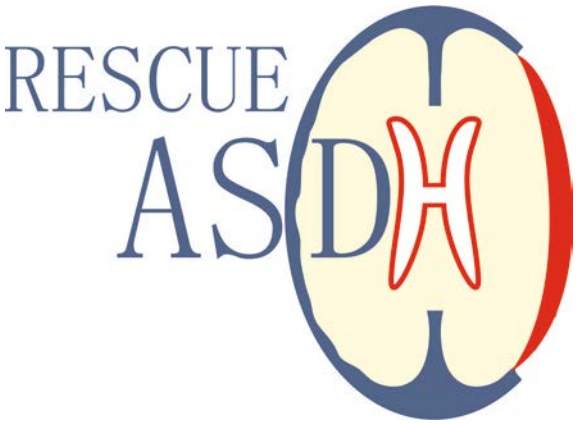

Randomised Evaluation of Surgery with Craniectomy for patients Undergoing Evacuation of Acute Subdural Haematoma (**RESCUE-ASDH**)

RESCUE-ASDH is a multi-centre, pragmatic, parallel group randomised trial comparing craniectomy vs. craniotomy for acute subdural haematoma patients.

CLINICAL TRIAL PROTOCOL

Protocol number:
Protocol version: **2.0**
Protocol date: **8th June 2015**

Clinical Trial Protocol

Trial Title:	Randomised Evaluation of Surgery with Craniectomy for patients Undergoing Evacuation of Acute Subdural Haematoma (RESCUE-ASDH)
Protocol Number:	RESCUE-ASDH14
ISRCTN Number:	ISRCTN8737 0545
Protocol Version:	2.0
Protocol date:	8th June 2015

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Protocol Signatures:

I give my approval for the attached protocol entitled "*Randomised Evaluation of Surgery with Craniectomy for patients Undergoing Evacuation of Acute Subdural Haematoma (RESCUE-ASDH)*" dated 8th June 2015.

Chief Investigator

Name: Professor Peter Hutchinson

Signature: _____

Date: _____

Site Signatures

I have read the attached protocol entitled "Randomised Evaluation of Surgery with Craniectomy for patients Undergoing Evacuation of Acute Subdural Haematoma (RESCUE-ASDH)" dated 8th June 2015 and agree to abide by all provisions set forth therein. I agree to abide by the guidelines of Good Clinical Practice.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

Principal Investigator

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Signature: _____

Date: _____

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Table of Contents

Abbreviations

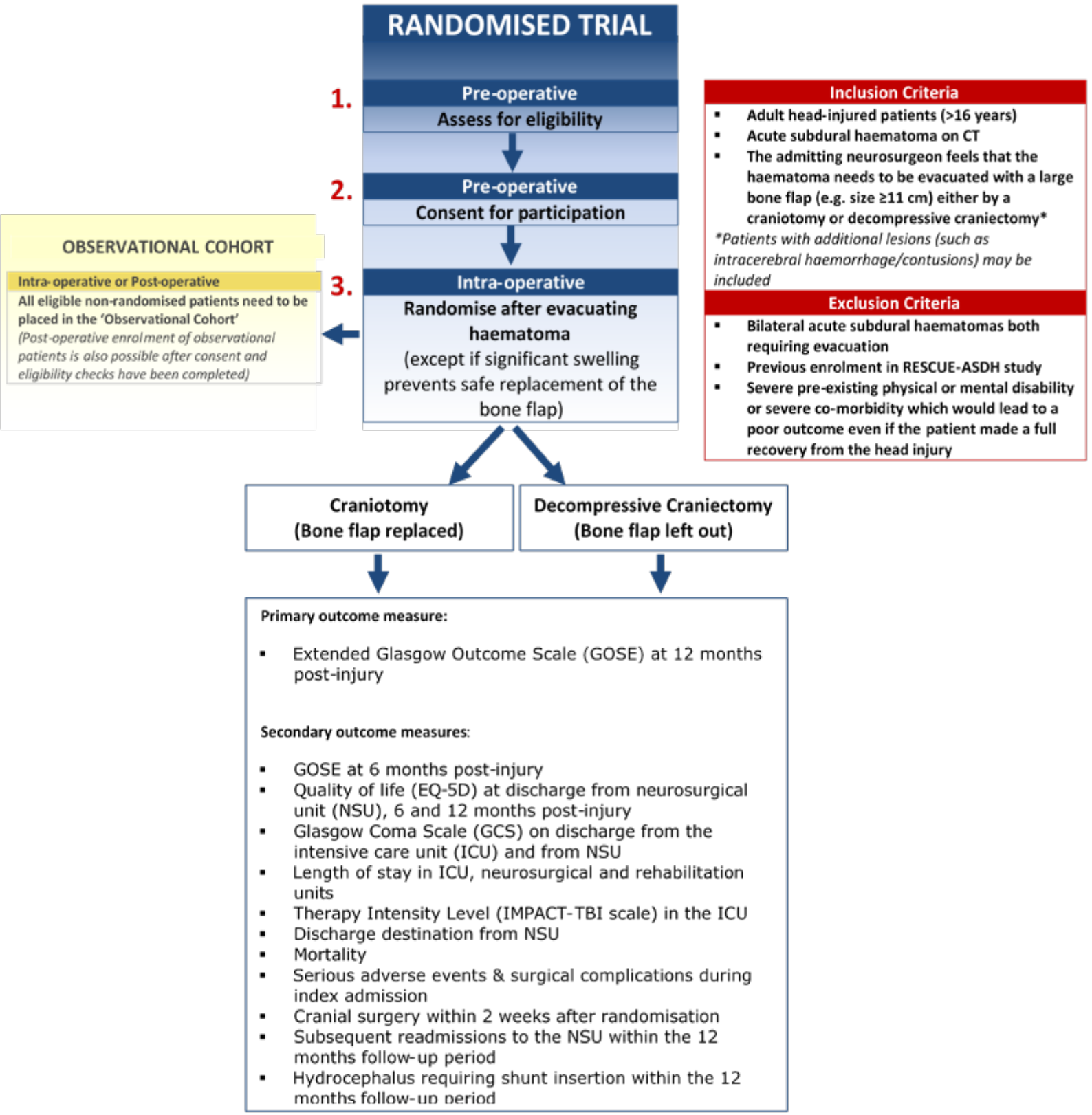
ASDH	Acute Subdural Haematoma
AWI Act 2000	the Adults with Incapacity (Scotland) Act 2000 (AWI Act 2000),
CA	Competent Authority
CI	Confidence Interval / Chief Investegator
CR	Craniotomy
CRF	Case Report Form
CT	Computed Tomography
DC	Decompressive Craniectomy
DMEC	Data Monitoring and Ethics Committee
DSUR	Development Safety Update Report
EQ-5D	EuroQol health status questionnaire – 5 Dimensions
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
GOSE	extended Glasgow Outcomes Scale
GP	General Practitioner
ICP	Intracranial Pressure
ICU	Intensive Care Unit
IMP	Investigational Medicinal Product
IMPACT-TBI	International Mission for Prognosis and Analysis of Clinical Trials in Traumatic Brain Injury
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic Resonance Imaging
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
NIMP	Non Investigational Medicinal Product
NSU	Neurosurgical Unit
PI	Principal Investigator
QALY	Quality Adjusted Life Year
R&D	Research and Development
RA	Regulatory Agency
RCT	Randomized Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SBNS	Society of British Neurological Surgeons
SAR	Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBI	Traumatic Brain Injury
TIL	Therapy Intensity Level
TMC	Trial Management Committee
TSC	Trial Steering Committee

1. Trial Synopsis

Title of clinical trial	Randomised Evaluation of Surgery with Craniectomy for patients Undergoing Evacuation of Acute Subdural Haematoma (RESCUE-ASDH)
Sponsor name	Joint sponsorship by the University of Cambridge and Cambridge University Hospitals NHS Foundation Trust
Medical condition or disease under investigation	Acute subdural haematoma (ASDH)
Purpose of clinical trial	We aim to perform a multi-centre, pragmatic, parallel group randomised trial in order to compare the clinical and cost-effectiveness of decompressive craniectomy versus craniotomy for the management of adult head-injured patients undergoing evacuation of an acute subdural haematoma (ASDH).
Primary objective	To detect an 8% absolute difference in the rate of favourable outcome at 1 year between decompressive craniectomy (43%) and craniotomy (35%) with a power of 90% and a 2-sided significance of 5%. This corresponds to an 8% treatment effect.
Secondary objective (s)	1. Compare the long-term clinical effectiveness of decompressive craniectomy versus craniotomy (1 year follow-up period). 2. Compare the adverse events and surgical complications between the two arms. 3. Undertake a detailed economic evaluation.
Trial Design	RESCUE-ASDH is a multi-centre, pragmatic, parallel group randomised trial. It will commence with Stage 1 (feasibility study) which will be followed by the Stage 2 (substantive study) if the progression criteria are met.
Trial Endpoints	Primary endpoint: -GOSE (extended Glasgow Outcome Scale) at 12 months post-injury Secondary endpoints: - GOSE at 6 months post-injury - Quality of life (EQ-5D) at discharge from neurosurgical unit (NSU), 6 and 12 months post-injury - Glasgow Coma Scale (GCS) on discharge from the intensive care unit (ICU) and from NSU - Length of stay in ICU, neurosurgical and rehabilitation unit - Therapy Intensity Level (IMPACT-TBI scale) in the ICU - Discharge destination from NSU - Mortality - Serious adverse events & surgical complications during index admission

	- Cranial surgery within 2 weeks after randomisation - Subsequent readmissions to the NSU within the 12 months follow-up period - Hydrocephalus requiring shunt insertion within the 12 months follow-up period - Health care services utilisation over 12 months - Detailed economic evaluation
Sample Size	Recruit 990 patients in the randomised trial (120 during 'Stage 1' and 870 during 'Stage 2')
Summary of eligibility criteria	The study is focusing on adult head injured patients who require an operation to evacuate an ASDH. Inclusion criteria: - Adult head-injured patients (aged >16 years) - Acute subdural haematoma on CT - The admitting neurosurgeon feels that the haematoma needs to be evacuated with a large bone flap (recommended size ≥11 cm anteroposterior diameter) either by a craniotomy or decompressive craniectomy* **Patients with additional lesions (such as intracerebral haemorrhage/contusions) may be included* Exclusion criteria: - - Bilateral acute subdural haematomas both requiring evacuation - Previous enrolment in RESCUE-ASDH study - Severe pre-existing physical or mental disability or severe co-morbidity which would lead to a poor outcome even if the patient made a full recovery from the head injury
Health technology being assessed	The two health technologies we wish to assess are the two most widely used surgical techniques for the evacuation of an ASDH: craniotomy and decompressive craniectomy (DC). The difference between these two procedures is that a bone flap is left out prior to closing the skin in the DC.
Procedures for safety monitoring during trial	Unblinded results will be forwarded to the Data Monitoring Committee who will address safety issues.
Criteria for withdrawal of patients on safety grounds	Subjects will be reviewed locally and patient withdrawal will be at the discretion of the treating team and local PI. Any significant adverse results will be reported to the Data Monitoring Committee via the Study Coordinating Centre.

