Surgical Trial In Traumatic intraCerebral Haemorrhage

Protocol

Version 2.2 /14th February 2012

HTA Grant No: 07/37/16
ISRCTN No: ISRCTN19321911
Sponsor No: 4792
Host No: BH080479
IRAS No: 09/H0502/68
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Sponsor: Newcastle upon Tyne Hospitals NHS Foundation Trust

Funding Source: NIH HTA 07/37/16

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Glossary

CPP	Cerebral Perfusion Pressure
CT	Computed tomography scan
CTU	Clinical Trials Unit
EDH	Extradural haematoma
GCS	Glasgow Coma Score
GOS	Glasgow Outcome Scale
ICP	Intracranial Pressure
ICH	Intracerebral Haemorrhage
SDH	Subdural haematoma
TICH	Traumatic Intracerebral Haemorrhage including contusion

Background

More than 150,000 patients with head injury are admitted to hospital each year in the UK. Of these about 20,000 are serious. One year after a serious head injury 35% of patients are dead or severely disabled. Intracranial haemorrhage occurs in more than 60% of serious head injuries in one or more of 3 types: extradural, subdural and intraparenchymal. Prompt surgical removal of significant subdural and extradural haemorrhage is of established and widely accepted value. Intraparenchymal haemorrhage is commoner than both the other types put together and is found in more than 40% of severe head injuries. It is clearly associated with a worse outcome but the role for surgical removal remains undefined. Several terms are used to describe the condition including traumatic intraparenchymal haemorrhage, traumatic intracerebral haemorrhage (TICH) and contusion. Our own prospectively collected data in over 7,000 head injured patients in Newcastle has shown that contusions are more common in older head injured patients and can occur in patients with less severe head injury.

Surgical practice in the treatment of TICHs differs widely. Several issues inform the debate:

a) Contused brain does not recover but appears as encephalomalacic brain tissue loss on convalescent phase imaging. This argues that removing TICHs does not increase tissue loss.
b) Extravasated blood is believed to be neurotoxic leading to secondary injury that may be avoided by surgical removal.
c) Larger TICHs may be associated with an ischaemic penumbra of brain tissue that could be salvaged.
d) Some TICHs expand to the point where they cause mass effect resulting in secondary brain injury.

The aim of early surgical TICH removal is to prevent secondary brain injury from these mechanisms. Use of the operation varies around the world. It is more frequently done in the Far East than in Europe or North America.

There have been trials of surgery for spontaneous ICH (including the ongoing MRC funded STICH II study http://research.ncl.ac.uk/stich/) but none so far of surgery for TICH. The Cochrane Review (2nd Edition) has shown benefit from surgical evacuation for surgical evacuation[1]. There are differences in the pathogenesis, clinical behaviour and outcome for the two conditions [2]. Patients suffering a TICH tend to be younger by about 15 years on average than patients suffering a spontaneous ICH and therefore the level of disability may have a large effect on their ability to return to work and their economic output. Traumatic ICHs are more likely to be lobar, to be superficial and to have a medium-sized volume (25-65 cc). These differences between the conditions mean that we cannot derive the role of surgery for TICH from results of the 13 published trials of surgery for spontaneous ICH but the STICH trial [3] showed a trend towards better outcome with surgery for the group of spontaneous supratentorial ICH that are most like TICH: superficial haematomas with no intraventricular bleed.

We already know that surgery is effective in patients with traumatic EDH and SDH and that early surgery is better than delayed. This is not known for TICH. If early surgery is of benefit to these patients, then implementation of early referral and diagnosis with immediate treatment may reduce death and disability in this specific group of head injured patients.

Several authors [4-6] have compared surgery with conservative treatment in single centre retrospective series and recommended surgery for larger TICHs even if patients were in an apparently good clinical state initially. Matheisen et al.[4] found that patients

with an admission Glasgow Coma Score of at least 6 and a lesion volume of at least 20ml who had surgery without previous neurological deterioration had significantly better outcomes than those who did not have surgery or had surgery after deterioration. None of the patients who had surgery before any deterioration died or were vegetative as opposed to 39% of those who had surgery after deterioration and 50% of those who did not have surgery. Choksey et al.[5] found that 38% of patients with a low GCS and a volume of the TICH >16ml who had surgery had a poor outcome compared to 56% of those who did not have surgery. Zumkeller et al.[6] found that the poor outcome rate in the operated patients was 29% compared to 59% in the non-operated group.

