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

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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 models[4] 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 al[10] (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 ≤ 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 ≤ 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 ≤ 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 TBI[9] 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 size[32] 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≤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 Anglia[39]); 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 model[40] 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***

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

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

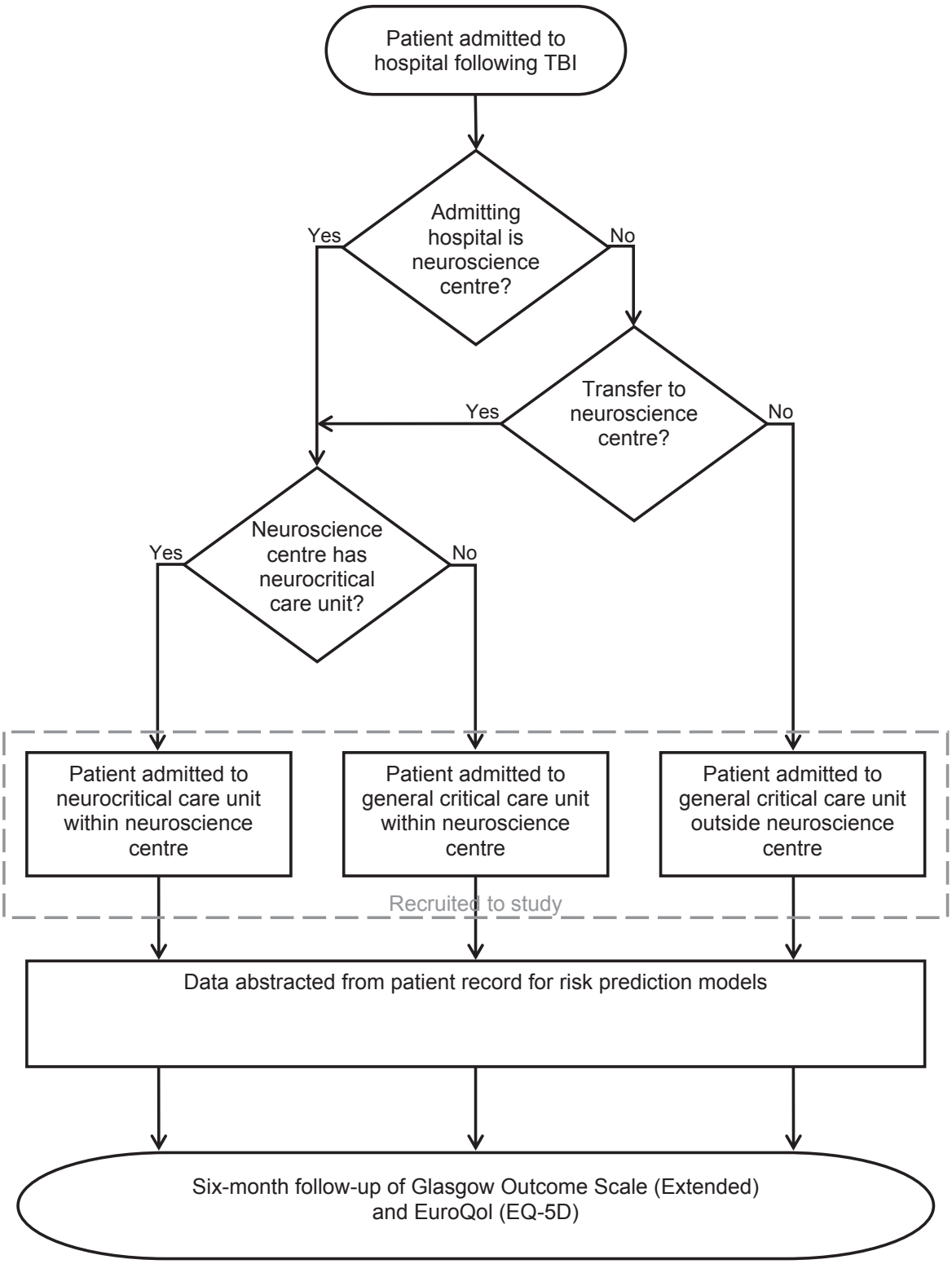
ICNARC holds professional liability insurance (certificate number A05305/0808, Markel International Insurance Co Ltd) to meet the potential legal liability of the sponsor for harm to participants arising from the management of the research. Indemnity to meet the potential legal liability of the sponsor 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.