2. Trial Flow Chart



3. Background

3.1 Existing research evidence

Head injury is common with approximately 900,000 people attending Emergency Departments per year in the UK [1]. The majority of patients sustain a mild Traumatic Brain Injury (TBI). However, the majority of fatal and unfavourable outcomes occur in patients with moderate or severe TBI, which account for approximately 10% of attenders. An estimated 1.2 million people live with some level of TBI-related disability in the UK, which has profound socio-economic consequences, as the prevalence is particularly high among children and young to middle-aged adults.

By far, the most important early consequence of TBI is the development of an intracranial haematoma (also known as a clot) [2]. Intracranial haematomas can be extradural (inside the skull but outside the dura mater which is the outermost covering of the brain), subdural (between the dura mater and the brain), intraparenchymal (within the brain) or a combination thereof. Without effective surgical management, an intracranial haematoma may transform an otherwise benign clinical course with the expectation of recovery, to a situation where death or severe disability will occur.

Studies conducted after the introduction of CT scanning report an incidence of acute subdural hematoma (ASDH) between 12 and 29% in patients admitted with severe TBI [3]. Studies looking at patients with ASDH requiring surgery quote mortality rates between 40 and 60%. The decision to operate on an ASDH is usually based on the patient's GCS score, pupillary exam, comorbidities, CT findings, age, and, in delayed decisions, ICP. Neurological deterioration over time is also an important factor influencing the decision to operate. Different surgical techniques have been advocated for the evacuation of an ASDH. Patients with an ASDH that require an operation to remove the clot are currently treated either with a craniotomy or a decompressive craniectomy (DC). The choice of operative technique is influenced by the surgeon's expertise, training, and evaluation of the particular situation. Some centres treat all SDH with decompressive craniectomies, whereas other centres used solely craniotomies [3].

3.2 Surgery for ASDH

Head-injured patients with acute subdural haematomas (ASDH) that require an operation to remove the clot are currently treated either with a craniotomy or a DC [2]. The steps of a craniotomy are: opening of the skin, removal of a piece of skull, removal of the clot, replacement of the piece of skull, closure of the skin. A DC is a similar procedure but the piece of skull is left out prior to closing the skin. The advantage of a DC is that it is very effective in controlling brain swelling which is often a problem in the days after the operation. When the swelling goes down, the patient has another operation to reconstruct their skull. The advantage of a craniotomy is that the patient will not need a later operation to rebuild the skull. However, this type of operation may fail to control the brain swelling in some patients [2]. Both approaches are widely used among neurological surgeons (although the indications may differ), therefore there is sufficient experience in the centres to setup a randomised trial.

3.3 Current practice for ASDH

Both procedures are carried out regularly in the NHS and worldwide. All neurosurgeons are able to perform both types of operation. With the objective of examining current practice patterns of surgical treatment for ASDH, we undertook a survey of members of the European Association of Neurosurgical Societies (EANS), Neurocritical Care Society, NeuroCritical Care Network (NCCNet), full members of the Society of British Neurological Surgeons (SBNS) and members of the British Neurosurgical Trainees

Association (BNTA) during October and November 2011 [4]. The questionnaire survey was approved by the Academic Committee of the SBNS (project no. NE0026). As part of the survey, we asked the following question: “When evacuating a traumatic ASDH, how often do you perform a primary DC (i.e. leave the bone flap out)”? This question was answered by 283 neurosurgeons (201 board-certified Consultants or equivalent; 82 trainees). There were 138 UK/Irish, 110 from other European countries, 13 North American and 22 respondents from various other countries. We decided to group together the responses of neurosurgeons working in countries with national representation to the EANS in order to have two similar-sized groups (UK/Irish and other European).We also think that these two groups have a degree of intrinsic homogeneity with respect to clinical neurosurgical practice. Although 41 % of the respondents use primary DC less than 25 % of the time, almost one-third use DC in more than 50 % of such cases. We found that a higher proportion of neurosurgeons from other European countries (48/110; 44 %) as compared with UK/Irish neurosurgeons (29/138; 21 %) use primary DC in more than half of ASDH cases ($p<0.001$). Another interesting finding was that of the 23 UK/Irish neurosurgical units with at least two Consultant respondents, only six units (26 %) showed intra-departmental agreement regarding the use of primary DC for ASDH. We do not think that the observed variation in practice can be fully explained by regional/national differences in trauma care systems or the epidemiology of TBI within Europe. Rather, we believe that the variation in practice reflects the lack of high quality evidence regarding the use of primary DC for ASDH evacuation.

3.4 Systematic reviews and the need for an RCT

A systematic review published by the Brain Trauma Foundation in 2006 concluded that research on the role of decompressive craniectomy (DC) versus craniotomy is the top key issue for future investigation likely to improve the care of patients with ASDH [2].

The Brain Trauma Foundation systematic review (literature search from 1975 to 2001) demonstrated the dearth of high-quality evidence addressing the effectiveness of the two main surgical procedures (craniotomy and DC) used for treating patients with ASDH [2]. The available evidence consists of retrospective studies only which do not usually address the effectiveness of the procedure.

We performed a systematic literature search from 2001 to April 2013 using the same search terms/methodology as the Brain Trauma Foundation investigators. We identified 16 published studies which present the outcome from ASDH. No prospective randomised studies comparing DC with craniotomy for patients with ASDH were found. Only 5 retrospective cohort comparison studies addressing the effect of the operative technique on outcome from ASDH were identified [3, 5-8]. A finding that was universal across these 5 studies was that patients undergoing DC had significantly more severe injuries compared to patients treated with a craniotomy.

All these studies have methodological weaknesses because of their observational designs, with limited details regarding patient selection, outcome assessment, and small sample sizes. It is not possible to draw meaningful conclusions from the available non-randomised studies and the evidence base for the use of one approach over the other is weak. A well designed and conducted randomized trial comparing the effectiveness and cost-effectiveness of craniotomy and DC is needed to inform current NHS practice, health policy and individual surgeon and patient clinical decision-making.

The cost of performing a craniotomy is approximately equivalent to that of a DC.
Following a DC, patients require reconstruction of their skull. However, a number of currently unknown parameters could render DC more cost-effective than craniotomy.

These parameters include: functional outcome, quality of life, length of stay in the intensive care unit and length of rehabilitation. An economic analysis, embedded within a pragmatic randomised trial, is required to establish the relative cost-effectiveness of the different procedures when adopted into routine clinical practice.

Currently, there is only class III evidence with retrospective studies investigating the role of DC as a primary procedure for ASDH.

3.5 Rationale for Trial

The two health technologies we wish to assess are the two most widely used surgical techniques for the evacuation of an ASDH: craniotomy and decompressive craniectomy (DC). The difference between these 2 procedures is that a bone flap is left out prior to closing the skin in the DC. The advantage of a DC is that it is effective in controlling brain swelling which is often a problem in the days after the operation. When the swelling goes down, the patient has another operation to reconstruct the skull (cranioplasty). The advantage of a craniotomy is that the patient will not need a later operation to rebuild the skull. However, it may fail to control brain swelling in some patients.

Five-year pilot data from a NHS neurosurgical unit (Cambridge) show that 56% of patients with ASDH were treated with a DC [2]. In this retrospective cohort comparison study, 91 patients had an operation for an ASDH. The standardised morbidity ratio was lower in individuals who received DC (0.75; 95% CI 0.51–1.07) than in those treated with a craniotomy (0.90; 95% CI 0.57–1.35). Although the standardised morbidity ratio 95% confidence intervals overlap, this study lends support to the hypothesis that DC may lead to better functional outcomes in comparison to craniotomy for adult head-injured patients with ASDH.

3.6 Benefits of proposed Trial

There is currently no high-quality evidence guiding surgeons as to which operation they should be offering as first line treatment to patients with ASDH. The results of a high-quality study will be used to inform future NICE head injury guidelines and the practice of neurosurgeons in the NHS and worldwide.

4. Aims and Objectives

4.1 Research aim of the trial

We aim to perform a multi-centre, pragmatic, parallel group randomised trial in order to compare the clinical and cost-effectiveness of decompressive craniectomy versus craniotomy for the management of adult head-injured patients undergoing evacuation of an acute subdural haematoma.

4.2 Study Objectives

4.2.1 Primary objective

To detect an 8% absolute difference in the rate of favourable outcome at 1 year between decompressive craniectomy (43%) and craniotomy (35%) with a power of 80% and a 2-sided significance of 5%. This corresponds to an 8% treatment effect.