Boto et al. [7] evaluated the characteristics of severely head-injured patients with basal ganglia TICH and found that they tended to enlarge in the acute posttraumatic period. They found that patients with a TICH of greater than 25ml and those in whom TICH enlargement or raised intracranial pressure had occurred had the worst outcomes. They suggested that these patients might benefit from more aggressive surgical treatment.

D'Avella et al. [8] published a series and suggested that non-comatose patients with smaller TICHs may be treated conservatively but that surgery is indicated for patients with larger TICHs. Most of their comatose patients who were severely injured had a poor outcome whatever treatment was used.

None of these studies involved randomisation into surgical and non surgical groups. They also differed in the characteristics of the parenchymal blood. Such uncontrolled observational studies are potentially misleading and a randomised controlled trial is needed.

Guidelines for the Surgical Management of Traumatic Brain Injury were published in 2006 in Neurosurgery (58: S2-1-62). These confirm that studies in this area have been observational and there is a lack of Class 1 evidence from well-designed randomised controlled trials [9]. Those studies that attempt to compare outcome between surgical and non-surgical groups cannot adequately control for known prognostic variables.

NICE have recommended in the Head Injury Update Full Guideline (2007) that research is needed to develop a consensus on criteria for lesions not currently considered to be surgically significant: namely TICH. This trial (STITCH(TRAUMA)) has been recommended by the latest NICE Head Injury Guideline Development Group.

This proposal (STITCH(TRAUMA)) is to evaluate the role of early surgical removal of traumatic intracerebral haematomas.

Trial Objectives

To determine whether a policy of early surgery in patients with traumatic intracerebral haemorrhage improves outcome compared to a policy of initial conservative treatment.

To assess the relative costs and consequences of early surgery versus conservative management in UK patients and those in a subgroup of countries covering the likely highest recruiting centres.

To confirm appropriate thresholds for intracranial pressure (ICP) and cerebral perfusion pressure (CPP) for clinical management of head injured patients with TICH in the subgroup of patients with such monitoring.

Trial Design

STITCH(TRAUMA) is an international multicentre pragmatic randomised parallel group trial comparing early surgical evacuation of TICH with initial conservative treatment. Only patients for whom the treating neurosurgeon is in equipoise about the benefits of early surgical evacuation compared to initial conservative treatment will be eligible for the trial. An independent 24-hour telephone and web-based randomisation service based in Aberdeen Clinical Trials Unit will be used. This will be backed by 24-hour availability of Trial Investigators who can advise on patient eligibility. Random allocation will be used to ensure that the two groups are balanced within geographic region with a minimisation algorithm based on age group and severity. Outcome will be measured at 6 and 12 months via a postal questionnaire using extended Glasgow Outcome Scale.

Additional data will be collected in those centres that practice invasive brain monitoring to see if there is evidence that such monitoring techniques add value to clinical decision making. This will give an unbiased assessment of the effect of clot removal or not on ICP/CPP. This analysis will help to evaluate whether monitoring ICP/CPP provides additional information that informs better clinical management (the third objective). Such monitoring is not mandatory for a patient to be enrolled in the trial.

Relevant health care costs will be assessed in the UK including length of hospital stay and the costs associated with surgical treatment (theatre time, consumables, overheads); health care resource use outside of hospital (e.g. district nurse, physiotherapy) together with productivity costs arising from absence from work; and additional costs for family members through extra caring responsibilities. Consequences will be measured by combining data on quality of life, measured using the EQ-5D with survival to generate Quality Adjusted Life Years (QALYs). Existing questionnaires will be used, or adapted for use, with TICH patients where appropriate, and will form an additional three-month postal questionnaire and part of the six-month and 12-month postal questionnaires for patients.

