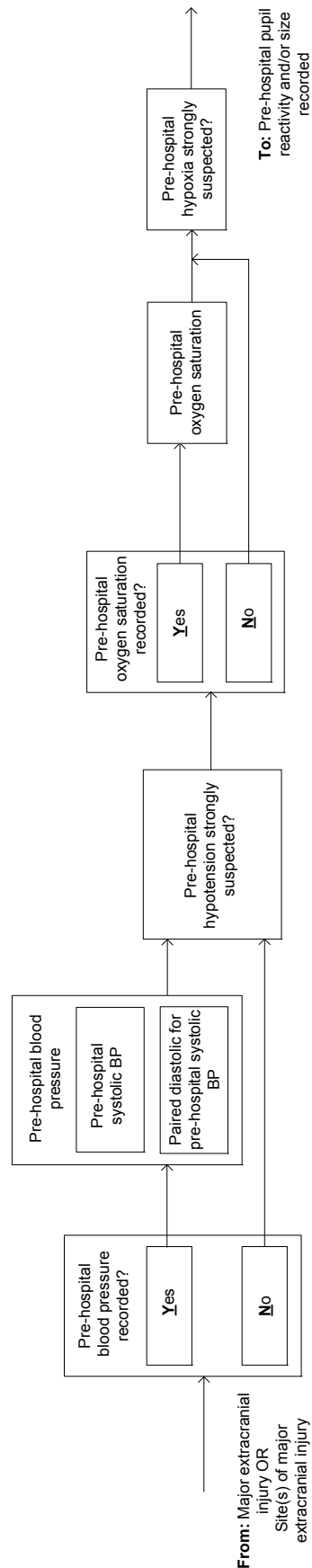
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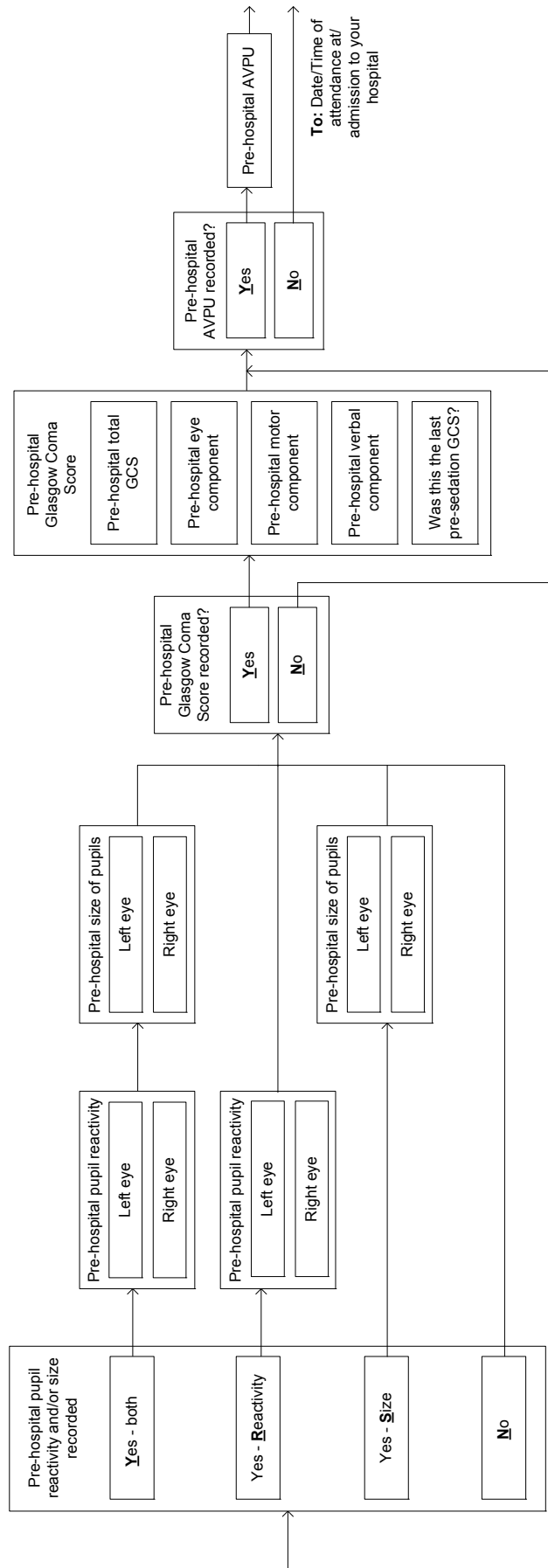
- flows run from left to right displaying the field
 - sections are indicated in the header of each page
-