4.2.2 Secondary objective

1. Compare the long-term clinical effectiveness of decompressive craniectomy versus craniotomy (1 year follow-up period).
2. Compare the adverse events and surgical complications between the two arms.
3. Undertake a detailed economic evaluation.

5. Trial Design

5.1 Statement of design

RESCUE-ASDH is a multi-centre, pragmatic, parallel group randomised trial.

It will commence with an internal pilot, the Stage 1 (feasibility study), which will be followed by the Stage 2 (substantive study) if the progression criteria are met:

I. If there is a >30% shortfall from the recruitment target (n=120) without an identifiable and correctable reason it would not be feasible to progress to the main trial.
II. No ethical or safety concerns raised by the independent Data Monitoring & Ethics Committee.

5.2 Participants

5.2.1 Number of Subjects

We plan to recruit 990 patients in the randomised trial (120 in Stage 1 - 870 in Stage 2).

5.2.2 Inclusion Criteria

To be included in the trial the patient must:

- Patients > 16 years
- Acute subdural haematoma on CT

The admitting neurosurgeon feels that the acute subdural haematoma needs to be evacuated with a large bone flap (recommended size ≥11 cm anteroposterior diameter) either by a craniotomy or decompressive craniectomy*

**Patients with additional lesions (such as intracerebral haemorrhage/contusions) may be included*

5.2.3 Exclusion Criteria

The presence of any of the following will preclude patient inclusion:

- Bilateral acute subdural haematomas both requiring evacuation
- Previous enrolment in RESCUE-ASDH study
- Severe pre-existing physical or mental disability or severe co-morbidity which would lead to a poor outcome even if the patient made a full recovery from the head injury

The proposed inclusion/exclusion criteria were extensively discussed during three open collaborators' meetings and peer-review by the academic committee of the Society of British Neurological Surgeons. This RCT is designed to test effectiveness in everyday practice with relatively unselected participants and under flexible conditions, in order to inform decisions about practice in a "real-world" setting. Patients with ASDH, for example, often present with other underlying brain injuries (contusions, intra-cerebral bleeds etc). The presence of these parenchymal injuries are therefore not an exclusion criterion for this study. The issue of exclusion of patients aged less than 16 years was discussed during the open collaborators' meetings and it was felt that the paediatric population has important differences in terms of incidence of ASDH, anatomy, physiology, pathophysiology, and rehabilitation needs compared to adults over the age of 16. The issue of exclusion of those with severe pre-existing physical or mental disability, or severe co-morbidity was also discussed and it was noted that this is standard in neurological/neurosurgical trials of this nature. The rationale is that patients who are severely disabled will have a poor outcome (as determined by the primary outcome measure) even if they made a full recovery from the head injury. Examples

would be a high level of dependence before the injury or severe irreversible associated injury such as complete spinal cord injury.

5.2.4 Participating Centres

Stage 1 aims to recruit 120 participants during 18 months. If the progression rules are met, Stage 2 will recruit 870 participants during 3.5 years.

We aim to set up both UK and approximately 20 international sites experienced in TBI clinical trials. Therefore, we expect that at least 50% of the patients will be randomised from UK sites. The substantial proportion of UK patients will ensure that the study findings are relevant to the NHS. However, the inclusion of some international sites will facilitate the uptake of study findings by the international community and will allow us to complete the study in a reasonable time frame.

5.2.5 Recruitment and informed consent

5.2.5.1 Participation in the study

Due to the life-threatening nature of the condition, the operation to remove an ASDH is undertaken as soon as possible after admission to a hospital with neurosurgical services on site. These patients will be incapacitated due to the head injury and therefore unable to give consent for trial entry themselves. If the next of kin is known/available they will be asked to give agreement to the patient entering the trial but often they are not present or cannot be traced or there is no time for a discussion with them. In these cases the operation to evacuate an ASDH will need to go ahead as it is a matter of life or death for the patient and the next of kin will be traced and informed after the operation.

Patients who are incapable of giving consent in emergency situations are an established exception to the general rule of informed consent in clinical trials. This is clearly acknowledged in the Declaration of Helsinki:

"Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative."

WMA Declaration of Helsinki 2008 – Ethical Principles for Medical Research Involving Human Subjects

Therefore for this study the following procedures will be followed for obtaining consent and enrolling patients into the trial.

5.2.5.2 Enrolment in the trial with next of kin agreement

If time allows and the next of kin is available, which is rarely the case, the treating clinician will have a brief discussion explaining the nature of the condition and that the operation is undertaken as a life-saving measure. This discussion may take place face to face but may take place over the telephone as neurosurgical units cover large geographical areas and there isn't enough time for the next of kin to get there in time. If the treating clinician believes that a discussion can be had without delaying the operation, then next-of-kin will be provided with information about the trial and asked

to sign the consultee declaration form. If next of kin objects to the inclusion of the patient in the trial, their views will be respected.

5.2.5.3 Enrolment in trial without agreement from next of kin

In many cases when the patient is brought into the emergency department following a severe head injury (for example after a road traffic accident or a fall) the next of kin is not known or cannot be traced.
Furthermore, due to the time critical nature of the operation it is expected that in the majority of cases there will not be sufficient time to discuss adequately about the trial with the next of kin and importantly allow him/her to consider whether enrolment is appropriate. Such a situation could also put the next of kin under undue pressure in circumstances that are already emotionally difficult and stressful. The treating surgeon should make a judgement as to whether a discussion about the trial can be had with the next of kin prior to the operation.
In cases where:

- The next of kin cannot be traced or there is no time to discuss trial participation with them prior to providing the treatment, and
- It is not possible to identify or consult an independent nominated consultee beforehand (e.g during out of hours emergencies).

The treating surgeon will take responsibility for entering the patient into the trial provided the following conditions are met and documented in the treating surgeon declaration form:

- The patient is in a life-threatening situation and urgent treatment (ASDH evacuation) is required without delay
- Urgent treatment is not possible to separate from inclusion in the trial
- The two procedures under comparison in this trial (craniotomy and DC) are both well established, routine procedures in the treating centre
- The treating surgeon is trained/experienced in performing both procedures
- The patient meets the eligibility criteria for trial entry

Every effort will be made to trace/contact the next of kin after the operation and provide them with information on the clinical trial and seek their agreement to continue participation in the trial. If the next of kin refuses for whatever reason the participant will be withdrawn and no further data will be collected.

5.2.5.4 Participants regaining capacity after surgery

If participants regain capacity while in the hospital they will be given information about the clinical trial and their consent will be sought to continue in the trial.
For participants who do not regain capacity whilst in the hospital there will no further actions taken by the research team to proactively monitor their capacity following their discharged from the hospital. Consent will be implied if completed follow up questionnaires completed by the participants themselves will be returned on an ongoing basis.
If a patient wishes to withdraw from the study at any time they will be given the option of having their data collected to date being retained for future analysis or destroyed.
If the patient dies before regaining capacity, retrospective agreement from the next of kin for trial entry will be sought. If the next of kin refuses, data already collected will not be included in the analysis.

We believe that the suggested approach meets the requirements of Declaration of Helsinki and the MCA 2005 for sites in England and Wales (Sections 30-33), as it will ensure that:

- despite lacking capacity, patients with ASDHs can still be enrolled in a trial which aims to answer an important question that will advance the treatment of future patients
- if the next of kin is available, a discussion about the trial will be had before the operation as long as the treating surgeon believes that this would not delay the operation
- if the next of kin is available but the treating surgeon believes that there isn't sufficient time to discuss the trial prior to the operation, enrolment of the patient will be possible as long as the conditions listed in section 5.2.5.3 and 5.2.5.4 of the protocol are met and documented

The inclusion of adults with incapacity in the trial from other UK countries and non-UK countries will be governed in accordance with the local legal frameworks (Appendix 1)

5.2.5.5 Non-Randomised patients (observational cohort)

- Intra-operative observational cohort will include eligible patients enrolled into the study who could not be randomised after evacuation of heamatoma due to significant swelling of the brain
- Post-operative observational cohort will include patients who had an ASDH removal surgery as part of their standard care and were enrolled into the study postoperatively. These patients must fulfill eligibility criteria as the randomised patients.

Paticipants will be followed up in a similar, less extensive manner, compared to the randomised participants.

The primary intent for collecting all eligible non-randomised patients in the RESCUE-ASDH trial is to assess potential selection bias that may be introduced as a result of factors outside the control of investigators. This is particularly relevant to focused trials in heterogeneous populations such as TBI patients. Also, the collection of this data is necessary to adequately report trial results according to the Consolidated Standards of Reporting Trials guidelines and to assess the generalizability of findings. Screening logs alone do not have the level of detail (patient outcomes etc.) to provide the data needed to analyse these factors. Consistency and accuracy in capturing all eligible non-randomised patients may further serve as an indicator of participating centre performance in this trial.

All eligible non-randomised patients will be enrolled as soon as it is feasible using the 'observational cohort'-option in telephone/web-based randomisation system. Relevant agreement/consent will be acquired as soon as it is feasible (pre- or post-operative) using the consent/enrolment forms outlined in section 5.2.5.6.