## REFERENCES


1. Knaus WA, Zimmerman JE, Wagner DP *et al*. APACHE-acute physiology and chronic health evaluation: a physiologically based classification system. *Crit Care Med* 1981;**9**:591-7.
2. Rowan KM, Kerr JH, Major E *et al*. Intensive Care Society's APACHE II study in Britain and Ireland--I: Variations in case mix of adult admissions to general intensive care units and impact on outcome. *BMJ* 1993;**307**:972-7.
3. Rowan KM, Kerr JH, Major E *et al*. Intensive Care Society's APACHE II study in Britain and Ireland--II: Outcome comparisons of intensive care units after adjustment for case mix by the American APACHE II method. *BMJ* 1993;**307**:977-81.
4. Harrison DA, Brady AR, Parry GJ *et al*. Recalibration of risk prediction models in a large multicenter cohort of admissions to adult, general critical care units in the United Kingdom. *Crit Care Med* 2006;**34**:1378-88.
5. Harrison DA, Parry GJ, Carpenter JR *et al*. A new risk prediction model for critical care: the Intensive Care National Audit & Research Centre (ICNARC) model. *Crit Care Med* 2007;**35**:1091-8.
6. Hyam JA, Welch CA, Harrison DA, Menon DK. Case mix, outcomes and comparison of risk prediction models for admissions to adult, general and specialist critical care units for head injury: a secondary analysis of the ICNARC Case Mix Programme Database. *Crit Care* 2006;**10 Suppl 2**:S2.
7. Livingston BM, Mackenzie SJ, MacKirdy FN, Howie JC. Should the pre-sedation Glasgow Coma Scale value be used when calculating Acute Physiology and Chronic Health Evaluation scores for sedated patients? Scottish Intensive Care Society Audit Group. *Crit Care Med* 2000;**28**:389-94.
8. Hayes JA, Black NA, Jenkinson C *et al*. Outcome measures for adult critical care: a systematic review. *Health Technol Assess* 2000;**4**:1-111.
9. Perel P, Edwards P, Wentz R, Roberts I. Systematic review of prognostic models in traumatic brain injury. *BMC Med Inform Decis Mak* 2006;**6**:38.
10. Hukkelhoven CW, Steyerberg EW, Habbema JD *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.
11. MRC CRASH Trial Collaborators. Predicting outcome after traumatic brain injury: practical prognostic models based on a large cohort of international patients. *BMJ* 2008;**336**:425-9.
12. Roberts I, Yates D, Sandercock P *et al*. Effect of intravenous corticosteroids on death within 14 days in 10008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial. *Lancet* 2004;**364**:1321-8.
13. Edwards P, Arango M, Balica L *et al*. Final results of MRC CRASH, a randomised placebo-controlled trial of intravenous corticosteroid in adults with head injury-outcomes at 6 months. *Lancet* 2005;**365**:1957-9.
14. Maas AI, Marmarou A, Murray GD *et al*. Prognosis and clinical trial design in traumatic brain injury: the IMPACT study. *J Neurotrauma* 2007;**24**:232-8.
15. Marmarou A, Lu J, Butcher I *et al*. IMPACT database of traumatic brain injury: design and description. *J Neurotrauma* 2007;**24**:239-50.
16. Steyerberg EW, Mushkudiani N, Perel P *et al*. Predicting outcome after traumatic brain injury: development and international validation of prognostic scores based on admission characteristics. *PLoS Med* 2008;**5**:e165.
17. Menon D, Harrison D. Prognostic modelling in traumatic brain injury. *BMJ* 2008;**336**:397-8.
18. Black N. Why we need observational studies to evaluate the effectiveness of health care. *BMJ* 1996;**312**:1215-8.
19. National Collaborating Centre for Acute Care. Head injury: Triage, assessment, investigation and early management of head injury in infants, children and adults. 2007. [http://www.nice.org.uk/cg56]

20. Neurocritical Care Stakeholder Group. Neurocritical care capacity and demand. 2006. [Available from http://www.bann.org.uk]
21. Menon D. Neurocritical care: turf label, organizational construct, or clinical asset? *Curr Opin Crit Care* 2004;**10**:91-3.
22. Smith M. Neurocritical care: has it come of age? *Br J Anaesth* 2004;**93**:753-5.
23. Patel HC, Bouamra O, Woodford M *et al*. Trends in head injury outcome from 1989 to 2003 and the effect of neurosurgical care: an observational study. *Lancet* 2005;**366**:1538-44.
24. Wilson JT, Edwards P, Fiddes H *et al*. Reliability of postal questionnaires for the Glasgow Outcome Scale. *J Neurotrauma* 2002;**19**:999-1005.
25. Bullinger M, Azouvi P, Brooks N *et al*. Quality of life in patients with traumatic brain injury-basic issues, assessment and recommendations. *Restor Neurol Neurosci* 2002;**20**:111-24.
26. Edwards P, Roberts I, Clarke M *et al*. Increasing response rates to postal questionnaires: systematic review. *BMJ* 2002;**324**:1183.
27. Brady AR, Harrison D, Black S *et al*. Assessment and optimization of mortality prediction tools for admissions to pediatric intensive care in the United kingdom. *Pediatrics* 2006;**117**:e733-e742.
28. Harrell FE, Jr., Califf RM, Pryor DB *et al*. Evaluating the yield of medical tests. *JAMA* 1982;**247**:2543-6.
29. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 1982;**143**:29-36.
30. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988;**44**:837-45.
31. Hosmer DW, Lemeshow S. Goodness of fit tests for the multiple logistic regression model. *Communications in Statistics* 1980;**A9**:1043-69.
32. Kramer AA, Zimmerman JE. Assessing the calibration of mortality benchmarks in critical care: The Hosmer-Lemeshow test revisited. *Crit Care Med* 2007;**35**:2052-6.
33. Cox DR. Two further applications of a model for binary regression. *Biometrika* 1958;**45**:562-5.
34. Brier GW. Verification of forecasts expressed in terms of probability. *Monthly Weather Review* 1950;**75**:1-3.
35. National Institute for Health and Clinical Excellence. Guide to the methods of Technology Appraisal: Draft for consultation. London: National Institute for Health and Clinical Excellence, 2007.
36. Department of Health PbR Team. Payment by Results Guidance 2008/09. London: Department of Health, 2007.
37. Grieve R, Nixon R, Thompson SG, Normand C. Using multilevel models for assessing the variability of multinational resource use and cost data. *Health Econ* 2005;**14**:185-96.
38. Grieve R, Nixon R, Thompson SG, Cairns J. Multilevel models for estimating incremental net benefits in multinational studies. *Health Econ* 2007;**16**:815-26.
39. Patel HC, Menon DK, Tebbs S *et al*. Specialist neurocritical care and outcome from head injury. *Intensive Care Med* 2002;**28**:547-53.
40. Hanley JA. The robustness of the "binormal" assumptions used in fitting ROC curves. *Med Decis Making* 1988;**8**:197-203.