RAINDS, NON-CMP V1.4: Patient

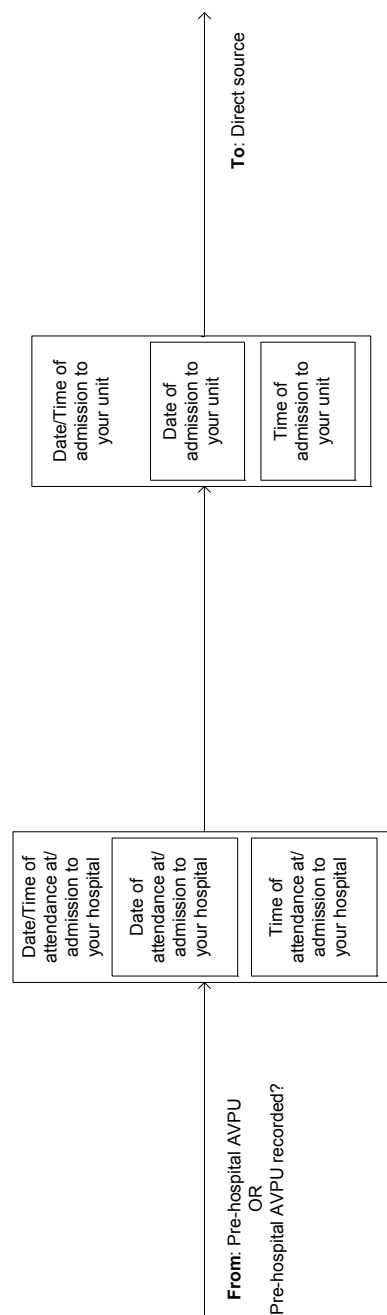


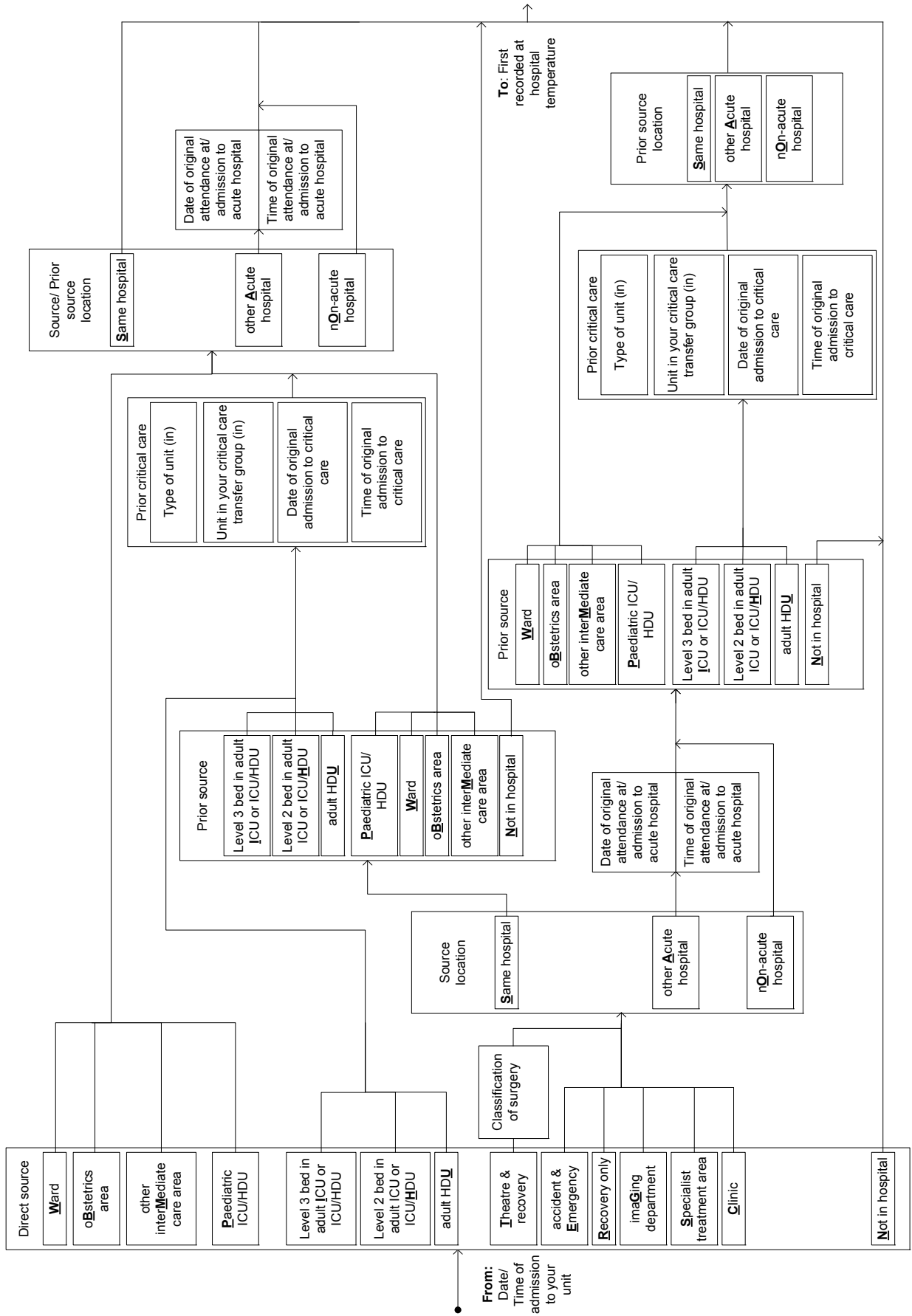


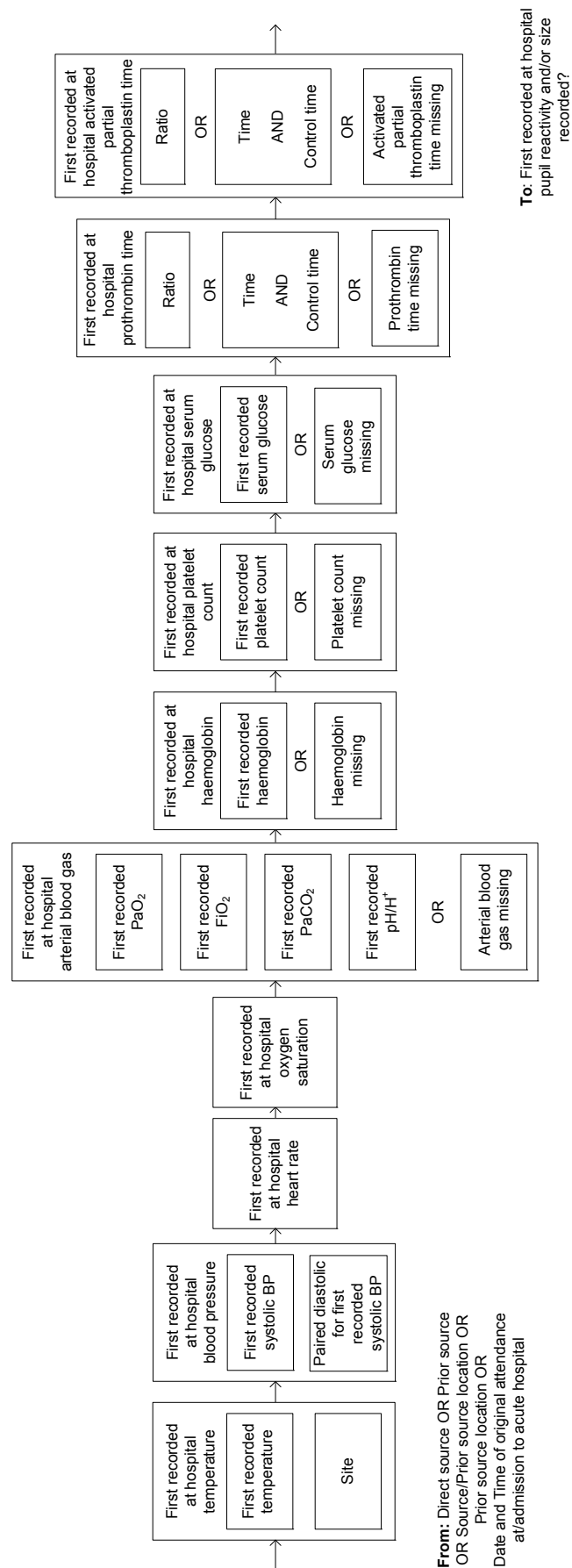


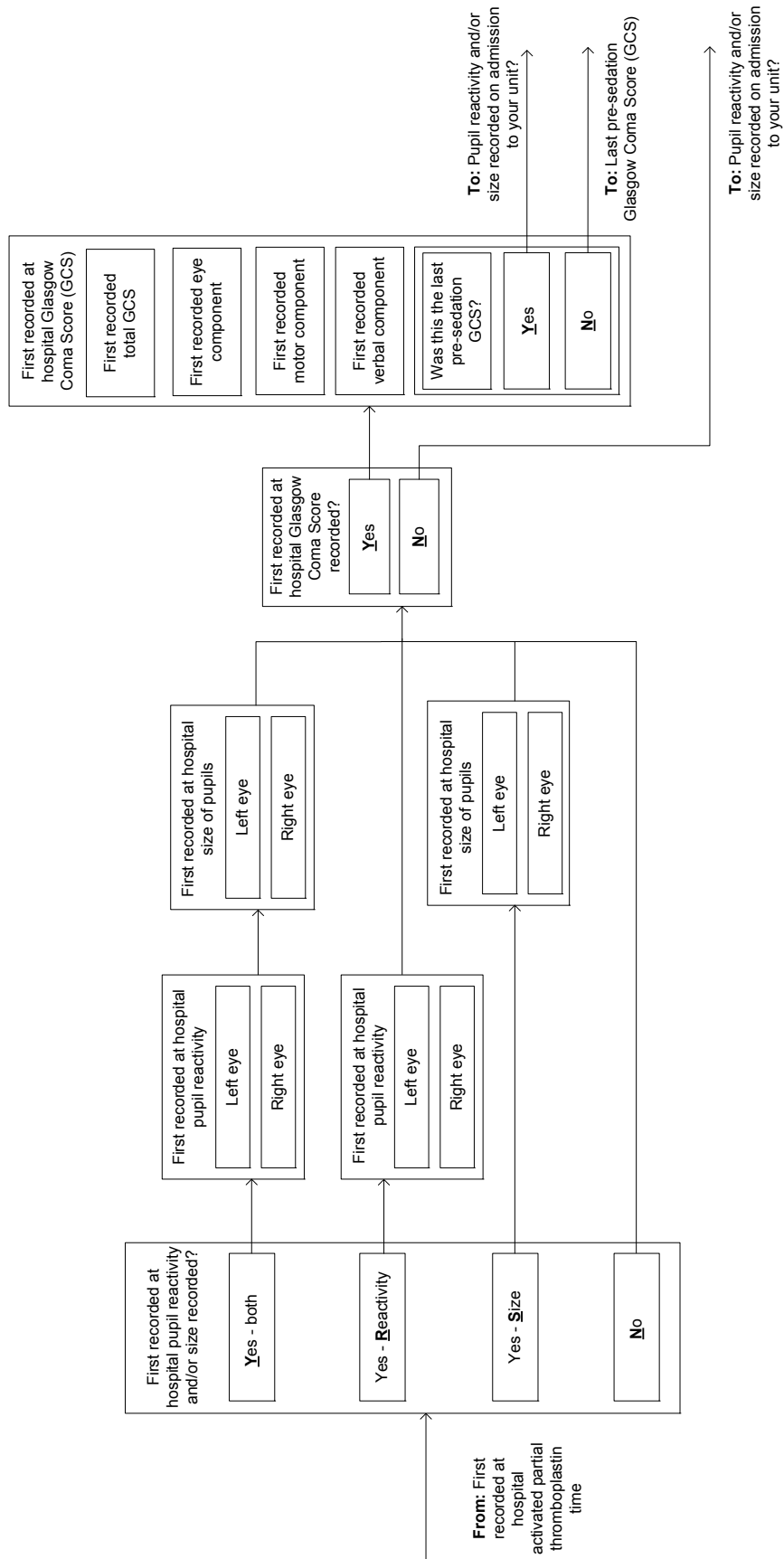


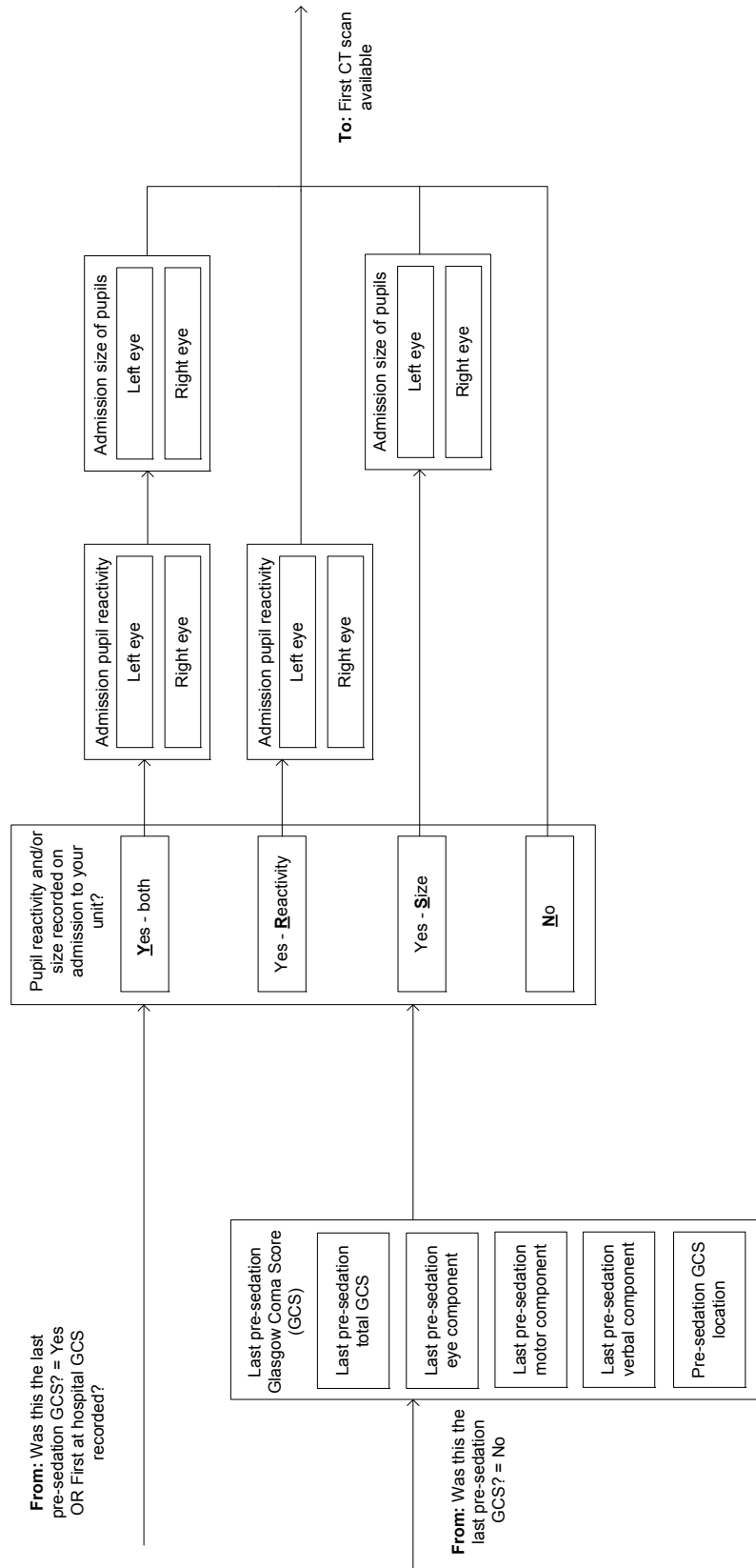
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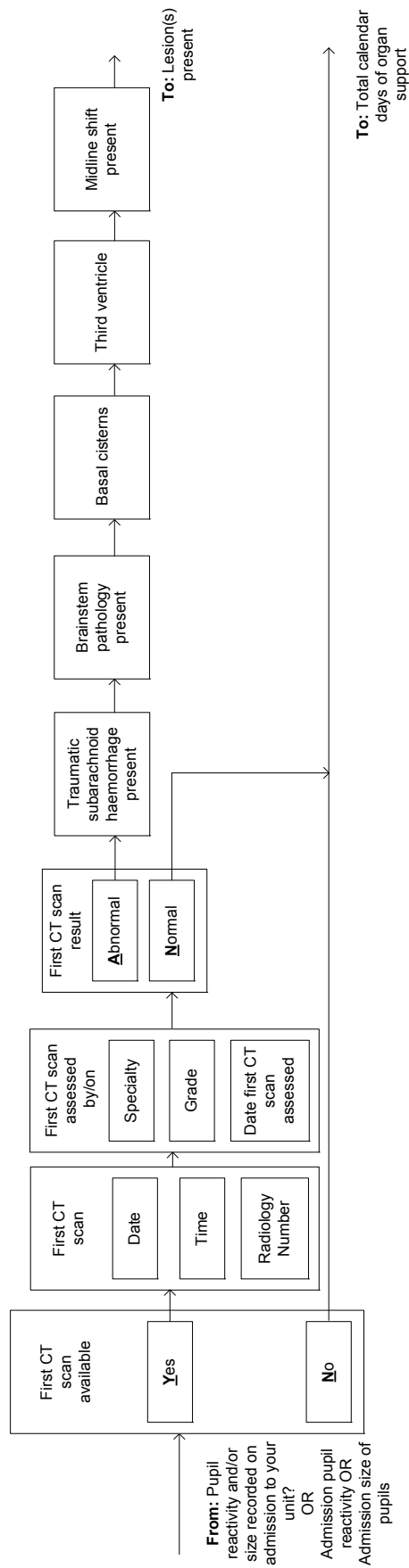