5.2.5.6 Consent procedure overview

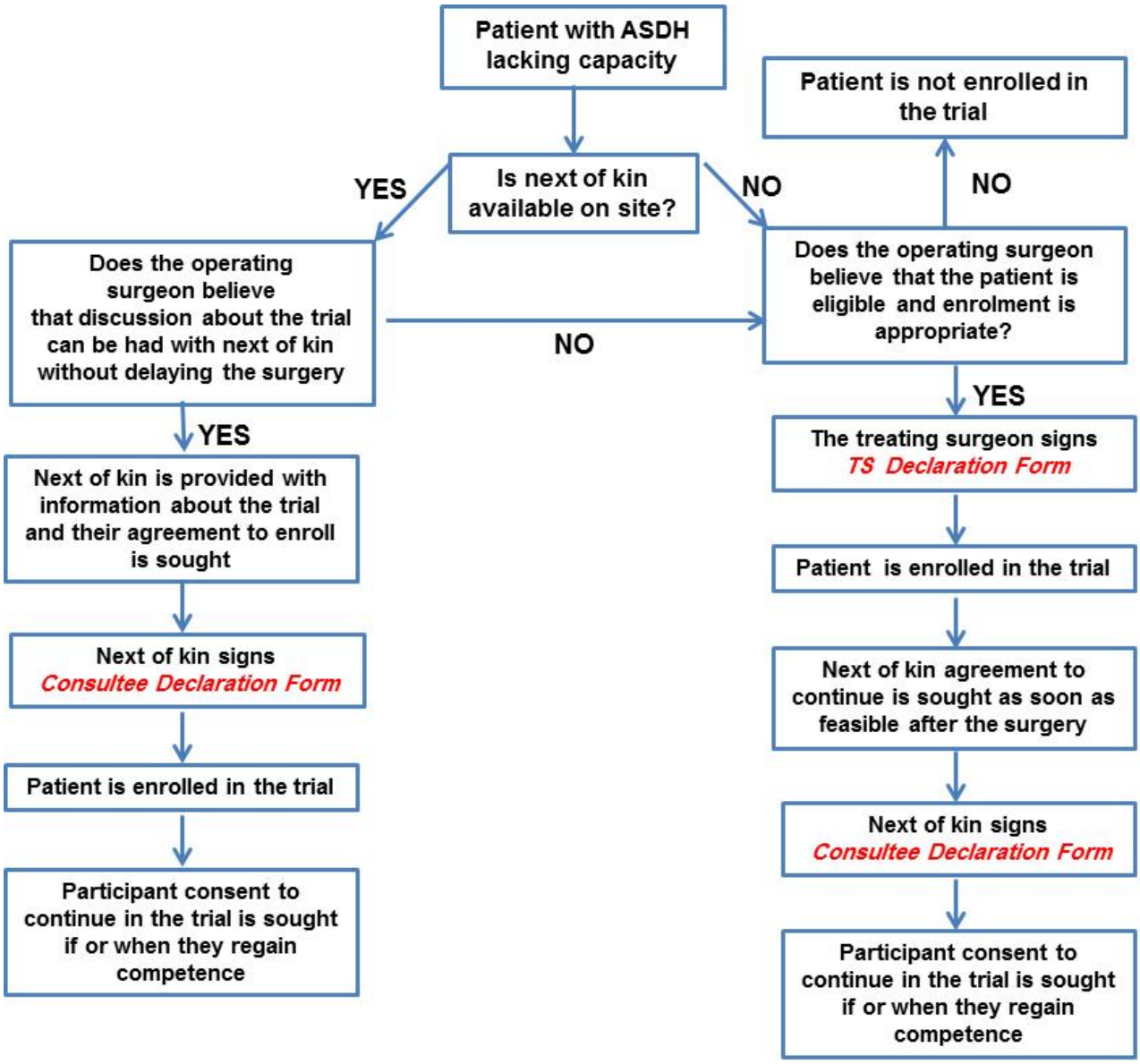


Figure 1. Consent Algorithm

5.3 Trial Interventions

Descriptions of the two surgical interventions and concomitant interventions within each group of the Rescue-ADSH trial are provided below, accompanied by details about surgeon expertise, context and how outcome will be assessed.

5.3.1 Craniotomy

The size and location of the incision will be chosen by individual surgeons. A large bone flap (recommended size ≥ 11 cm) anteroposterior diameter (AP diameter) must be

raised. The subdural haematoma is evacuated according to the surgeon's preference. Surgeons may evacuate other associated haematomas at their discretion. The bone flap must be replaced and fixed with an appropriate fixation system (plates and screws or titanium clamp system). Floating or hinged flaps are prohibited. Dural reconstruction, closure techniques for other tissue layers, and use of subgaleal wound drains are left to the surgeon's discretion. The use of intra-cranial monitoring devices is encouraged. The advantage of a craniotomy is that the patient will not need a later operation to rebuild the skull. However, it may fail to control brain swelling in some patients.

5.3.2 Decompressive Craniectomy

The size and location of the incision will be chosen by individual surgeons. A bone flap of at least 11cm (AP diameter) must be raised. The subdural haematoma is evacuated according to the surgeon's preference. Surgeons may evacuate other associated haematomas at their discretion. The bone flap should not be replaced at the end of the operation. The dura should either be left open or a non-constricting duroplasty undertaken, according to surgeon preference. Closure techniques for other tissue layers are flexible. The use of subgaleal drains is discretionary; however, suction drains should be avoided. The use of intra-cranial monitoring devices is encouraged. The use of compressive head bandages is discouraged. The advantage of a DC is that it is effective in controlling brain swelling which is often a problem in the days after the operation. When the swelling goes down, the patient has another operation to reconstruct the skull (cranioplasty).

5.3.3 Concomitant interventions

A CT scan is usually undertaken in the post-operative period. Other pre, peri- and post-operative interventions may be performed according to surgeon and centres' standard practice. Cranioplasty (DC group only) should ideally occur within 6 months of the index procedure, although the technique used is discretionary.

5.3.4 Treatment Context

Surgical interventions will be delivered within specialist neurosurgical units. Immediate post-operative care will occur within an intensive care setting. Equipment used to perform both operations will be entirely at the discretion of the operating surgeons and teams. The day of discharge will be at the clinical team's discretion.

5.3.5 Surgeon Expertise

Surgical interventions will be undertaken by consultant neurosurgeons (or equivalent), or trainees working within the team. Trainees may operate independently or under supervision, depending on whether they are competent to undertake the procedure unassisted.

5.4 Trial endpoints

5.4.1 Primary endpoint

The primary endpoint will be the GOSE (extended Glasgow Outcome Scale) at 12 months post-injury. The use of the GOSE as a core global outcome measure is recommended by the interagency TBI Outcomes Workgroup and the International Mission for Prognosis and Analysis of Clinical Trials in TBI group (IMPACT Common Data Elements).

5.4.2 Secondary endpoint

The secondary endpoints are:

- GOSE at 6 months post-injury

- Quality of life (EQ-5D) at discharge from neurosurgical unit (NSU), 6 and 12 months post-injury
- Glasgow Coma Scale (GCS) on discharge from the intensive care unit (ICU) and from NSU
- Length of stay in ICU, neurosurgical and rehabilitation unit
- Therapy Intensity Level (IMPACT-TBI scale) in the ICU
- Discharge destination from NSU
- Mortality
- Serious adverse events & surgical complications during index admission
- Cranial surgery within 2 weeks after randomisation
- Subsequent readmissions to the NSU within the 12 months follow-up period
- Hydrocephalus requiring shunt insertion within the 12 months follow-up period
- Health care services utilisation over 12 months
- Detailed economic evaluation

5.5 Sample size calculation & statistical analyses

5.5.1 Sample Size

Retrospective studies suggest a favourable outcome in about 35% of patients undergoing evacuation of ASDH. A formal sample size calculation was performed using nQuery Advisor Version 7.0, using a Wilcoxon-Mann-Whitney rank-sum test for ordered categories. The calculated sample size is 990 patients (900 total include 10% drop out rate; 495 in each arm) in order to detect an 8% absolute difference in favourable outcome [90% power and 2-sided significance 0.05 (35% vs 43%)]. This corresponds to being able to detect an 8% treatment effect. Mortality is recorded as part of the GOSE (death – GOSE score 1), so it will not impact on loss to follow-up. In addition, a simulation study was undertaken to look at the impact on statistical power of covariate (age, GCS motor score and pupillary reaction) adjustment over and above the ordinal analysis. The simulation study confirmed that the planned sample size of 990 patients, will give over 90% power to detect an 8% treatment effect. Therefore, we intend to use the proportional odds model adjusted for covariates in the analysis of the trial.

In a medium-sized neurosurgical unit, approximately 20 patients with ASDH undergo surgery each year. If 10-20% of patients are not recruited due to consent refusal by the participant/next-of-kin (as estimated on the basis of community survey findings) then approximately 15 patients will have valid consent. For patients with consent, the operating surgeon will have to decide intra-operatively as to whether they are suitable for randomisation. For example, if the brain is bulging outside the margins of the skull, the bone flap cannot be replaced without damaging the brain. This patient would not be suitable for randomisation. On the basis of pilot data, we are estimating that 30-50% of patients will be suitable for randomisation. Hence, it is reasonable to assume that at least 5 out of 15 patients with valid consent will be suitable for randomisation (average recruitment 5 patients/site/year). This rate of recruitment was reached following discussions with the Principal Investigators. There is broad consensus that this rate of recruitment is realistic and feasible.

During Stage 1, we expect that 120 patients will be randomised. During Stage 2, we expect that 870 patients will be randomised.

5.5.2 Statistical Methods

Outcome in this study will be measured using the GOSE. Conventionally scales such as this are analysed by dichotomising the ordinal scale into a binary scale: ‘unfavourable’ versus ‘favourable’ and an odds ratio calculated. A significant number of patients will not

have a realistic chance of crossing the threshold between 'unfavourable' and 'favourable' outcome, and will not contribute data to the analysis. The crude odds ratio is therefore not a meaningful effect measure for a large number of patients. It discards much relevant information, reducing both the clinical relevance of the results and the statistical efficiency of the analysis. We therefore consider it more appropriate to quantify prognostic effects across the full range of the GOSE.

Based on IMPACT recommendations (NIH-funded International Mission for Prognosis and Analysis of Clinical Trials in TBI project), our statistical analysis will use an ordinal approach, based on proportional odds methodology with covariate adjustment [19]. The IMPACT recommendations have been endorsed by the ABIC (American Brain Injury Consortium), EBIC (European Brain Injury Consortium), International Neurotrauma Society and National Neurotrauma Society (USA). Gillian McHugh (RESCUE-ASDH statistician) and Prof Gordon Murray (who has advised on the sample size and analysis of RESCUE-ASDH) are both IMPACT co-investigators.