## 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**

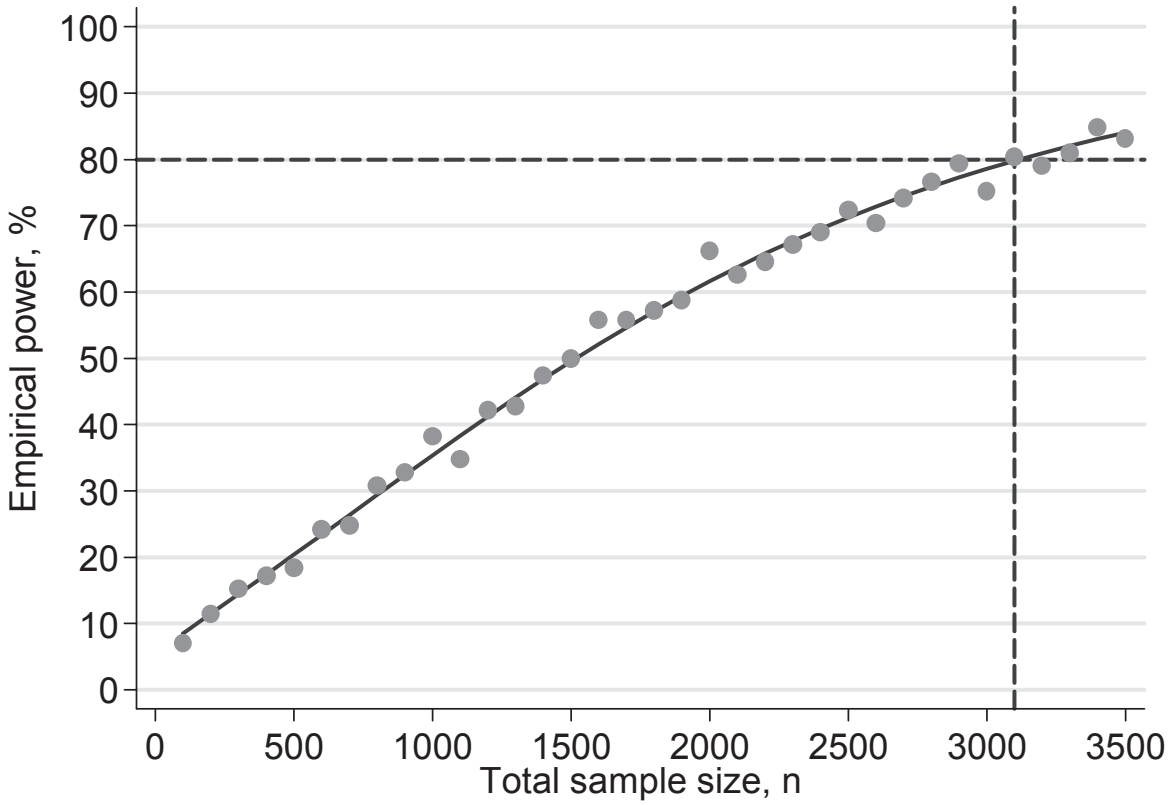
(("brain injuries"[MH] OR "craniocerebral trauma"[MH]) OR ("brain injuries"[TI] OR "traumatic brain injury"[TI] OR "brain trauma"[TI])) AND (brain[TI] OR brain*[TI] OR coma[TI] OR conscious*[TI] OR cranio*[TI] OR skull[TI]) AND ("Case-Control Studies"[MH] OR "Cohort Studies"[MH] OR "Follow-Up Studies"[MH]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

  - 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.