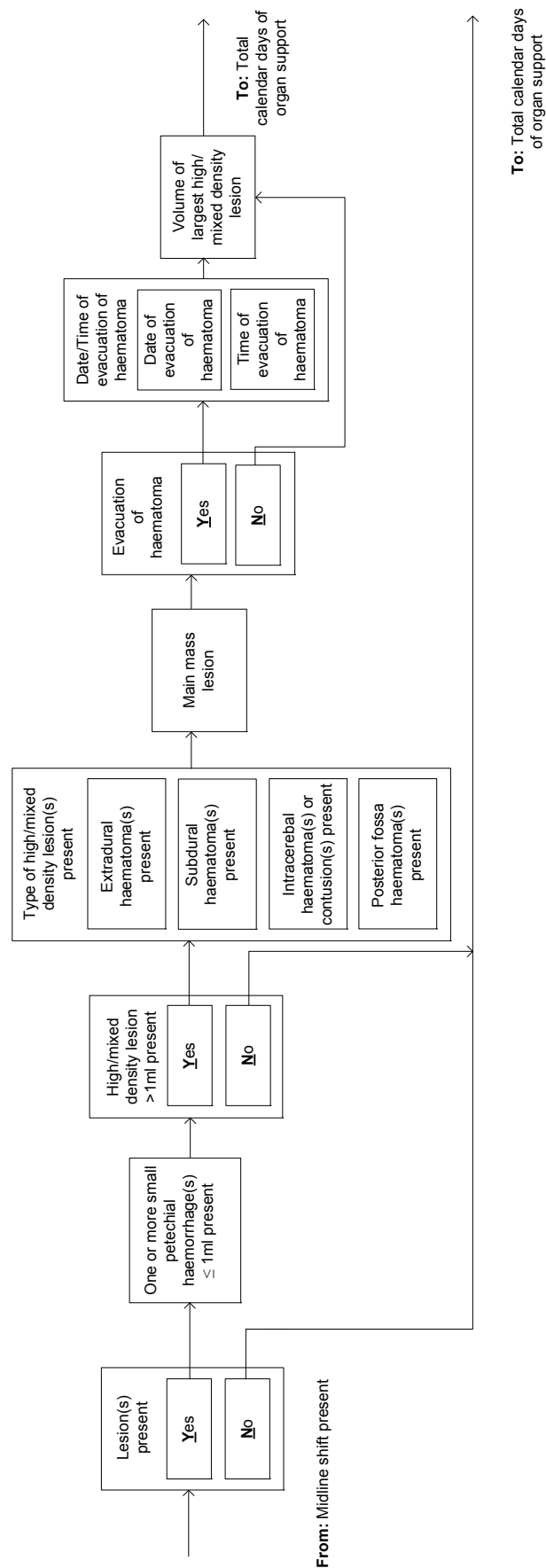


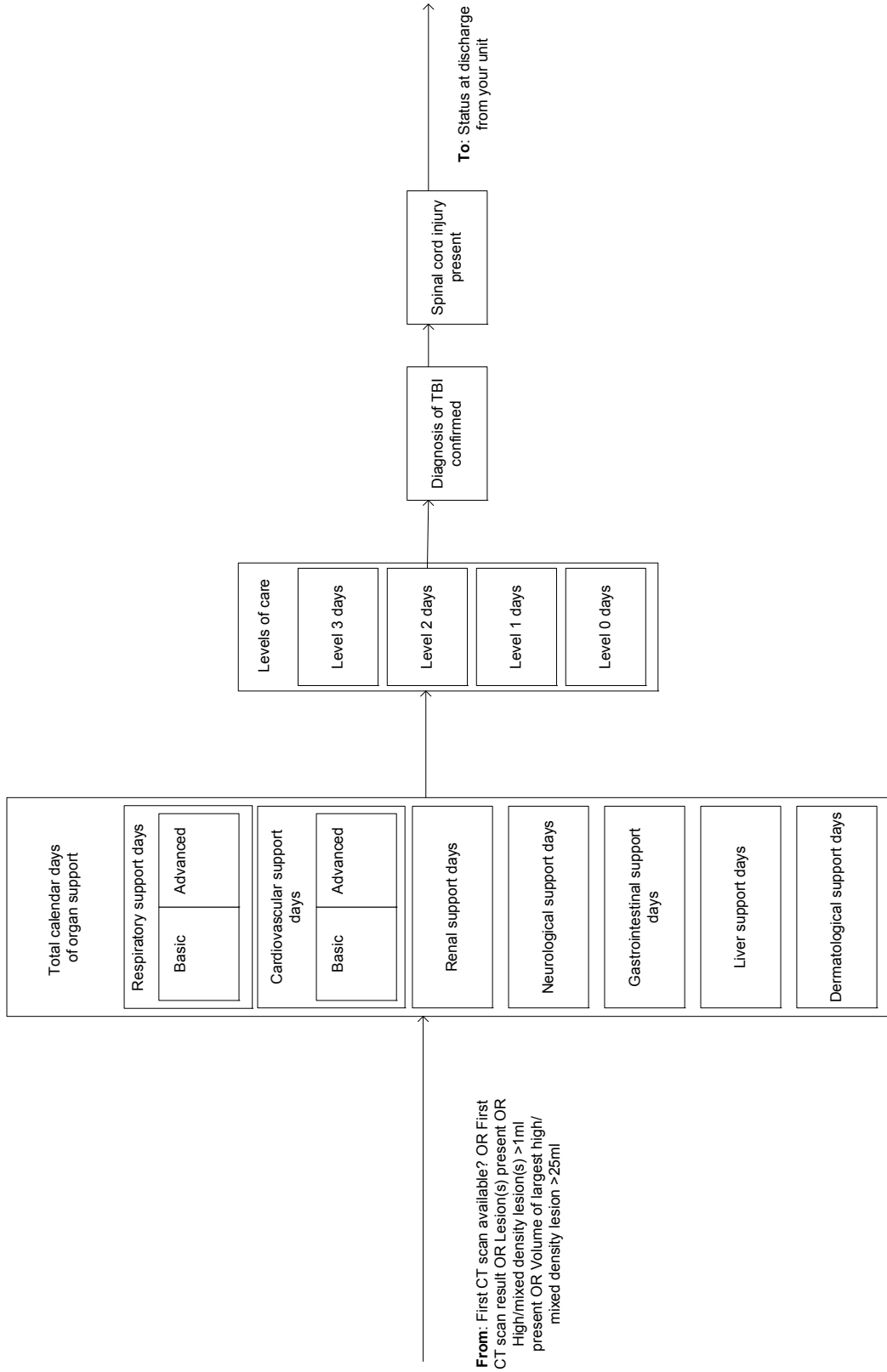


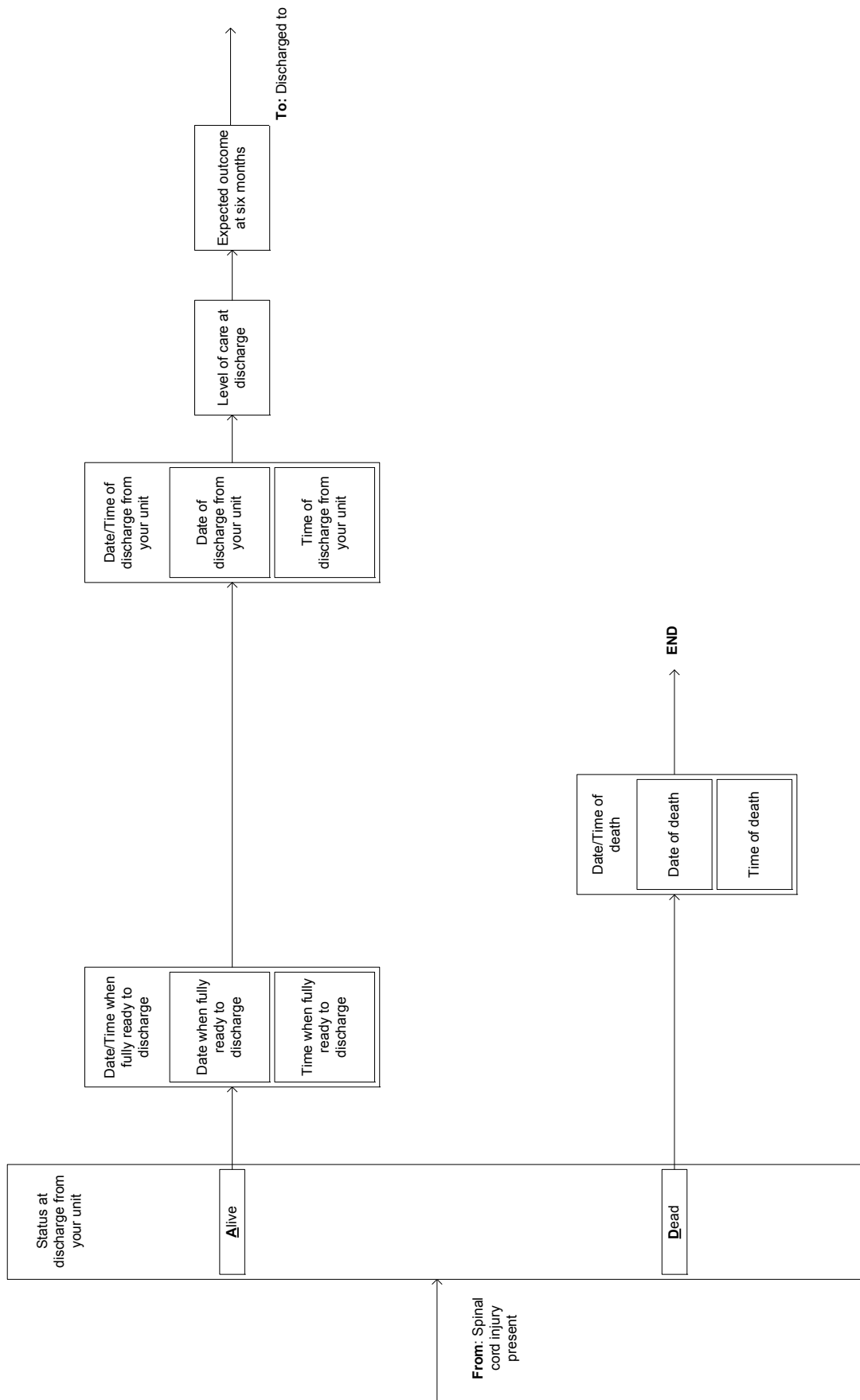


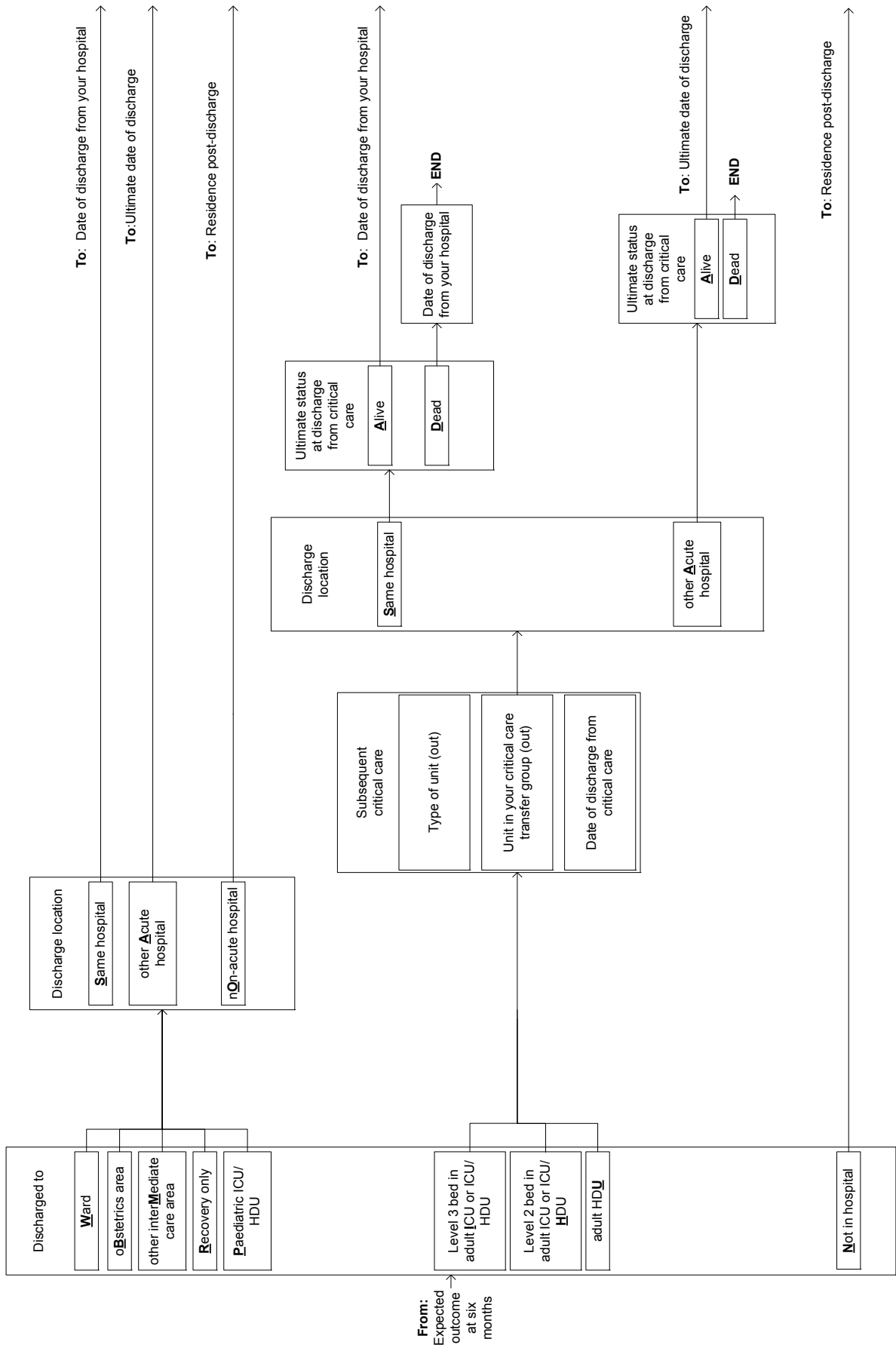


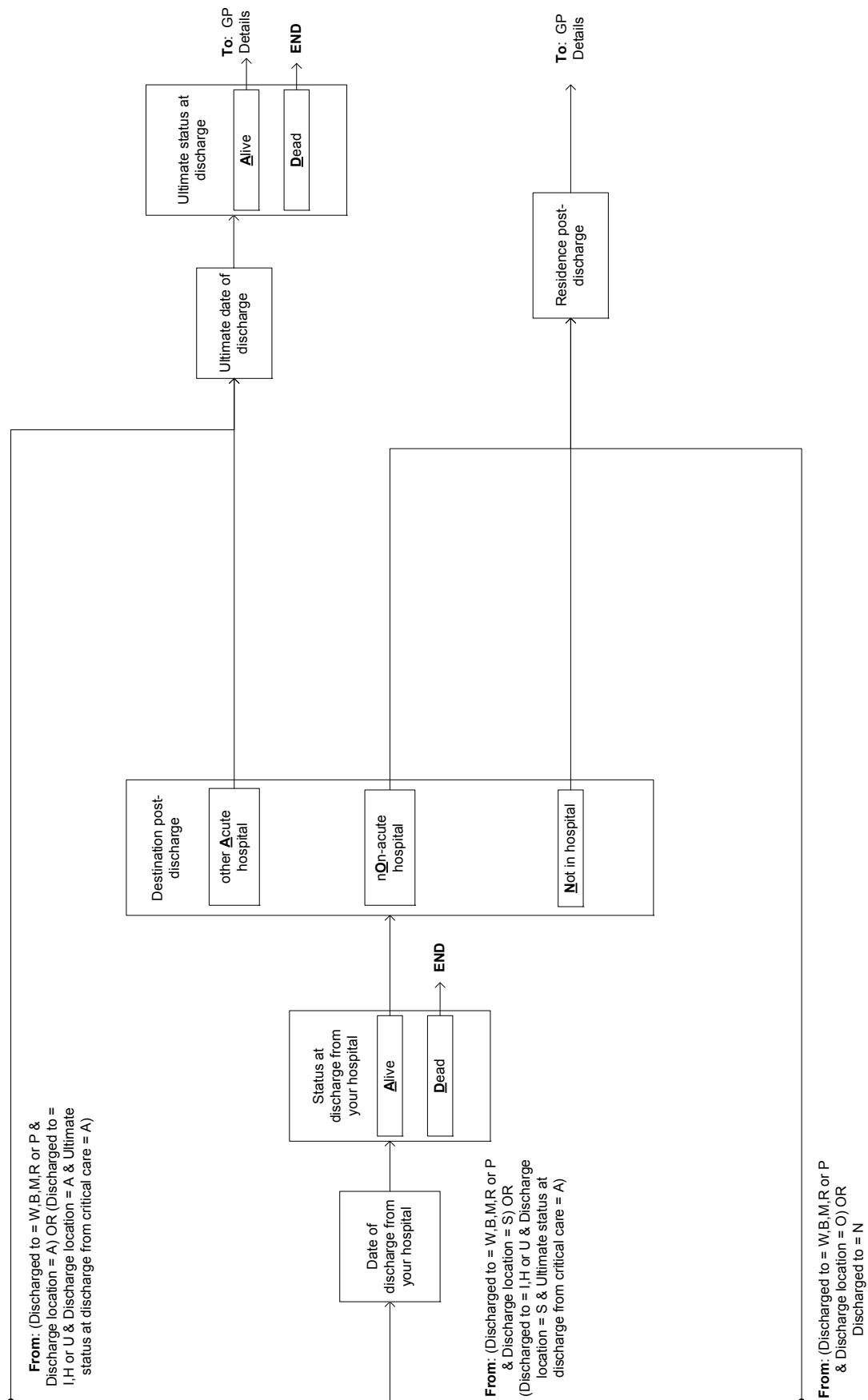


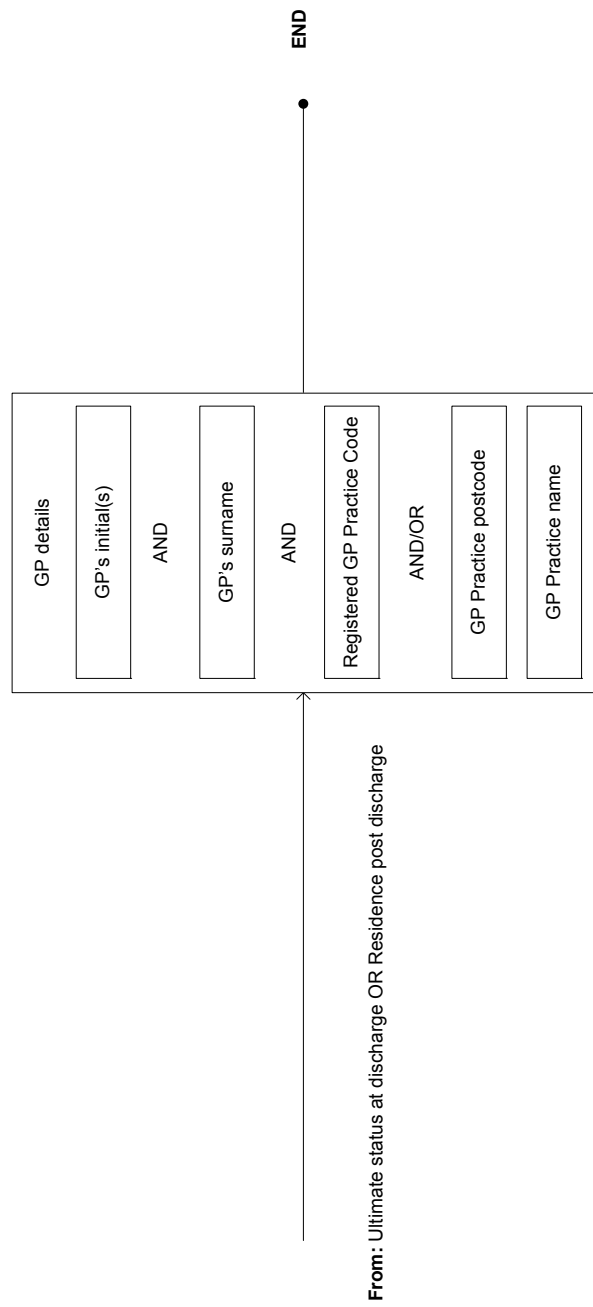












Appendix 5 Risk Adjustment In Neurocritical care study follow-up materials

GP letter, Version 4.4, 08/01/10



ICNARC
Tavistock House
Tavistock Square
London WC1H 9HR
tel +44 (0)20 7554 9770
fax +44 (0)20 7388 3759
email rain@icnarc.org

<Name of GP>
<Address1>
<Address2>
<City>
<County>
<Postcode>

<Date>

Dear <Name of GP>

Re: <Patient's name>, NHS number: <NHS number>, RAIN Study number: <RAIN number>

As I'm sure you are aware, five months ago, <name> spent time in intensive care following an acute traumatic brain injury. In two weeks time, we intend to write to them to invite them to participate in the above research study. RAIN aims to better understand recovery from head injury to inform care for future patients (NHS Research Ethics Committee Reference Number: 09/MRE09/10). Patient participation is entirely voluntary.

Naturally, to avoid the distress of receiving a letter addressed to a recently deceased family member, we would be very grateful if you would inform us as to whether your records indicate if <Patient's name> is alive or not and if alive confirm that <Patient name> is currently residing at the address shown on the attached form. We will not contact them until we hear back from you.

There are four possible ways to inform us, please either:

- enter these data onto the web based form (<web address>), using the confidential RAIN Study number <RAIN number> assigned to <Patient name>, or
- post the form to the above address; or
- fax the completed form to 020 7388 3759; or
- telephone Dr Gita Prabhu, RAIN Study Coordinator on 020 7554 9770.

<Patient name> (or their carer) will be asked to complete a health survey questionnaire (incorporating the Extended Glasgow Outcome Score and the EQ-5D) so we can assess their recovery and use of health services.

If you have any questions about the RAIN Study, then please do not hesitate to contact us on 020 7554 9770.

Thank you for your time.

Yours sincerely

Dr Gita Prabhu (RAIN Study Coordinator)
Dr David Harrison (Chief Investigator)
Intensive Care National Audit & Research Centre (ICNARC)

www.icnarc.org

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GP Form, Version 1.4, 08/01/10



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fax +44 (0)20 7388 3759
email rain@icnarc.org

Understanding recovery from head injury to inform care

NHS Research Ethics Committee (Reference Number: 09/MRE09/10)

Chief Investigator: Dr David Harrison, RAIN Study Coordinator: Dr Gita Prabhu

We would be very grateful if you would provide the following information.

Our records indicate that <Name of patient> (<ref number>) is:

Alive

Dead

If alive, our records indicate that this patient is currently residing at:

<Address1>

<Address2>

<City>

<County> <Postcode>

Yes

No

If no please provide the patient's current address below:

Date form was completed: / /

Completed by : _____

On behalf of <Name of GP>

<Address1>

<Address2>

<City>

<County> <Postcode>

Please either:

- enter these data onto the secure web based form (<web address>); or
- post the form to the above address; or
- fax the completed form to 020 7388 3759; or
- telephone Dr Gita Prabhu, RAIN Study Coordinator on 020 7554 9770.