The choice of ordinal logistic regression is based on the results of statistical research and trials, which showed that ordinal methods can increase statistical power substantially, equivalent to allowing a reduction of over 40% in the sample size without loss of statistical power. Ordinal logistic regression analysis is similar to logistic regression analysis, but it simultaneously estimates multiple odds ratios instead of just one. The number of odds ratios it estimates is equivalent to the number of ordered categories minus one. The ordinal regression model assumes that the odds ratio for each potential split of the GOSE is constant no matter which cutpoint is taken, i.e. it follows a proportional odds model; this assumption can be tested with a formal test of goodness of fit. The final estimated effect size is a pooled estimate of the common odds ratio. The conventional fixed dichotomy method will be done as a sensitivity analysis.

Analysis will be performed on an intention-to-treat basis. Ordinal analysis methodology (as described) will be undertaken but dichotomised outcome (alive/dead; favourable/unfavourable) will also be reported. Pre-defined subgroups for exploratory analyses will include: age below or above 65 years; age below or above 40 years; evidence of parenchymal injury on initial CT head or not; initial GCS ≤8 or not; post-operative ICP monitoring or not.

A full analysis plan will be agreed prior to the examination of any data.

5.5.3 Interim Analyses

No futility or interim analysis is planned.

5.6 Trial Process

5.6.1 Criteria for the premature termination of the trial

No criteria are set for early termination of the study. An unbiased ongoing review of data will be performed by the DMEC, which could potentially discuss any potential termination with the trial steering committee.

Stage 1 (feasibility study) will be followed by Stage 2 (substantive study) if the progression criteria are met (see section 5.1).

5.6.2 Definition of the end of the trial

The end of the study is the date of the last 12 month follow up of the last study participant.

5.7 Trial Procedures

5.7.1 Randomisation Procedure

Following enrolment in the study, suitability for randomisation will be assessed in the operating room by the operating neurosurgeon (see Trial Flow chart). A secure web-based or telephone randomisation service will be used for the randomisation of suitable patients. The following information will be required in order to randomise a patient: age, best pre-intubation Glasgow Coma Scale (GCS), pre-operative pupillary reactivity, CT findings. Suitably trained operating theatre staff will access the secure web site and enter the above information. The system will provide an immediate allocation along with the patient identifier number for the trial. A confirmatory email will be sent to the email addresses of the members of the study team at the site randomising the patient. The 24-hour randomisation service will be backed by 24-hour availability of Trial Investigators (or delegated person) who can advise on patient eligibility. Blocked randomisation will be used, with a block size of 4 and allocation ratio of 1:1, and subjects are allocated randomly within each block. Allocation will be stratified by country / geographical region (UK / Other European countries / North America / Australia / Other), age group (<40, 40-65, >65 years), severity of injury (GCS 3-8, GCS 9-15), and CT findings (parenchymal injury, no parenchymal injury).

Eligible non-randomised participants () will have the operation (i.e. craniotomy or DC) deemed to be in their best interests by the operating surgeon. This group of eligible but non-randomised patients will be followed-up in a similar manner to randomised patients.

5.7.2 Blinding

Patients, relatives and treating doctors cannot be blinded due to the nature of the intervention (after a craniectomy a skull defect is noticeable until a cranioplasty is undertaken). The follow-up questionnaires will be collected centrally (Cambridge CTU) and outcome scores will be determined by two outcome adjudicators independently. The outcome adjudicators will be blinded to the allocation of patients. Any patient for whom there is disagreement will be discussed in the outcomes adjudication committee. The members of this committee will also be blinded to the allocation of patients.

In the international sites, the same procedure will be followed with the difference that local staff will be responsible for sending postal questionnaires to patients. If a telephone or face-to-face interview needs to be undertaken in order to complete the questionnaires, a standard operating procedure will ensure strict separation between staff conducting these interviews and staff that are involved in the acute care of recruited patients. Questionnaires from international sites will also be returned to the Cambridge CTU and outcome scores will be determined as described above.

5.7.3 Subject withdrawal criteria

Each participant has the right to discontinue their part in the study at any time. If an unconscious participant regains capacity and makes a request to be withdrawn from the study then this is accepted. Incapacitated participants may also be withdrawn from a study if the consultee requests withdrawal. In addition, the investigator may withdraw the participant from their allocated treatment arm if subsequent to randomisation a clinical reason for not performing the surgical intervention is discovered. All discontinuations and withdrawals will be documented. If a participant wishes to discontinue, data collected up until that point will be included in the analyses, unless the participant expresses a wish for their data to be destroyed. For those patients, their vital status will be checked one year after the intervention from the national mortality databases.

5.7.4 Co-Enrolment

It is possible that there may be eligible patients either already enrolled in other trials, or who may be suitable for another trial after enrolment to the RESCUE-ASDH trial. If the RESCUE-ASDH TMG becomes aware of another RCT at one of our recruiting centres targeted at a similar patient group with similar endpoints, we will discuss these issues with the Chief Investigator/TMG of the other RCT.
In order to make a decision about the opportunity for co-enrolment we will consider the following criteria outlined in the 'Co-enrolment to Critical Care Studies and Trials in the UK Guidance Document, December 2012'
[http://www.ics.ac.uk/latest_news/JICS_co_enrolement accessed 25.7.13].

- The processes and measures used in one study is not introducing bias by altering responses to those used in the other study.
- The information obtained in one study is not altering clinical decision making or treatment in a way that could introduce bias to the other study.
- The two protocols are compatible in terms of the allowed treatments, technologies, procedures, and treatment protocols.
- No high chance of an imbalance in the numbers of patients from one study allocated to the treatment groups in the other study.
- The inclusion in multiple research studies is not altering the characteristics of the control groups in a way that might alter study power and generalizability.
- The numbers of patients being co-enrolled are being tracked and reported back to each study management team.
- Screening patients for multiple studies in a single centre is not introducing selection bias to any of the studies.

If these criteria are met a Trial Co-enrolment Agreement will be drawn up and signed by both Chief Investigators. Co-enrolment will be recorded in patient records and case report forms.

5.7.5 Other Methodological Issues

5.7.5.1 Surgeon effect

In each unit, the operations will be performed by any of the consultant, staff grade or trainee neurosurgeons. Their total number typically exceeds 15 in most units. The large number of surgeons and the wide skill mix should minimise the 'surgeon effect' although it will be examined descriptively.

5.7.5.2 Clustering

Clustering will be explored in Stage 1, but clustering by surgeon is not anticipated as the way in which the procedures differ is not affected by surgical skill (bone flap replaced or left out prior to wound closure). In addition, both interventions involved are routine and it is unlikely that surgical outcome will be affected by surgical experience. Given the relatively small number of patients to be recruited per centre (on average five per centre per year), clustering by centre will be examined descriptively.

5.7.5.3 Crossovers

There is no reliable data regarding the number of patients who after initially undergoing a craniotomy eventually require a DC in this context. In addition, such an occurrence will not be considered a cross-over in the context of the trial because RESCUE-ASDH aims to be a pragmatic trial of two 'strategies' for managing patients with an ASDH rather than an explanatory trial. However, 'return to operating theatre for cranial

surgery within 2 weeks after randomisation' is a secondary endpoint; therefore, the trial will be able to determine the rate of returns to theatre for DC following a craniotomy.

5.7.5.4 Covariates

Factors included in the randomisation process (i.e. age, severity of injury, pupillary reactivity) will be included as covariates in the primary analysis with centre included as a random effect.

5.7.5.5 Missing data

For the primary analysis missing data will be assumed to be missing at random (MAR). A sensitivity analysis will be carried out by performing a complete case analysis. As the relevant covariates need to be recorded before a patient can be randomised, we aim to have no missing baseline data. There is also an excellent track record for UK-led neurosurgical trials in achieving extremely high rates for follow-up (STICH, STICH II and RESCUEicp trials).

5.7.5.6 Secondary analyses

Secondary analyses will be reported for the two pre-specified binary outcomes: dead vs. alive and unfavourable vs. favourable outcome. The GOSE categories of death, vegetative state, lower severe disability and upper severe disability will be taken as an unfavourable outcome. Favourable outcome will be defined as the GOSE categories: lower moderate disability, upper moderate disability, lower good recovery and upper good recovery.

5.8 Procedures and Assessments

5.8.1 Screening Evaluation

The neurosurgical on-call team is responsible for the admission of head-injured patients. Therefore, the on-call team will be responsible for identifying eligible patients following the criteria stated in sections 5.2.2 and 5.2.3 of this protocol. Consent will be obtained as described in section 5.2.5 and eligible patients will be enrolled on the trial.

5.8.2 Baseline Assessments

- Socio-demographic details
- Medical history (including comorbidities and relevant medications)*
- Injury related events*
- FBC, Coagulation, Electrolytes, Urea*
- CT scans*
- Neurological assessment*
- Glasgow Coma Scale (GCS)*
- Surgery related data*

**performed as part of routine clinical practice*

5.8.3 Assessment during discharge from ICU and NSU

- Glasgow Coma Scale (GCS)
- Therapy Intensity Level (TIL) in the ICU
- Quality of Life (EQ-5D) patient questionnaire – NSU discharge only
- Informed consent (see section 5.2.5)

5.8.4 Follow up Assessments

Following discharge from the acute setting (neurosurgical unit), patients will be followed up at 6 and 12 months post-injury with the GOSE and the EQ-5D. The length of follow-up is 1 year. This is in keeping with the recommendation of the IMPACT group.