	Screening	Prerandomisation	<12 hours	Day 1 -5	Day 5 (+/-2)	Day14 *	Day 90	Day 180	Day 360
Diagnostic CT	X								
INR	X								
Informed consent		X							
Baseline data		X							
Surgery (if randomised to early surgery)			X						
ICP (if monitored)				X					
GCS/Focal signs				X					
CT scan					X				
Hospital data						X			
GOS						X		X	X
Rankin								X	X
EQ-5D							X	X	X
Carer Activities (UK only)							X	X	X
Resource Use (UK only)							X	X	X

* 14 days or at death or discharge which ever occurs earliest

UK only

Surgical group only

ICP monitored subgroup

Pilot Study

An internal pilot phase [10] will be conducted with criteria for stopping the trial early if the recruitment of centres and/or patients is slower than projected or if unexpected difficulties arise in signing up collaborating centres.

The target will be to have not less than 12 centres signed up at the end of year 1. If this target is met then the pilot will continue until a second point when the trial has a total of 12 recruiting centre-years. If at this point the average recruitment rate is less than 2 per centre-year the trial will be terminated.

Screening logs

Screening logs will be maintained by each centre to record: the patients admitted to the neurosurgical unit with any traumatic ICH; whether they are eligible for the trial or not and whether they are recruited or not (and if not, why not, if the reason can be ascertained). These will be used to provide a context for the study, to monitor recruitment rates and as the basis for constructing the CONSORT diagram for reporting the trial.

Centre Recruitment

The centres recruited will be those already collaborating successfully with the team in other studies (STICH, STICH II, RescueICP) plus those identified by the various networks: TARN (Trauma Audit and Research Network), EBIC (European Brain Injury Consortium) and EMN (Euroacademia Multidisciplinaria Neurotraumatologica), BrainIT, EANS (European Association of Neurosurgical Societies), GNAMED (Scottish and Newcastle Neurosurgery Research Group), SBNS (Society of British Neurological Surgeons) and BNRG (British Neurosurgery Research Group).

Only centres that can demonstrate effective trial experience and previous adherence to trial guidelines with high follow-up rates will be eligible to take part. In order to be eligible a centre must be able to recruit a minimum of one patient per year. They must be able to communicate with the research team. (At least one member of the local team must be proficient in English and provide contact details where they can be reached easily to support the local centre and respond to the trial management team in Newcastle). They must be able to provide CT scans of sufficient quality to the study centre in Newcastle. They must be able to arrange follow-up for patients with limited literacy.

Each centre will be required to obtain ethical approval and other permissions as needed to conform with local and national legislation and governance frameworks and to provide documentary evidence to the trial management team that these permissions are in place, prior to site registration and initiation. Each site will also be required to sign an agreement with the sponsor (Newcastle upon Tyne Hospitals NHS Foundation Trust) and the contractor (Newcastle University). Applications by the lead collaborator in each centre for ethical approval (or SSA in the UK) will be supported by the trial manager and the clinical lead for the centre and country in which the centre is located. Also within the UK, R&D approval will be sought in respect of all participating centres and the study will be open to audit ('for cause' or as part of the routine 10% check) by the appropriate research governance teams in the participating Trusts. A member of the study team will also visit centres with high volume recruitment or where there are concerns about patient eligibility (identified by central monitoring) to confirm patient existence and

monitor adherence to the trial protocol , against pre-determined, risk-based criteria (we do not anticipate conducting 100% site data verification).

Patient Recruitment

All appropriate patients who are considered for STITCH(TRAUMA) must have a CT scan to confirm the diagnosis and the size and location of the haematoma. Any clotting or coagulation problems must be corrected prior to randomisation in line with standard clinical practice.

Inclusion Criteria

- Adults aged 14 or over
- Evidence of a TICH on CT with a confluent volume of attenuation significantly raised above that of the background white and grey matter that has a total volume greater than 10mls calculated by (width x height x length)/2 in cm .
- Within 48 hours of head injury.
- Clinical equipoise: only patients for whom the responsible neurosurgeon is uncertain about the benefits of either treatment are eligible.

Exclusion Criteria

- A significant surface haematoma (EDH or SDH) requiring surgery. (The indications for intervention for these patients are already very well defined.)
- Three or more separate haematomas fulfilling inclusion criteria.
- If the haemorrhage/contusion is located in the cerebellum.
- If surgery can not be performed within 12 hours of randomisation.
- 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 (Examples would be a high level of dependence before the injury or severe irreversible associated injury such as complete spinal cord injury).
- Permanent residence outside a study country preventing follow up.
- Patient and/or relative has a strong preference for one treatment modality.