Thank you for your time

RAIN letter, Version 5.2, 08/01/10

RAIN Risk Adjustment In
Neurocritical care

ICNARC
Tavistock House
Tavistock Square
London WC1H 9HR
tel +44 (0)20 7554 9770
fax +44 (0)20 7388 3759
email rain@icnarc.org

<Name of participant>
<Address1 >
<Address2>
<City>
<County>
<Postcode>

<Date>

Dear <Name of participant>

I am <Name of Local Investigator>, <job title> and I was involved in your care when you were admitted to our intensive care unit six months ago at <Name of hospital>. Our intensive care unit is participating, with other units, in a research study aiming to better understand recovery from head injury to inform care for future patients. As part of this study, we would like to know about your recovery. All we need you to do is to answer the enclosed, two, short questionnaires.

If you do not wish to take part, then please return the uncompleted questionnaires in the FREEPOST envelope and you will receive no further contact about the Study. Please note: your current and future care will not be affected whether you decide to, or not to, participate in this Study.

If you are the carer for the person to whom this letter is addressed and they are unable to read it, we would be very grateful if you would take the time to look through this letter and Information Sheet on their behalf. If you feel that they would like to participate, then please complete the questionnaires on their behalf. By better understanding the recovery of the person you care for, we hope to improve the care for future patients with head injuries.

The RAIN Study is being conducted by a health research charity called ICNARC (the Intensive Care National Audit & Research Centre). The aim of the Study is to investigate why some patients make a better recovery than others. To do this, we need to know about your recovery. We will compare the information you provide us in these questionnaires to information about your head injury and treatment that was collected by staff from the critical care unit during your stay in intensive care. I have included an Information Sheet with this letter. This will give you more detailed information about the Study. The Study has been approved by an NHS Research Ethics Committee (Reference Number: 09/MRE09/10).

- If you agree to participate, please sign the Consent Form (yellow sheet) and then we would be grateful if you would complete the enclosed questionnaires (blue and green sheets); this should only take around 15 minutes. Please return all of these in the FREEPOST envelope.
- If you are unable to complete the questionnaires on your own, then please ask one of your relatives/carers/friends to help you. Please return all of these in the FREEPOST envelope.

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<date>

Page 2

- If you do not wish to take part then please return the uncompleted questionnaires in the FREEPOST envelope and you will receive no further contact about the Study.

If you have any questions regarding the RAIN Study, then please do not hesitate to contact Dr Gita Prabhu, the RAIN Study Co-ordinator, on 020 7554 9770.

Finally, if you would like some information about head injuries or support in your recovery, Headway is a charity that provides this help and support to people and to those who care for them. Headway can be contacted on this freephone number: 0808 800 2244 or by email to helpline@headway.org.uk. Alternatively, your local rehabilitation unit may be able to offer advice (<tel: >).