In the UK/Irish sites, follow-up will be undertaken by postal questionnaires (GOSE and the EQ-5D) which will be sent to patients by the trial co-ordinator. Once filled in, postal questionnaires will be returned to the Cambridge CTU using pre-paid envelopes. A phone call will act as a reminder for those who have not responded. If necessary, postal questionnaires will be re-sent. However, in some cases a structured telephone interview will need to be undertaken bya member of the research team , for example, if there are practical difficulties with filling in or returning the form. The GP will be contacted prior to sending out postal questionnaires to ensure that the patient is alive. A member of the research team will be blinded to the allocation of patients. This procedure has achieved a good return of outcome questionnaires in the RESCUEicp study (>93% which is high for a head injury study). The GOSE and EQ-5D questionnaires will be collected centrally and outcome scores will be determined by two outcome adjudicators independently.

In the international sites, the same procedure will be followed with the difference that local staff will be responsible for sending postal questionnaires to patients. If a telephone or face-to-face interview needs to be undertaken in order to complete the questionnaires, a standard operating procedure will ensure strict separation between staff conducting these interviews and staff that are involved in the acute care of recruited patients. Questionnaires from international sites will also be returned to the Cambridge CTU and outcome scores will be determined as described above.

Table 1. Data collection at the different assessment points

	Baseline	Discharge ICU	Discharge NSU	6 Months Post-injury	1 Year Post-injury
Socio-demographic details	X				
Medical History*	X				
Injury related events*	X				
Routine Baseline Assessments*#	X				
Surgery Related Data*	X				
Glasgow Coma Scale (GCS)*	X	X	X		
Therapy Intensity Level (TIL)		X			
Extended Glasgow Outcome Scale (GOSE)***				X	X
Quality of life (EQ-5D)***			X	X	X
Resource use questionnaire***					X

** These are routine assessment done as part of standard trauma workup.*

 # Neurological assessment, Laboratory Results, CT Findings

**** These are questionnaires completed by the study participants.*

Reasons for the non-completion of questionnaires will be recorded. Missing or erroneous items on questionnaire measures will be handled according to the questionnaire developers' scoring manuals.

5.8.5 Economic Evaluation

Costs will be estimated from the viewpoint of the NHS and personal social services (PSS). Resources consumed in hospital will thereby be monitored along with other items such as community rehabilitation and physiotherapy. Additionally, data on absence from work and the level of informal care will also be collected. Hospitals will be asked to provide data on the resource use by individual participants as part of their initial admission post-injury (including surgical procedures, imaging investigations (e.g. CT / MRI scans) and time in ICU and on the NSU), this could be via a download of the Patient Level Information and Costing Systems PLICS data at the hospital site. Additionally, participants (or relatives/friends) will be asked to report levels of resource use after this time point (post-discharge from the NSU) up to 12 months-post injury. Appropriate unit costs e.g. [9] will subsequently be assigned to each item of resource use for a standard price year. The incremental cost of craniotomy compared to DC, over the 12 month trial period, will then be estimated by comparing the mean cost in each arm of the study.

Consequences will be measured by combining data on quality of life, measured using the EQ-5D-5L [10] with survival to generate Quality Adjusted Life Years (if the participant can't complete the EQ-5D themselves, we will request that a relative/friend complete the proxy version). This will enable a cost-utility analysis to be conducted. The incremental QALY gain associated with craniotomy compared to DC will subsequently be estimated over the 12 month trial period. We also propose to undertake a cost-effectiveness analysis based on the primary outcome – the GOSE. The costs will be estimated as specified above, but as well as being assessed in relation to QALYs (for the cost-utility analysis), we will also assess in relation to the GOSE (cost-effectiveness analysis).

Both the aforementioned cost-effectiveness and cost-utility analyses will initially be undertaken as within-trial analyses. Additionally, if there is a difference in outcome at 1 year then there would be the potential for benefits to accrue to the individual over a number of years. This would mean that the within trial analysis may not capture all relevant costs and benefits and may not give a true picture of cost-effectiveness. For this reason we will also estimate a probabilistic long run economic model. It is expected that this will comprise two parts. Firstly, we will construct a decision tree to use the results of the trial to assign individuals to various relevant health states. A long run Markov model will then estimate costs and benefits (QALYs) over the expected life time of participants.

The structure of these models will be developed in consultation with clinical experts. Data to inform the model will be taken from the trial, the non-randomised cohort, and where necessary, from the literature or from expert opinion.

The above analyses will enable both the incremental cost and incremental effect associated with craniotomy compared to DC to be estimated. Assuming dominance does not occur (where one option is estimated to be more effective and less costly than the other option), the incremental cost-effectiveness ratio of the more costly option will be estimated and assessed in relation to a range of cost-effectiveness thresholds e.g. £20,000-£30,000 per QALY is recommended by NICE [26]. The associated level of uncertainty will also be characterised. Sensitivity analysis will subsequently be undertaken e.g. to assess whether the cost-utility results are robust when only self-report data are used.

6. Trial management

6.1 Trial Management Committee (TMC)

The trial will be managed by a TMC, which will meet face to face or by teleconference regularly for the duration of the study. The TMC will be chaired by the Chief Investigator and will include the trial Coordinator, co-applicants, and trainee representatives.

The trial coordinating centre will prepare all the trial documentation and data collection forms, specify the randomisation scheme, develop and maintain the study database, check data quality as the trial progresses, monitor recruitment and carry out trial analyses in collaboration with the clinical investigators.

6.2 Day-to-day management

The Principal Investigator at each participating centre will be responsible for ensuring adherence with the study protocol, compliance with the consent process and accurate collection of trial data. Research teams at these centres will be responsible for identifying eligible patients, taking consent, randomising patients and collection of trial data.

6.3 Monitoring of sites

6.3.1 Initiation visit

Before the study commences meetings will be organised by the trial coordinating centre with all identified local Principal Investigators in neurosurgical units participating in this study. These sessions will ensure that personnel involved fully understand the protocol, CRFs and the practical procedures for the study.

6.3.2 Site monitoring

Monitoring will be carried out during the conduct of the trial to check for protocol adherence as well as procedures for patient screening, informed consent taking and documentation, patient trial registration, and accuracy of trial data collected. There will be central monitoring, remote monitoring as well as periodic on site visits to participating sites as appropriate or triggered.

6.4 Trial Steering Committee and Data Monitoring and Ethics Committee

The Trial Steering Committee (TSC) will provide overall supervision with respect to the conduct of the study. Professor Tony Bell (St George's, University of London) has agreed to be the independent chairman.

The ethical and safety aspects of the trial will be overseen by an independent Data Monitoring and Ethics Committee (DMEC) which will be chaired by Professor Martin Smith (The National Hospital for Neurology and Neurosurgery, London). DMEC meetings will be timed so that reports can be fed into the TSC meetings.

7. Assessment of Safety

Data on adverse events will be collected in this trial as secondary outcomes and will be presented to the independent Data Monitoring Committee (DMC) for unblinded review.

7.1 Definitions

7.1.1 Adverse event (AE)

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product/treatment which does not necessarily have a causal relationship with this treatment.
An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use

of a medicinal product, whether or not considered related to the medicinal product/treatment

Please note: Recording of all adverse events must start from the point of Informed Consent regardless of whether a patient has yet received the treatment.

7.1.2 Adverse reaction (AR)

All untoward and unintended responses to a medicinal product/treatment. All adverse events judged by either the reporting investigator or the Sponsor as having a reasonable causal relationship to a medicinal product/treatment qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

7.1.3 Unexpected adverse events/reaction

For the purposes of this trial, an unexpected adverse event/reaction will be one the nature, or severity of which is not consistent with the studied surgical approach or the underlying injuries caused by the trauma. Adverse events and reaction should be considered as unexpected if not listed as per definition in sections 7.2 and 7.3.

The term “severe” is often used to describe the intensity (severity) of a specific event. This is not the same as “serious,” which is based on patient/event outcome or action criteria.

7.1.4 Serious adverse event (SAE)

In research other than CTIMPs, an SAE is defined as an untoward occurrence that:

- results in death
- is life-threatening
- requires hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- is otherwise considered medically significant by the investigator.

Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe.

7.2 Expected procedure related adverse events

Despite being a common neurosurgical procedure, DC and craniotomies are inherently associated with their own difficulties and complications. They can be best classified in terms of perioperative, early, intermediate and late. The following adverse events are ‘expected’:

Perioperative	**Early**	**Intermediate**	**Late**
- Expansion of mass lesions	- External herniation of the brain	- Subdural hygromas	- Hydrocephalus
- Development of new mass lesions	- Development of mass lesions	- Wound complications other than infection	- Syndrome of the Trephined
- Stroke	- Epilepsy	- Surgical Site Infections	- Surgical Site Infections
- Vascular injuries	- Stroke	- Meningitis	- Epilepsy
		- Subdural empyema	
		- Intracerebral abscess	
		- Epilepsy	

Perioperative

The relief of the tamponade effect following bone removal and hematoma evacuation in patients with severe TBI may facilitate expansion of underlying contusions. The same

mechanism can explain the development of contralateral mass lesions such as extradural haematomas.

Early
External herniation of the brain is frequent in the first few days following decompression. Potential adverse effects of external cerebral herniation include compression of cortical veins within the herniated segment of brain and subsequent venous infarction of the herniated tissue. Postoperative epilepsy may occur although the mechanism is not fully understood.

Intermediate
Subdural hygromas are common after decompressive craniectomy occurring in 25-60% of cases. They are thought to occur as a consequence of either the traumatic rupture of the dura–arachnoid interface, altered CSF dynamics or increased cerebral perfusion following decompression. Most hygromas resolve spontaneously without need for intervention. Infection can occur within the first month or in a delayed fashion after surgical intervention. Scalp incisions and trauma bone flaps tend to be larger in this group of patients to facilitate adequate evacuation of the hematoma and decompression. The vascular supply of the flap can be compromised resulting in ischaemia or necrosis of the flap. The large bone flap can traverse the frontal sinus and mastoid air cells, providing a potential direct route of infection and risk of meningitis and subdural empyema. Additionally, the patient population is often relatively immunocompromised due to their underlying condition and therefore more prone to surgical site infections and other systemic infections.