There is no specified upper age limit. The need for clinical equipoise and explicit exclusion of patients with severe pre-existing physical or mental disability or severe co-morbidity which might lead to a poor outcome even if the patient made a good recovery from the head injury excludes the older less able patient while allowing a fit older person to be included. Haematoma rates are known to be more common in the older head injured patient.

Consent procedure

Written witnessed informed consent of the patient or relative must be obtained by trained neurosurgical staff prior to randomisation. The member of neurosurgical staff will provide a written information sheet and allow as much time as possible to discuss the options. One copy of the consent form will be given to the patient, one will be filed in the patient notes and one will be filed with the trial documentation. If the patient is unable to give consent themselves due to the nature of the haemorrhage a personal representative will be approached to give consent on behalf of the patient. The personal representative will be the person with a close personal relationship with the patient who is themselves capable and willing to consent on behalf of the patient. (If the patient is unable to consent and the closest relative is not available the patient cannot be included in the study.)*

* In Scotland, if proxy consent is necessary this should be obtained from the welfare guardian or, if there is none, from the nearest relative.

Randomisation (treatment allocation)

Before randomisation, a one page form will be completed by the responsible neurosurgeon recording demographic (age, gender) and clot characteristics (site, side, ABC measures to define volume) and status at randomisation (GCS, pupils equal and reacting or not). This information will be required in order to randomise the patient.

The clinician will either telephone the independent 24-hour telephone randomisation service based in Aberdeen CTU (+44 (0) 1224 273661) or access the randomisation web site (https://viis.abdn.ac.uk/HSRU/stitch) and enter the randomisation information. At the end of the randomisation phone call/web data entry process the neurosurgeon will be informed of the patient identifier number for the trial and the treatment group the patient is allocated to. The neurosurgeon will record this information on the randomisation form and then fax the form to the STITCH(TRAUMA) Office. If the site has problems contacting the randomisation service they will be able to contact a member of the project team using the study backup number (+44 191 222 5764).

The data manager will check this information against the information received from the randomisation centre and enter the data into an anonymised password protected database. A list of patient names and study numbers will be kept in a separate file to ensure patient confidentiality is maintained.

The 24-hour randomisation service will be backed by 24-hour availability of Trial Investigators who can advise on patient eligibility. Details of our out of hours advice service will be given by an answering service when investigators call the study backup number (+44 191 222 5764) during evenings or weekends.

Allocation will be stratified by geographic region, with a minimisation algorithm based on age group, and severity (as measured by whether the pupils are equal and reacting or not) and with a random component (i.e with probability of 80%).

Trial interventions

The two trial interventions are early evacuation of the haematoma by a method of the surgeon's choice (within 12 hours of randomisation), combined with appropriate best medical treatment versus best medical treatment combined with delayed (more than 12 hours after randomisation) evacuation if it becomes appropriate later. Both groups will be monitored according to standard neurosurgical practice.

If the patient is randomised to early surgery this should be undertaken as soon as possible and within 12 hours of randomisation.
Best medical treatment may include (depending on the practices within the centre) monitoring of ICP or other modalities and management of metabolism, sodium osmotic pressure, temperature and blood gasses.

All patients will also have an additional CT scan at about five days (+/- 2 days) to assess changes in the haematoma size with and without surgery. This will enable us to demonstrate the proportion of the clot removed by surgery or the changes in volume of the clot without surgery.

Compliance

Patients or their relatives may withdraw consent for an operation, or conversely request an operation after randomisation, thereby leading to crossover between the arms. These are rare events but in surgical trials it is common for the patient's condition to change over time and a patient randomised to initial conservative treatment may deteriorate and require surgery later. Such crossovers and the reasons for them will be documented.

Information will be collected about the status (GCS and focal signs) of patients through the first five days of their trial progress and ICP/CPP measures in invasively monitored

patients in order to be able to describe the change in status that leads to a change in equipoise for the treating neurosurgeon, and subsequent surgery in patients initially randomised to conservative treatment.