Thank you very much for your time.

Yours sincerely

<Name of Principal/Local Investigator>
<Job title>, <hospital>
On behalf of the RAIN Study group.

Enclosed:

- Information Sheet
- Consent Form (yellow sheet)
- Your Health - Questionnaire (blue sheets)
- Health Services Questionnaire (green sheets)
- FREEPOST envelope
- Pen

Information sheet, Version 1.8, 08/01/10



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email rain@icnarc.org

INFORMATION SHEET

Understanding recovery from head injury to inform care

NHS Research Ethics Committee (09/MRE09/10)
Chief Investigator: Dr David Harrison, RAIN Study Coordinator: Dr Gita Prabhu

We would like to invite you to take part in a research study to help improve the care of patients who have suffered a traumatic brain injury (TBI). To do this we need you to fill out two short health questionnaires. The information below explains why we are doing this research and what it involves. Please read this information carefully so you can make an informed decision. If you have any questions please contact the RAIN Study team who will be more than happy to help. **Please note: your current and future care will not be affected whether you decide to, or not to, participate in this study.**

What is Traumatic Brain Injury?

Traumatic brain injury (TBI) is when a strike or knock to the head affects the normal functioning of the brain. There are many causes of TBI, such as a fall or a road traffic accident. The symptoms can vary from feeling sick or dizzy, to a brief loss of consciousness, to coma. Recovery after TBI is also varied. Some patients make a full recovery but others are left with a disability. If you would like some information about head injuries or support in your recovery, Headway is a charity that provides this help and support to people and to those who care for them. Headway can be contacted on this freephone number: 0808 800 2244 or by email to helpline@headway.org.uk. Alternatively, your local rehabilitation unit may be able to offer advice (<tel: >)

How will RAIN help TBI patients?

The overall aim of the Risk Adjustment In Neurocritical care (RAIN) Study is to improve the outcome and care given to patients who had a TBI. We are looking at patients who were admitted to critical care units to find why some people make a better recovery than others.

Many factors contribute to whether a person makes a good recovery. These include the type of injury, the health and age of the patient, where they were cared for and the medical treatment given. As every patient is different it can be difficult to know when/if a patient should be moved to another critical care unit, or when to start a particular treatment. We need to analyse data from thousands of patients to find what links the patients who have a positive outcome. The information that you provide us is vital for us to help improve the care for patients who have a TBI.

What would I have to do to take part in the study?

1. You would need to sign the Consent Form (yellow sheet).
This allows us to use information collected during your stay in hospital. This includes the type of injury you had, the treatments you received for that injury and which hospital(s) you stayed in.

2. You would need to fill out the health questionnaires (blue and green sheets). This will help us understand how well you are since your injury. This should only take about 15 minutes to complete.