Late
Hydrocephalus is a common problem after TBI with reported rates up to 30%. It may develop merely as a consequence of the primary brain injury, but it is suggested that the altered CSF dynamics thought responsible for the development of subdural hygromas could also be contributory to the development of hydrocephalus. Patients with symptomatic hydrocephalus may benefit from insertion of a shunt. Syndrome of the trephined is a delayed complication that presents weeks to months following surgery that affects small numbers of DC patients. Symptoms usually resolve post-cranioplasty.

7.3 Expected disease related & systemic adverse events

I. Pulmonary:
a. Pneumonia
b. Pneumothorax
c. Atelectasis
d. Aspiration
e. Pleural effusion/empyema
f. Ventilator-related complications
g. Adult respiratory distress syndrome
h. Respiratory failure
i. Need for prolonged mechanical or positive pressure airway ventilation

II. Cardiac:
a. Myocardial infarction
b. Arrhythmia
c. Heart failure
d. Angina
e. Pericardial effusion
f. Pericarditis

III. Renal:
a. Urinary tract infection
b. Renal failure maybe requiring full renal support
c. Renal dysfunction
d. Urinary retention
e. Haematuria

IV. Thrombotic:
a. Deep vein thrombosis
b. Pulmonary embolism
c. Mesenteric thrombosis
d. Other thromboses (e.g. limb)

V. Hepatobiliary:
a. Pancreatitis
b. Liver failure
c. Hepatitis

VI. Bowel:
a. Infective diarrhoea or colitis (e.g. Clostridium difficile)
b. Diarrhoea of other causes
c. Bowel ischaemia
d. Ileus

VII. Wound other than craniotomy or craniectomy:
a. Infection
b. Dehiscence

VIII. Other miscellaneous general complications:
a. Decubitus ulcer
b. Other infections (e.g. MRSA)
c. Anaesthetic-related complication
d. Anaemia, coagulopathy
e. Pyrexia
f. Septicaemia

7.4 Recording and evaluation of adverse events

This clinical trial is being conducted in a critical emergency condition using two surgical approaches that are widely and commonly used. It is important to consider the natural history of the critical medical event affecting each patient enrolled, the expected complications of this event, and the relevance of the complications to the procedures.

All adverse events, including expected systemic and procedure related adverse events, will be assessed by the Investigator and recorded in detail in medical notes and Case Report Forms (CRFs). Abnormalities in laboratory test results or other investigations will only be recorded on CRFs or collected as clinical trial data if they are considered to be clinically significant.

Adverse events recorded on CRFs during the study will be sent to CCTU. At the conclusion of the study, all adverse events will be subject to statistical analysis, and the analysis and subsequent conclusions will be included in the final study report.

Adverse events will be reviewed at TSC meetings.

Individual adverse events should be evaluated by the investigator. This includes the evaluation of its seriousness, expectedness and causality

7.5 Assessment of causality

I. **Definitely:** A causal relationship is clinically/biologically certain. This is therefore an Adverse Reaction
II. **Probable:** A causal relationship is clinically / biologically highly plausible and there is a plausible time sequence between onset of the AE and administration of the treatment and there is a reasonable response on withdrawal. This is therefore an Adverse Reaction.
III. **Possible:** A causal relationship is clinically / biologically plausible and there is a plausible time sequence between onset of the AE and administration of treatment. This is therefore an Adverse Reaction.
IV. **Unlikely:** A causal relation is improbable and another documented cause of the AE is most plausible. This is therefore an Adverse Event.
V. **Unrelated:** A causal relationship can be definitely excluded and another documented cause of the AE is most plausible. This is therefore an Adverse Event.

7.6 Clinical assessment of severity

I. **Mild:** The subject is aware of the event or symptom, but the event or symptom is easily tolerated
II. **Moderate:** The subject experiences sufficient discomfort to interfere with or reduce his or her usual level of activity
III. **Severe:** Significant impairment of functioning; the subject is unable to carry out usual activities and / or the subject's life is at risk from the event.

7.7 Severity of complications

I. The need for re-intervention of these sorts:
   a. bedside procedure (e.g insertion if chest drain, ascites drain, drainage, abscess or wound)
   b. medical intervention (e.g. antibiotics, TPN, blood transfusion)
   c. invasive procedure without general anaesthesia (surgical or radiological)
   d. invasive procedure, general anaesthesia or single organ failure
   e. invasive procedure, general anaesthesia, single organ failure or multi-organ failure

II. The need to return to intensive care:
   a. mechanical ventilation
   b. organ support
   c. invasive monitoring
   d. tracheostomy

III. In-hospital death

IV. Readmission to hospital following discharge

7.8 Reporting unexpected serious adverse events (SAEs)

In this trial only serious adverse events (as defined in section 7.1.4) and surgical complications that are unexpected (as defined in section 7.1.3) will need to be reported as SAEs for the following reasons:

- Enrolled patients will be suffering from TBI therefore will be already experiencing

a number of SAEs as defined in section 7.1.4

- In severe TBI patients, post-operative complications are not unexpected nor infrequent, often causing an extension of the patient's hospital admission.
- Adverse events which might reasonably occur as a consequence of the intervention procedure studied or that are part of the natural history of the primary event of TBI or expected complications of TBI will be collected as primary or secondary endpoints and used in the statistical analysis.

The Investigator is responsible for assessing all AE for seriousness, expectedness and relatedness Expected AEs/SAEs are listed in sections 7.2 and 7.3 above.

Reportable SAEs should be notified to CCTU and the Sponsor immediately but not more than 24 hours of the CI becoming aware of the event. The Sponsor has to keep detailed records of all SAEs reported to them by the trial team.

The subject will be actively followed up, and the investigator (or delegated person) will provide information missing from the initial report within ten working days of the initial report. The investigator (or delegated person) will provide follow-up information each time new information is available, using the SAE Follow-up Report form until the SAE has resolved or a decision for no further follow-up has been taken.

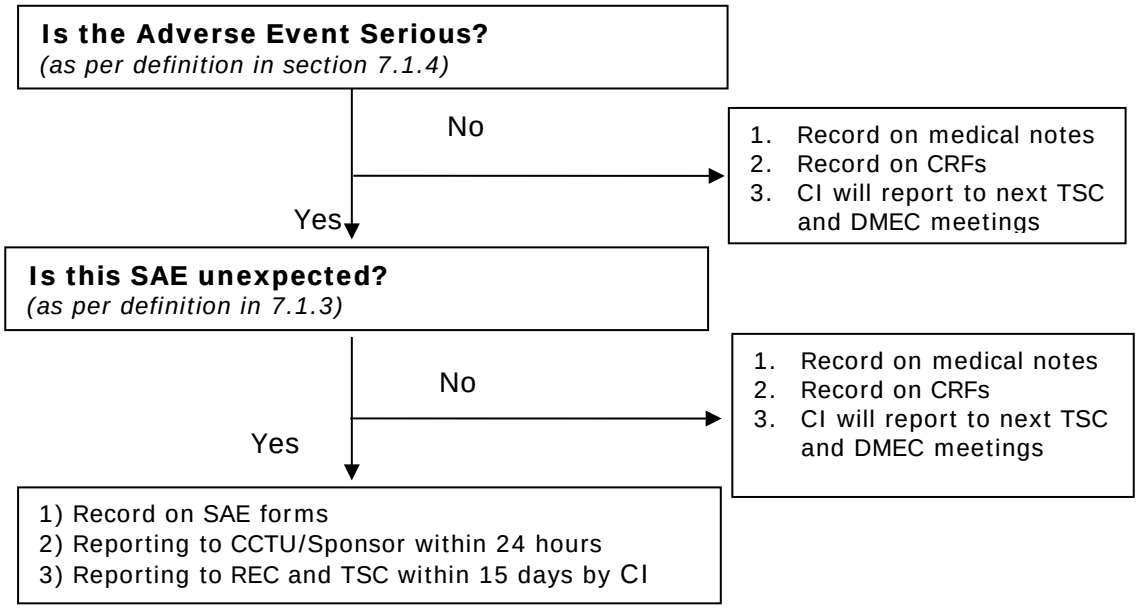
All SAEs will be reviewed at TSC meetings. Reportable SAEs should be notified to the TSC within 7 days.

All SAEs that are both related to the procedure and unexpected (as per definition in section 7.1.3) should also be reported to the main REC within 15 days of the CI becoming aware of the event.

7.8.1 Who should report and whom to report to?

The Sponsor delegates the responsibility of notification to the REC and any other investigators to the Chief Investigator. The Chief Investigator should report all the relevant safety information previously described, to the Sponsor and to the main REC and inform all other investigators concerned of relevant safety information that could adversely affect the safety of trial participants.

Figure 2 Serious adverse event reporting flow chart for all participating centres



8. Ethical considerations

8.1 Consent

The Informed consent form must be approved by the REC or the relevant national Ethics Committee (for non UK sites) and must be in compliance with GCP, local regulatory and legal requirements. The investigator must ensure that each trial participant, or his/her legally acceptable representative, is fully informed about the nature and objective of the trial and possible risks associated with their participation.

Informed consent will be obtained following the procedure outlined in section 5.2.5 of the protocol and in accordance with: the Declaration of Helsinki for enrolling patients into trials in an emergency situation; the Mental Capacity Act (2005) for sites in England and Wales; the Adults with Incapacity (Scotland) Act 2000 for sites in Scotland; common law in Northern Ireland. For non UK sites, local national laws and regulations for entering mentally incapacitated subjects into clinical trials will be followed (Appendix 1) The investigator will retain the original of each patients signed informed consent in the Investigator Site File (ISF).

Should a patient require a translation of the trial documentation by a locally approved interpreter/translator, it is the responsibility of the investigator to use locally approved translators.