Compliance with treatment allocation will be monitored by the data manager. In surgical trials patients allocated to the non-surgical arm of the trial may later deteriorate and surgeons may intervene. This was the case in the MRC funded STICH trial [3], in trials of cardiac surgery compared with angioplasty, in the MRC funded back pain trial [11] and in the SPORT trials [12]. These crossover rates to surgery were 26%, 28%, 28% and 30% respectively. While surgical trials will always have such crossovers when surgeons perceive that there is value in operating on patients who deteriorate after initial randomisation into the conservative limb of the trial, we must understand, monitor and report the rates of such crossovers. The aim is to achieve as high compliance as possible but experience and the above literature suggest that it is neither practical nor ethical to have 100% compliance with conservative treatment. During the recruitment of centres and at investigator meetings the importance of clinical equipoise and minimising crossovers will be emphasized and any crossover occurring within twelve hours of randomisation will be investigated. Centres exhibiting high crossover rates may be withdrawn from the study.

Data Collection

To preserve confidentiality all patients will be allocated a unique study identifier during the randomisation process which will be used on all data collection forms and questionnaires. Only a limited number of members of the research team will be able to link this identifier to patient identifiable details. These will be necessary in order to carry out centralised follow-up. All study documentation will be held in secure offices and the study research team will operate to a signed code of confidentiality. A clinical data management software package will be used for data entry and processing, allowing a full audit trail of any alterations made to the data post entry.

Any previously collected data will be retained for patients who subsequently withdraw from the trial. This data will be anonymised and kept confidential.

Randomisation

Before randomisation, a one page form will be completed by the responsible neurosurgeon recording demographic (age, gender) and TICH characteristics (site, side, ABC measures to define volume) and status at randomisation (pupils equal and reacting or not). This information will be required in order to randomise the patient.

Two week/discharge

At two weeks after randomisation or at discharge or death (whichever occurs first) the discharge/2 week form will be completed by the responsible neurosurgeon. This form will record the date, the event that triggers the form and the patient's status at that time, whether the patient has had surgery (and why if randomised to initial conservative treatment or why not if randomised to early surgery), the patient's GCS and localising features for the five days following randomisation, the occurrence of any adverse events (including death, pulmonary embolism, deep vein thrombosis, surgical site infection) following randomisation, past medical history and status prior to the ictus. This form together with copies of the randomisation CT scan and the 5-day post randomisation CT scan (as detailed below) should be sent to the STITCH(Trauma) office at the Neurosurgical Trials Unit in Newcastle UK within two weeks. The data manager will enter the data into the anonymised password protected database.

CT scans

Copies of two CT scans are required: the diagnostic CT scan prior to randomisation and a 5-day scan. All patients will have undergone a diagnostic CT scan as standard practice. The 5-day scan will be performed between 3 and 7 days after randomisation. Many patients will receive this as part of standard treatment and the study will accept and use any scan taken for clinical purposes during this period. Only patients who do not receive such a scan during this period will require an additional scan.

The preferred scan will be CT scan with volume acquisition 32X 0.5 mm (or equivalent); 120Kv 400mA (or equivalent; 220 FOV. The angle should be parallel with the anterior cranial fossa, coverage from base of skull to vertex; reconstruct 5mm whole head, soft tissue filter.

The preferred method of sending CT scans will be in Dicom compatible format. Dicom images (on separate CDs for the two time points) will be sent anonymised with patient identifier. They will be checked by the data manager initially on receipt at the STICH-TRAUMA office to ensure that the haematoma characteristics at randomisation conform to the required inclusion criteria. Where protocol deviations are suspected the data manager will arrange for the scan to be viewed by a trained reader immediately and if their suspicions are confirmed the centre will be contacted immediately to prevent repetitions.

The data manager will load the scans into a specialised password protected scan management programme. The scans will then be allocated a separate randomly created identifier by the data manager, so that it will not be possible for the reader to identify the before and after scans of the same patient. The scans will be stored in locked cabinets. A separate list identifying patient identifier and scan identifier will be kept by the data manager.

The CT scans will be analysed subsequently by trained readers using the scan management programme. Their passwords will only give access to scans blinded to treatment group and patient identity following a defined protocol.