Enclosed is a pen to fill out the forms and a FREEPOST envelope to return the Consent Form and questionnaires to us.

Do I have to take part?

No. It is up to you whether or not you take part.

- If you agree to participate, then please sign the Consent Form (yellow sheet) and then we would be grateful if you would complete the enclosed questionnaires (blue and green sheets); this should only take around 15 minutes.
- If you do not wish to take part then please return the uncompleted questionnaires in the FREEPOST envelope and you will receive no further contact about the Study.

How safe is my information?

The information collected is sent to a health research charity called ICNARC (the Intensive Care National Audit & Research Centre) for analysis. ICNARC has a secure computer system and a strict information security policy (approved by the Department of Health). All ICNARC staff sign a contract agreeing to keep data secure and confidential. It is forbidden to remove patient data from the premises. ICNARC is registered under the Data Protection Act (Reg. No.: Z6289325). Anonymised data collected as part of this study will be stored securely for five years following the end of the study.

What will happen to the results of the study?

The results may help improve the care of TBI patients in critical care. We hope these data will answer questions such as: When are treatments effective? When should TBI patients be moved to another critical care unit? How do the patient's initial symptoms relate to their outcome? The Study should be completed in February 2012. If you would like to be sent a copy of the results please contact the RAIN Study team.

Who do I contact about the study?

If you have any questions, concerns or complaints, please contact the RAIN Study Coordinator, Dr Gita Prabhu (address and telephone number overleaf).

IF THE PERSON YOU CARE FOR IS UNABLE TO GIVE INFORMED CONSENT

We would like the person you care for to take part in a research study. This study will help future patients who suffer a traumatic brain injury. If the person you care for is not well enough to decide for himself/herself whether or not to participate, we ask if you could read through this sheet carefully. We would like you to give your opinion as to whether or not you think your relative/friend/partner would object to taking part in this research.

If you feel that the person you are caring for would agree to take part in this research, please could you sign the yellow Consent Form and state your name and relationship to the patient in the 'consultee' section, then complete the questionnaires. A FREEPOST envelope is provided for you to return the Consent Form and questionnaires. Thank you for your time and consideration.

Thank you for taking the time to read this sheet

Consent form, Version 1.7, 08/01/10



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CONSENT FORM

Chief Investigator: Dr David Harrison

Improving the treatment of adult patients with acute traumatic brain injury

Please **initial** boxes

- 1 I confirm that I have read and understood the Information Sheet (v1.8) for the above study and have had the opportunity to ask questions.
- 2 I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason and without any future medical care or legal rights being affected.
- 3 I understand that sections of my care record have been looked at by responsible individuals involved with the study. I give my permission for these individuals to use this information for the Study.
- 4 I understand that information held by the NHS and records maintained by The NHS Information Centre may be used to keep in touch with me and follow up my health status.
- 5 I agree to take part in the above Study.

Name of participant:
(block capitals)

Today's date:

Signature:

(Where patients are unable to sign, a consultee should sign here and state their name and relationship to the participant below)

For the consultee

Name of consultee:
(block capitals)

Relationship to the participant

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Participant reference number



YOUR HEALTH - QUESTIONNAIRE

We would be grateful if you would complete this questionnaire. We would like to understand how you have been feeling since leaving the intensive care unit.

There are no right or wrong answers. We have found the best way to answer the questions is to go with your first instinct; whatever you think is the correct response for you.

A pen is provided and a FREEPOST envelope for return of the questionnaire.

Please complete today's date below:

____ / ____ / ____
Day Month Year

Please also let us know whether you completed this questionnaire:

- Alone
- With help
- Or it was completed by someone who cares for you

NOW PLEASE TURN THE PAGE TO START THE QUESTIONNAIRE ►

If you do not wish to complete this questionnaire, please return the unanswered questionnaire in the FREEPOST envelope provided.

Your current and future care will not be affected whether you decide to, or not to, fill out this questionnaire.

Participant reference number

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

- I have no problems in walking about
- I have some problems in walking about
- I am confined to bed

Self-Care

- I have no problems with self-care
- I have some problems washing or dressing myself
- I am unable to wash or dress myself

Usual Activities (*e.g. work, study, housework, family or leisure activities*)

- I have no problems with performing my usual activities
- I have some problems with performing my usual activities
- I am unable to perform my usual activities

Pain/Discomfort

- I have no pain or discomfort
- I have moderate pain or discomfort
- I have extreme pain or discomfort

Anxiety/Depression

- I am not anxious or depressed
- I am moderately anxious or depressed
- I am extremely anxious or depressed

Participant reference number

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

**Your own
health state
today**

Best
imaginable
health state

100

90

80

70

60

50

40

30

20

10

0

Worst
imaginable
health state

Participant reference number

The following questions are about changes in your lifestyle since your injury. There are also some questions about how things were before the injury. The questions can be answered by you, or by a close relative or friend, or by you both together. We are interested in the recovery you have made up to now.

Please answer each question by ticking one box which is true for you.

1. Before the injury were you able to look after yourself at home?

Yes

No

2. As a result of your injury do you now need help in the home?

I do not need help or supervision in the home

I need some help in the home, but not every day

I need help in the home every day, but I could look after myself for at least 8 hours if necessary

I could not look after myself for 8 hours during the day

I need help in the home, but not because of the injury

3. Before the injury did you need help to shop?

Yes

No

4. As a result of your injury do you now need help to shop?

I do not need help to shop

I need some help, but I can go to local shops on my own

I need help to shop even locally, or I cannot shop at all

I need help to shop, but not because of the injury

Participant reference number

5. Before the injury did you need help to travel?

- Yes
- No

6. As a result of your injury do you now need help to travel?

- I do not need help to travel
- I need some help, but can travel locally on my own (e.g. by arranging a taxi)
- I need help to travel even locally, or I cannot travel at all
- I need help to travel but not because of the injury

7. Employment before the injury:

- | | |
|--|--|
| <input type="checkbox"/> Working | <input type="checkbox"/> Looking for work |
| <input type="checkbox"/> Caring for family | <input type="checkbox"/> Studying as a student |
| <input type="checkbox"/> Retired | <input type="checkbox"/> None of these (e.g. unfit for work) |

8. As a result of your injury has there been a change in your ability to work?*(or to study if you were a student; or to care for your family if you were the main caregiver)*

- I can still do the same work
- I can still work, but at a reduced level (e.g. change from full-time to part-time, or change in level of responsibility)
- I am unable to work, or only able to work in sheltered workshop
- My ability to work has changed, but not because of the injury

9. Before the injury did you take part in regular social and leisure activities outside home (at least once a week)?*Social and leisure activities include: going out to a pub or club, visiting friends, going to the cinema or bingo, going out for a walk, attending a football match, taking part in sport*

- Yes
- No

10. As a result of your injury has there been a change in your ability to take part in social and leisure activities outside home?

- I take part about as often as before (the activities may be different from before)
- I take part a bit less, but at least half as often
- I take part much less, less than half as often
- I do not take part at all
- My ability to take part has changed for some other reason, not because of the injury

Participant reference number

11. Before the injury did you have any problems in getting on with friends or relatives?

- Yes
 No

12. As a result of your injury are there now problems in how you get on with friends or relatives?

- Things are still much the same
 There are occasional problems (less than once a week)
 There are frequent problems (once a week or more)
 There are constant problems (problems every day)
 There are problems for some other reason, not because of the injury
-

13. Are there any other problems resulting from your injury which have interfered with your daily life over the past week?

*(Problems sometimes reported after head injury: **headaches, dizziness, tiredness, sensitivity to noise or light, slowness, memory failures, and concentration problems.**)*

- I have no current problems
 I have some problems, but these do not interfere with my daily life
 I have some problems, and these have affected my daily life
 I have some problems for other reasons, not because of the head injury

14. Before the injury were similar problems present?

- I had no problems before, I had minor problems
 I had similar problems before
-

Are there any other comments that you would like to make?

(Please continue on a separate sheet if you wish)



HEALTH SERVICES QUESTIONNAIRE

We would be grateful if you would complete this questionnaire. It will help us understand the care you needed after leaving the intensive care unit.

The RAIN Study aims to improve care for patients who have suffered a traumatic brain injury.

A pen is provided and a FREEPOST envelope for return of the questionnaire. Please answer multiple choice questions by putting a ✓ in ONE BOX for each question.

Please complete today's date below:

____ / ____ / ____
Day Month Year

Please also let us know whether you completed this questionnaire:

- Alone
- With help
- Or it was completed by someone who cares for you

NOW PLEASE TURN THE PAGE TO START THE QUESTIONNAIRE ►

If you do not wish to complete this questionnaire, please return the unanswered questionnaire in the FREEPOST envelope provided.

Your current and future care will not be affected whether you decide to, or not to, fill out this questionnaire.

The questions refer to ALL health services that you have used since leaving the hospital on [insert date], and before [insert date].

Part 1. Hospital Stay

A Since you left hospital on [insert date] have you stayed overnight in hospital for any reason (this includes hospital stays that were not due to your head injury)?

- No - Go to Part 2
- Yes - Please give details about the number of stays below

B For EACH TIME you stayed in hospital please answer the following

	Number of nights		1-3 nights	4-10 nights	11 or more nights	Did you spend any part of your stay in intensive care?
1 st stay	<input type="text"/>	or...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2 nd stay	<input type="text"/>	or...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3 rd stay	<input type="text"/>	or...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4 th stay*	<input type="text"/>	or...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

**If you have stayed in hospital overnight more than 4 times, please could you provide information on these further hospital stays in Part 6 of the questionnaire.*

Part 2. Hospital outpatient visits

Outpatient visits are when a patient comes to the hospital to see a specialist (e.g. neurologist) but does not stay overnight.

A Since you left the hospital on [insert date] have you visited hospital outpatients about ANY ASPECT of your health?

- No - Go to Part 3
- Yes - Please give details about the number of outpatients visit(s) below

B Number of visits or... 1-3 visits 4-10 visits 11 or more visits

Part 3. Visits to health care providers

A Since you left the hospital on [insert date] have you VISITED any of the health care providers listed below?