All trial documentation in a different language (other than English), including the translation and back translation of documents must be reviewed and approved by the Sponsor prior to use. All sections of the approved documents must appear in the translation. The translated version must be appropriately dated and version controlled.

8.2 Ethics Committee Review

For UK sites, ethics review of the protocol for the trial and other trial related essential documents (e.g. Participant Information Leaflets and Consent Forms) will be carried out by a an appropriate Research Ethics Committee (REC) before the start of the trial. Any subsequent amendments to these documents will be submitted to the REC for approval prior to implementation.

Annual reports will be submitted to the REC in accordance with national requirements. It is the Chief Investigator's responsibility to produce the annual reports as required.

For sites outside the UK, the trial will be conducted in accordance with the local regulatory requirements and laws as applicable.

8.3 Risks and anticipated benefits for trial participants and society

All participants will undergo one of the two standard operations currently carried out in routine care of ASDH patients.

The potential risks and theoretical benefits are well described for the two procedures; they will be discussed with the patients/representatives when informing them of the study.

In terms of societal benefits of the study, the trial will inform guidelines for treating ASDH patients thereby not prolonging the current situation of uncertainty.

9. Research governance

This study will be conducted in accordance with:

- The Good Clinical Practice (GCP) guidelines

- The Research Governance Framework for Health and Social Care
- Declaration of Helsinki
- Mental Capacity Act 2005 (for sites in England and Wales)
- Adults with Incapacity (Scotland) Act 2000 – for sites in Scotland
- Applicable local regulatory guidelines and laws

9.1 Sponsorship, Financial and Insurance

The trial is sponsored by Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge. The study will be funded by a NIHR Health Technology Assessment Programme grant awarded to Professor Peter Hutchinson, Department of Clinical Neurosciences, University of Cambridge.

All NHS Foundation Trusts, as members of the NHS Clinical Negligence Scheme for Trusts, will accept full financial liability for harm caused to participants in the clinical trial caused through the negligence of its employees and honorary contract holders. There are no specific arrangements for compensation should a participant be harmed through participation in the trial but no-one has acted negligently.

The University of Cambridge will arrange insurance for negligent harm caused as a result of protocol design and for non-negligent harm arising through participation in the clinical trial.

9.2 NHS approval

All trial documents and any subsequent amendments will be approved by the Sponsor prior to submission to the REC. Evidence of REC favourable opinion will be submitted to each participating Trust's R & D department for information and local approval.

9.3 Protocol Compliance and Breaches of GCP

Prospective, planned deviations or waivers to the protocol are not allowed by the Sponsor and must not be used.

Protocol violations, deviations, non-compliances, or breaches are departures from the approved protocol. They can happen at any time, but are not planned. They must be adequately documented on the relevant forms and reported to the CI and Sponsor immediately.

Deviations from the protocol which are found to occur constantly will not be accepted and will require immediate action and could potentially be classified as a serious breach.

Any potential/suspected serious breach of GCP must be reported immediately to the Sponsor without any delay.

9.4 Investigators' responsibilities

Investigators will be required to ensure that local research approvals have been obtained and that any contractual agreements required have been signed off by all parties before recruiting any participant. Investigators will be required to ensure compliance to the protocol and study manual and with completion of the CRFs. Investigators will be required to allow access to study documentation or source data on request for monitoring visits and audits performed by the Sponsor or trial team or any regulatory authorities.

Investigators will be required to read, acknowledge and inform their trial team of any amendments to the trial documents approved by the REC that they receive and ensure that the changes are complied with.

9.5 GCP training

All trial staff must hold evidence of relevant and adequate training that is appropriate for their responsibilities in this trial according to GCP guidelines This training should be updated in accordance with local Trust policy.

9.6 Monitoring and Auditing

The study will be monitored and audited in accordance with the Sponsor's policy, which is consistent with the Research Governance Framework. All study related documents will be made available on request for monitoring and audit by the sponsor.

10. Data protection and participant confidentiality

10.1 Data protection

All investigators and trial site staff involved in this trial must comply with the requirements of the Data Protection Act 1998 and Trust policy with regards to collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

10.2 Data handling, storage and sharing

10.2.1 Data handling

All data collected from the trial will be entered into a paper Case Report Form (pCRF) which will be anonymised. All trial data in the pCRF must be consistent with the relevant source documents. The pCRFs will be completed, dated and signed by the investigator or designee in a timely manner. It remains the responsibility of the investigator for the timing, completeness, legibility and accuracy of the pCRFs. The CRF will be accessible to trial coordinator(s), data managers and investigators as required.

For participating centres, a copy of the completed CRFs will be sent or faxed to the trial coordination centre (CCTU) at Cambridge and the originals retained at the local site. The investigator will also supply the trial coordination centre with any required, anonymised background information from the medical records as required.

The investigators will ensure that the CRFs and other trial related documentation are sent to the trial coordination centre containing no patient identifiable information.

All CRF pages must be clear, legible and completed in black ink. Any errors should be crossed with a single stroke so that the original entry can still be seen. Corrections should be inserted and the change dated and initialled by the investigator or designee. Typing fluid must not be used.

All data from the CRF will be entered into a purpose-designed trial database. Information capable of identifying individuals and the nature of treatment received will be held in a separate encrypted and secured database and will be only available to selected members of the study team. Access to the database will be via a secure password-protected web-interface. Data will be entered promptly and data validation and cleaning will be carried out throughout the trial. Standard operating procedures (SOPs) for database use, data validation and data cleaning will be available and regularly maintained.

10.2.2 Data storage

All study documentation will be retained in a secure location during the conduct of the study and following end of trial archived according to the specified time in local policies.

10.2.3 Source Data

To enable peer review, monitoring and /or audit, the investigator must agree to keep records of all participating patients (sufficient information to link records e.g. CRFs, hospital records and samples), all original signed informed consent forms and copies of the CRF pages.

Source data includes but is not limited to:

- Informed Consent Form
- Medical records
- ECG, Test print outs
- Imaging studies
- Prescriptions
- Patient Questionnaires

11. Dissemination of findings

The findings will be disseminated by usual academic channels, i.e. presentation at international meetings and peer-reviewed publications. A full report for the HTA will be written on completion of the study. A lay summary of the results will be provided to patient organisations.

12. Publication policy

The study team shall ensure that the outcome of the research is prepared for publication in a suitable peer-reviewed journal and shall ensure that it, and any other publication, shall acknowledge the NIHR's financial support and carry a disclaimer as he NIHR may require or in the absence of direction from the NIHR a notice as follows:

"This report is independent research funded by the National Institute for Health Research (Health Technology Assessment, 12/35/57 - Randomised Evaluation of Surgery with Craniectomy for patients Undergoing Evacuation of Acute Subdural Haematoma (RESECUE-ASDH)). The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health"

13. References

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14. APPENDIX 1

COUNTRY SPECIFIC CONSENT PROCESS AND OTHER RELEVANT PROTOCOL INFORMATION: **SCOTLAND**

(this appendix will be amended as appropriate, to contain any specific information required for each country)

This study will recruit critically ill patients who will be incapacitated due to the head injury and therefore unable to give consent for trial entry themselves. On admission the patient will be assessed by the treating clinician to establish if he/she is competent or has 'capacity' to consent. This assessment of capacity will be documented.
Consent will be sought from each eligible patient's nearest relative or Guardian/Welfare Attorney as defined in the hierarchy of informed consent for an incapacitated adult in the Adults with Incapacity (Scotland) Act 2000 (AWI Act 2000) Part 5.
Written consent will be sought soon after the patient has been admitted to the Intensive Care Unit Oral and written information relating to the study will be provided to this designated person by a member of the research team with the delegated responsibility for taking informed consent.

Guardian/Welfare Attorney

The treating clinician or nurse in charge of the patient's care will look through the patient's medical notes and documents to identify any guardian or welfare attorney who has power to consent to the patient's participation in the trial.
In accordance with AWI Act 2000:

- a guardian shall include a reference to a guardian (however called) appointed under the law of any country to, or entitled under the law of any country to act for, an adult during his incapacity, if the guardianship is recognised by the law of Scotland;
- a welfare attorney shall include a reference to a person granted, under a contract, grant or appointment governed by the law of any country, powers (however expressed) relating to the granter's personal welfare and having effect during the granter's incapacity.

If the Guardian/Welfare Attorney is available they will be informed about the trial by the treating clinician or a member of the research team and given a copy of the information sheet. If they decide that the patient is suitable for entry into the trial they will be asked to give consent on behalf of the incapacitated adult.

The patient's Guardian/Welfare Attorney may not visit the patient in the hospital soon after admission therefore telephone consent will be taken. If possible written consent will be obtained afterwards.

Nearest Relative

In a situation where there is no such guardian or welfare attorney available, the participant's nearest relative will be approached and provided with information about the trial. In accordance with the AWI Act 2000 and the Mental Health (Scotland) Act 1984, "nearest relative" means (in order from highest to lowest):

- Spouse;
- Child;
- Father or mother;
- Brother or sister;
- Grandparent;
- Grandchild;

- Uncle or aunt;
- Nephew or niece

If the patient's nearest relative decides that the patient is suitable for entry into the trial they will be asked to give consent on behalf of the incapacitated adult.

In some cases, the patient's nearest relative may not be present when they are admitted to the hospital and may not attend the unit at that time. In usual circumstances, the treating clinician will contact the nearest relative as soon as possible after the patient is admitted. They will give the relevant information about the trial during this telephone call and ask to consent for the patient to be enrolled in the trial.

If telephone consent is obtained, written consent will be recorded as soon as possible after the surgery.

After consent is obtained, the patient will only enter the trial if they meet all the entry criteria. This will be explained to the patient's relative during the process of obtaining consent.

If the patient is unable to consent and the patient's nearest relative or guardian/Welfare attorney is not available the patient cannot be included in the study.