- No - Go to Part 4
- Yes - Please give details about your visits below

B For EACH PROVIDER please answer the following

Did you visit this provider?	Number of visits		1-3 visits	4-10 visits	11 or more visits
GP <input type="checkbox"/>	_____	or...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Nurse at your GP clinic <input type="checkbox"/>	_____	or...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Nurse at hospital or elsewhere <input type="checkbox"/>	_____	or...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Health visitor <input type="checkbox"/>	_____	or...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Part 4. Visits to your home by health care providers

A Since you left the hospital on [insert date] have you had HOME VISITS from any of the following health care providers about ANY ASPECTS of your health?

- No - Go to Part 5
- Yes - Please give details about your visits below

B For EACH HOME VIST please answer the following

Were you visited at home by this provider?	Number of visits		1-3 visits	4-10 visits	11 or more visits
GP <input type="checkbox"/>	_____	or...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Nurse from your GP clinic <input type="checkbox"/>	_____	or...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Occupational therapist <input type="checkbox"/>	_____	or...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Health visitor or District nurse <input type="checkbox"/>	_____	or...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Part 5. Visits to other service providers

A Since you left the hospital on [insert date] please indicate whether you have had ANY contact (either visits to the provider or home visits) with any of the following service providers about ANY ASPECT of your health?

- No - Go to Part 6
- Yes - Please give details below

B For EACH PROVIDER please answer the following

Have you had contact with any of these providers?	Number of visits	1-3 visits	4-10 visits	11 or more visits
Clinical psychologist <input type="checkbox"/>	_____ or...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Speech and language therapist <input type="checkbox"/>	_____ or...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Occupational therapist <input type="checkbox"/>	_____ or...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Mental health service <input type="checkbox"/>	_____ or...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Hospital discharge coordinator <input type="checkbox"/>	_____ or...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Counsellor <input type="checkbox"/>	_____ or...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Physiotherapist <input type="checkbox"/>	_____ or...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Cognitive behavioural therapist <input type="checkbox"/>	_____ or...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Continuing care nurse <input type="checkbox"/>	_____ or...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Social worker <input type="checkbox"/>	_____ or...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Art therapist <input type="checkbox"/>	_____ or...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Health Services Questionnaire, Version 2.5, 08/01/10, Participant reference number

Part 6. Other services not listed so far

A Since you left the hospital on [insert date] have you had further hospital stays or used ANY other health care services for ANY ASPECT of your health that you haven't included above?

No - Go to Part 7

Yes - Please give details below

B For EACH PROVIDER please answer the following

Type of service provider	Number of visits	Reason
e.g. Neurological rehabilitation centre	4	Check-up

Part 7. Comments

Your views are important to us. Please feel free to provide any other comments you have when completing the questionnaire in the box below.

Thank you for help

If you would like to ask us any questions about completing the questionnaire please email or call:

Gita Prabhu
rain@icnarc.org
020 7388 9770

Richard Grieve
Richard.Grieve@lshtm.ac.uk
020 7927 2255

Telephone Interview Schedule RAIN Study six month follow-up

1. Hello. I am (*interviewer's name*). I am calling about a medical research study we are carrying out to improve the care of people who have suffered a head injury. Can I speak to (*name*)?

If (*name*) did not answer the phone say the first two lines of 1., when *he/she* picks up the telephone and then continue through the numbered points.

If (*name*) is **unable to consent** go to the **red sheet**.

If you are speaking to (*name*):

2. The study is being carried out by ICNARC, the Intensive Care National Audit & Research Centre. It involves answering a few questions about your current health to help us improve the care of people who have had a head injury. Would you have time for me to tell you a little about what is involved now, this would only take a few minutes, or could I phone you back at a time that is more convenient to you? Would you be interested in hearing more about the Study?

If the patient does not want to take part in the study, thank them for their time. Interview ends.

If the patient would prefer to be **called back** at another time go to the **green sheet**.

If the patient is happy to continue:

3. We have been contacting people who have suffered a head injury to find out how well they have recovered since leaving the Intensive Care Unit. This will help us improve the care of future patients. By linking the medical treatments you received in hospital and the type of injury you had to how well you feel now, we can discover why some people make a better recovery than others. For instance this could then help doctors understand which treatments are best for which patients.
4. If you agree to take part in the study all you need to do is answer a few questions on how you have been feeling since your head injury. This will take about 10 minutes to complete. We would then link this information to which hospitals you stayed in and the medical treatments you received.
5. We are covered by the Data Protection Act. All information is kept on secure servers and no personal data is allowed off the premises. The results of the study will be published and if you would like a copy of the final results I can send this to you.

If yes note the participant's request.

6. Importantly, taking part in the study would not affect your medical care, but it will help future patients who suffer a head injury.
7. Would you be interested in taking part in the study?

If the patient says ‘no’, thank them for their time. Interview ends.

If the patient says ‘yes’:

8. Thank you for agreeing to take part. Would you be happy to answer the questions now? It will only take about 10 minutes to complete.

If the participant would prefer to arrange another time - go to the box at the end of this page:

9. Before we start the questions, remember there are no right or wrong answers. We have found that the best way to answer the questions is to go with your first instinct, whatever you think is the correct response for you.
10. The questions are about changes in your lifestyle since your injury. There are also some questions about how things were before the injury. We are interested in the recovery you have made up to now.

Fill out the questionnaire (**blue sheet**)

1. When would be a convenient time for me to call back?

Time

Date

When calling the participant back:

1. This is (*interviewer's name*) I called on *date* about a research study we are carrying out looking at people that suffered a head injury. You mentioned that you would be interested in taking part in the study and asked me to call you back today.
2. The questions will take about 10 minutes to complete, would you be happy to answer the questions now?

If yes go to question 9 above

If no rearrange another time

Patient is unable to consent

1. Is there someone I could speak to someone who cares for (*name*)?

If the person who we need to speak to is not available, then arrange a time to **call back later**. Go to **green sheet**.

If the carer is happy to continue/the appropriate carer is given the phone:

2. This study is being carried out by ICNARC, the Intensive Care National Audit & Research Centre. It involves answering a few questions about the current health of (*name*) to help us improve the care of people who have had a head injury. Would you have time for me to tell you a little about what is involved now, it will only take a few minutes, or could I phone you back at a time that is more convenient to you?

If the carer does not want to take part in the study, thank them for their time. Interview ends.

3. If you agree to take part in the study all you need to do is answer a few questions on how (*name*) has been since *his/her* head injury. This will take about 10 minutes to complete. We would then link this information to which hospitals (*name*) stayed in and the medical treatments *he/she* received.
4. We are covered by the Data Protection Act. All information is kept on secure servers and no personal data is allowed off the premises. The results of the study will be published and if you would like a copy of the final results I can send this to you.

If yes note the carer's request.

5. Importantly, taking part in the study would not affect (*name's*) medical care, but it will help future patients who suffer a head injury.
6. If (*name*) is not well enough to decide for *himself/herself* whether or not to participate. We would like you to give your opinion as to whether or not you think (*name*) would object to taking part in this research. If you feel that (*name*) would be interested in taking part in the study, would you be willing to answer a few questions about *his/her* health?

If the carer says 'no', thank them for their time. Interview ends.

If the carer says 'yes':

7. Thank you for agreeing to take part. Would you be happy to answer the questions now? It will only take about 10 minutes to complete.

If the carer would prefer to arrange another time - go to the box at the end of this page

If the carer is happy to continue:

8. Before we start the questions remember there are no right or wrong answers. We have found that the best way to answer the questions is to go with your first instinct, whatever you think is the correct response.
9. The questions are about changes in (*name's*) lifestyle since the injury. There are also some questions about how things were before the injury. We are interested in the recovery (*name*) has made up to now.

Fill out the questionnaire (**blue sheet**)

1. When would be a convenient time for me to call back?

Name:

Relationship to participant:

Time

Date

When calling the participant back:

1. This is (*interviewer's name*) I called on *date* about a research study we are carrying out looking at people that suffered a head injury. You mentioned that you would be interested in taking part in the study on behalf of (*name*) and asked me to call you back today.

2. The questions will take about 10 minutes to complete, would you be happy to answer the questions now?

If 'yes' go to question 8 above

If 'no' rearrange another time

Patient/Carer wishes to be called back

If patient:

1. What time would be best for me to call you?

Time:

Date:

If carer:

1. Could you tell me the name of the person I should call concerning the care of (*name*)?

Name:

Relationship to patient:

2. What time would be best for me to call (*name*)?

Time:

Date:

When calling back:

1. This is (*interviewer's name*) could I speak to (*name*)?
2. I called on *date* about a research study aiming to help patients who have suffered a traumatic brain injury. You asked if I could call you back today. I would like to ask you a few questions about your current health to help us improve the care of people who have had a head injury. Would you have time for me to tell you a little about the study?

If the patient/carers does not want to take part in the study, thank them for their time. Interview ends.

If the patient would prefer to be **called back** at another time go to the start of this sheet.

If the patient is happy to continue go to **question 3 (front sheet)**.

If the carer is happy to continue go to **question 2 (red sheet)**.

If the patient says 'no', thank them for their time. Interview ends.

Patient/carer agrees to take part in the RAIN Study

This form was completed via telephone interview by:

Name (interviewer):

Name (interviewee):

If a carer, state the relationship of interviewee to participant:

Date:

1. Before the injury were you able to look after yourself at home? Yes No

2. As a result of your injury do you now need help in the home? (please tick one box)

I do not need help or supervision in the home

I need some help in the home, but not every day

I need help in the home every day, but I could look after myself for
at least 8 hours if necessary

I could not look after myself for 8 hours during the day

I need help in the home, but not because of the injury

3. Before the injury did you need help to shop? Yes No

4. As a result of your injury do you now need help to shop? (please tick one box)

I do not need help to shop

I need some help, but I can go to local shops on my own

I need help to shop even locally, or I cannot shop at all

I need help to shop, but not because of the injury

5. Before the injury did you need help to travel? Yes No

6. As a result of your injury do you now need help to travel? (please tick one box)

I do not need help to travel

I need some help, but can travel locally on my own
(e.g. by arranging a taxi)

I need help to travel even locally, or I cannot travel at all

I need help to travel but not because of the injury

7. Employment before the injury: (please tick one box)

Working

Looking for work

Caring for family

Studying as a student

Retired

None of these (e.g. unfit for work)

8. As a result of your injury has there been a change in your ability to work? (or to study if you were a student; or to care for your family if you were the main caregiver)

I can still do the same work

I can still work, but at a reduced level (e.g. change from full-time to part-time, or change in level of responsibility)

I am unable to work, or only able to work in sheltered workshop

My ability to work has changed, but not because of the injury

9. Before the injury did you take part in regular social and leisure activities outside home (at least once a week)? Yes No

Social and leisure activities include: going out to a pub or club, visiting friends, going to the cinema or bingo, going out for a walk, attending a football match, taking part in sport.

10. As a result of your injury has there been a change in your ability to take part in social and leisure activities outside home? (please tick one box)

I take part about as often as before
(the activities may be different from before)

I take part a bit less, but at least half as often

I take part much less, less than half as often

I do not take part at all

My ability to take part has changed for some other reason, not because of the injury

11. Before the injury did you have any problems in getting on with friends or relatives?
Yes No

12. As a result of your injury are there now problems in how you get on with friends or relatives? (please tick one box)

- Things are still much the same
- There are occasional problems (less than once a week)
- There are frequent problems (once a week or more)
- There are constant problems (problems every day)
- There are problems for some other reason, not because of the injury

13. Are there any other problems resulting from your injury which have interfered with your daily life over the past week? (Problems sometimes reported after head injury: **headaches, dizziness, tiredness, sensitivity to noise or light, slowness, memory failures, and concentration problems.**)

(please tick one box)

- I have no current problems
- I have some problems, but these do not interfere with my daily life
- I have some problems, and these have affected my daily life
- I have some problems for other reasons, not because of the head injury

14. Before the injury were similar problems present? (please tick one box)

- I had no problems before, I had minor problems
- I had similar problems before

Are there any other comments that you would like to make?

(Please continue overleaf if you wish)

Appendix 6 Sensitivity analysis: external validation of risk prediction models in original (non-imputed) data sets

TABLE 54 Numbers of admissions and events included in validation data sets: mortality at 6 months

Risk model	All patients	Eligible for model	Complete data
Number of admissions			
Hukkelhoven	2881	1744	1459
IMPACT Core	2881	2455	2281
IMPACT Extended	2881	2330	1994
IMPACT Lab	2881	1951	1724
Mortality at 6 months, n (%)			
Hukkelhoven	748 (26.0)	398 (22.8)	333 (22.8)
IMPACT Core	748 (26.0)	685 (27.9)	636 (27.9)
IMPACT Extended	748 (26.0)	648 (27.8)	559 (28.0)
IMPACT Lab	748 (26.0)	538 (27.6)	475 (27.6)

TABLE 55 Discrimination: mortality at 6 months

Risk model	All patients	Eligible for model	Complete data
c-index (95% CI)			
Hukkelhoven	0.782 (0.763 to 0.801)	0.771 (0.744 to 0.797)	0.793 (0.765 to 0.821)
IMPACT Core	0.755 (0.735 to 0.776)	0.752 (0.730 to 0.774)	0.756 (0.733 to 0.778)
IMPACT Extended	0.779 (0.760 to 0.798)	0.784 (0.764 to 0.805)	0.794 (0.772 to 0.816)
IMPACT Lab	0.773 (0.754 to 0.792)	0.790 (0.768 to 0.812)	0.798 (0.774 to 0.821)

TABLE 56 Calibration: mortality at 6 months

Risk model	All patients	Eligible for model	Complete data
Hosmer–Lemeshow test, chi-squared statistic [p-value]			
Hukkelhoven	15.7 [0.11]	16.6 [0.08]	21.0 [0.02]
IMPACT Core	101 [<0.001]	98 [<0.001]	102 [<0.001]
IMPACT Extended	52 [<0.001]	68 [<0.001]	62 [<0.001]
IMPACT Lab	7.3 [0.69]	14.0 [0.17]	13.5 [0.20]
Cox calibration regression, α (95% CI) β (95% CI) [p-value]			
Hukkelhoven	0.06 (−0.07 to 0.18) 1.04 (0.94 to 1.14) [0.64]	−0.06 (−0.23 to 0.11) 1.04 (0.91 to 1.17) [0.21]	−0.03 (−0.21 to 0.15) 1.18 (1.02 to 1.33) [0.003]
IMPACT Core	−0.46 (−0.56 to −0.36) 0.98 (0.89 to 1.08) [<0.001]	−0.47 (−0.57 to −0.37) 0.97 (0.87 to 1.08) [<0.001]	−0.49 (−0.59 to −0.38) 0.98 (0.88 to 1.09) [<0.001]
IMPACT Extended	−0.30 (−0.41 to −0.20) 1.03 (0.93 to 1.12) [<0.001]	−0.34 (−0.45 to −0.23) 1.07 (0.96 to 1.18) [<0.001]	−0.34 (−0.46 to −0.22) 1.12 (1.00 to 1.24) [<0.001]
IMPACT Lab	−0.01 (−0.13 to 1.07) 0.98 (0.88 to 1.07) [0.89]	−0.08 (−0.21 to 0.06) 1.05 (0.93 to 1.17) [0.10]	−0.04 (−0.19 to 0.10) 1.12 (0.99 to 1.25) [0.029]

TABLE 57 Overall fit: mortality at 6 months

Risk model	All patients	Eligible for model	Complete data
Brier's score			
Hukkelhoven	0.153	0.143	0.138
IMPACT Core	0.166	0.174	0.173
IMPACT Extended	0.156	0.161	0.159
IMPACT Lab	0.155	0.156	0.154

TABLE 58 Numbers of admissions and events included in validation data sets: unfavourable outcome at 6 months

Risk model	All patients	Eligible for model	Complete data
Number of admissions			
Hukkelhoven	2422	1447	1206
CRASH Basic	2422	2206	2050
CRASH CT	2422	2111	1940
IMPACT Core	2422	2060	1914
IMPACT Extended	2422	1959	1675
IMPACT Lab	2422	1639	1447
Unfavourable outcome at 6 months, n (%)			
Hukkelhoven	1481 (61.1)	868 (60.0)	730 (60.5)
CRASH Basic	1481 (61.1)	1340 (60.7)	1241 (60.5)
CRASH CT	1481 (61.1)	1278 (60.5)	1171 (60.4)
IMPACT Core	1481 (61.1)	1323 (64.2)	1228 (64.2)
IMPACT Extended	1481 (61.1)	1256 (64.1)	1077 (64.3)
IMPACT Lab	1481 (61.1)	1052 (64.2)	931 (64.3)

TABLE 59 Discrimination: unfavourable outcome at 6 months

Risk model	All patients	Eligible for model	Complete data
c-index (95% CI)			
Hukkelhoven	0.740 (0.721 to 0.760)	0.726 (0.700 to 0.752)	0.731 (0.703 to 0.759)
CRASH Basic	0.733 (0.712 to 0.753)	0.731 (0.710 to 0.752)	0.732 (0.710 to 0.754)
CRASH CT	0.739 (0.719 to 0.759)	0.745 (0.724 to 0.766)	0.745 (0.723 to 0.766)
IMPACT Core	0.731 (0.710 to 0.751)	0.725 (0.703 to 0.748)	0.726 (0.703 to 0.749)
IMPACT Extended	0.744 (0.724 to 0.763)	0.743 (0.721 to 0.765)	0.745 (0.721 to 0.769)
IMPACT Lab	0.749 (0.730 to 0.769)	0.753 (0.729 to 0.777)	0.753 (0.727 to 0.778)

TABLE 60 Calibration: unfavourable outcome at 6 months

Risk model	All patients	Eligible for model	Complete data
Hosmer–Lemeshow test, chi-squared statistic [p-value]			
Hukkelhoven	412 [<0.001]	248 [<0.001]	184 [<0.001]
CRASH Basic	996 [<0.001]	896 [<0.001]	795 [<0.001]
CRASH CT	400 [<0.001]	291 [<0.001]	254 [<0.001]
IMPACT Core	242 [<0.001]	220 [<0.001]	193 [<0.001]
IMPACT Extended	336 [<0.001]	239 [<0.001]	201 [<0.001]
IMPACT Lab	560 [<0.001]	320 [<0.001]	286 [<0.001]
Cox calibration regression, α (95% CI) β (95% CI) [p-value]			
Hukkelhoven	0.67 (0.57 to 0.76) 0.71 (0.57 to 0.76) [<0.001]	0.61 (0.49 to 0.73) 0.70 (0.60 to 0.80) [<0.001]	0.59 (0.46 to 0.73) 0.71 (0.46 to 0.73) [<0.001]
CRASH Basic	0.99 (0.88 to 1.10) 0.71 (0.63 to 0.78) [<0.001]	0.98 (0.86 to 1.10) 0.71 (0.63 to 0.79) [<0.001]	0.95 (0.83 to 1.08) 0.71 (0.62 to 0.79) [<0.001]
CRASH CT	0.59 (0.50 to 0.69) 0.65 (0.58 to 0.72) [<0.001]	0.55 (0.45 to 0.65) 0.68 (0.60 to 0.75) [<0.001]	0.52 (0.42 to 0.62) 0.67 (0.59 to 0.75) [<0.001]
IMPACT Core	0.61 (0.51 to 0.70) 0.82 (0.73 to 0.91) [<0.001]	0.63 (0.53 to 0.73) 0.80 (0.70 to 0.90) [<0.001]	0.61 (0.51 to 0.71) 0.80 (0.69 to 0.90) [<0.001]
IMPACT Extended	0.70 (0.60 to 0.79) 0.81 (0.72 to 0.90) [<0.001]	0.69 (0.59 to 0.80) 0.81 (0.71 to 0.90) [<0.001]	0.68 (0.57 to 0.79) 0.81 (0.70 to 0.91) [<0.001]
IMPACT Lab	0.87 (0.77 to 0.98) 0.79 (0.71 to 0.87) [<0.001]	0.84 (0.72 to 0.96) 0.79 (0.69 to 0.89) [<0.001]	0.84 (0.71 to 0.97) 0.79 (0.68 to 0.90) [<0.001]

TABLE 61 Overall fit: unfavourable at 6 months

Risk model	All patients	Eligible for model	Complete data
Brier's score			
Hukkelhoven	0.222	0.228	0.223
CRASH Basic	0.258	0.258	0.255
CRASH CT	0.222	0.217	0.216
IMPACT Core	0.220	0.217	0.216
IMPACT Extended	0.221	0.215	0.213
IMPACT Lab	0.234	0.222	0.222

A decorative graphic consisting of numerous thin, parallel green lines that curve from the left side of the page towards the right, creating a sense of movement and depth.

**EME
HS&DR
HTA
PGfAR
PHR**

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