Follow-up

Postal questionnaires have previously been designed for the STICH and STICH II study and translated into most languages required. If new countries with different languages are recruited, then the national Investigator will be asked to arrange translation and another principal investigator from the country will be asked to check the translation. Postal follow-up will occur at six months for all patients and also at 12 months for those recruited more than six months prior to the end of recruitment. The patient's GP (in the UK) or consultant (outside the UK) will be contacted at four and a half months to check that the patient is alive and to confirm his/her place of residence. At this time we will also request completion of the major adverse events form to include death, pulmonary embolism or deep vein thrombosis and stroke. The six-month outcome questionnaire will be mailed to the patient at five months for completion by the patient or relative if the patient is unable to complete it themselves. If necessary a reminder will be sent at six months and telephone follow-up at seven months by "blinded" clerical or nursing staff to enhance response rates. In countries where the postal system is poor patients will be requested to attend a follow-up clinic at which the questionnaire will be distributed and collected. In countries where literacy or language/dialect are problematic a 'blinded' interviewer will administer the questionnaire. This methodology, developed for use and applied to good effect in STICH and STICH II, will be used in STITCH(TRAUMA).

The costs associated with surgical treatment (theatre time, consumables, overheads) will be collected from published resources and local cost surveys undertaken by the study health economist. Length of stay, health care resource use outside of hospital, together with productivity costs arising from absence from work, and additional costs for family

members through extra caring responsibilities will be collected using the additional three month postal questionnaire and extended six month and 12 month postal questionnaires in the UK. Consequences will be measured by combining data on quality of life with survival to generate Quality Adjusted Life Years. This will include measurement of health care costs, quality of life (EQ-5D), work absence (WHO Health and Performance Questionnaire-Clinical Trial Version) and carer activities (measured by Discrete Choice Experiment developed by HERU). EQ-5D and survival will be collected for all patients by the postal outcome questionnaires in order to generate QALYS for the whole study and for a UK only analysis.

Serious Adverse Events

Serious adverse events will be recorded on the Major Adverse Events form. Serious adverse events are adverse experience that result in any of the following outcomes:

death,
is life-threatening,
requires inpatient hospitalization or prolongation of existing hospitalization,
results in persistent or significant disability or incapacity.

All SAEs should be reported to the STITCH Office within 7 days of the local investigator becoming aware of the event and to the local ethics committee or other regulatory bodies as required.

All data will be entered into an anonymised password protected database by the data manager. Paper copies of questionnaires will kept in locked cabinets in a locked room.

Outcome Measures

PRIMARY: Unfavourable outcome will be death or severe disability which will be defined using a prognosis based 8 point Glasgow Outcome Scale/ Modified Rankin Scale [3, 13].

SECONDARY: Rankin, EQ-5D, Mortality, Survival, Major Adverse Events (death, pulmonary embolism or deep vein thrombosis, infection, rehaemorrhage), QALYs, Total health care costs, social costs

Structured postal questionnaires will be used. Versions containing the extended Glasgow Outcome Scale, Rankin and EQ-5D already exist and have been translated into most of the necessary languages.

The Glasgow Outcome Scale is the specific measure for head injury and the eight-point scale provides more sensitivity than the five-point scale. For patients with a very poor prognosis an outcome of good recovery, moderate disability or upper severe disability would be regarded as a favourable outcome. For patients with a better prognosis favourable outcome would be good recovery or moderate disability. A structured postal version has been developed [14]. The Rankin scale is widely used as a functional outcome measure in stroke and will allow comparison of results between this study of patients with traumatic ICH and studies of patients with spontaneous ICH. EQ-5D is the standard measure of quality of life incorporating a utility value and has been developed in many languages.

Health Service Cost Implications

There are no health service cost implications because indications for surgery remain variable and haphazard and the trial simply systematises the current variability. In

addition, as shown in the in the economic analysis in STICH there is no difference in health service costs between the two treatment regimes. The only additional cost is for the extra CT and centres will receive a per patient payment to include the cost of this extra CT.

Sample size

Previous studies have suggested a favourable outcome in the non-operated group of about 40% and a favourable outcome in the surgical group of about 60-70%. However this was in observational studies. Assuming a favourable outcome (good recovery or moderate disability on the Glasgow Outcome Scale) of 50% from conservative treatment a total sample size of 776 would be required to show a 10% benefit (i.e. 50% vs. 60%) from surgery ($2p<0.05$) with 80% power. A safety margin of 9.5% is built in to allow for loss to follow-up making a total sample size of 840 to be recruited and randomised (420 per arm).

In order to achieve this sample size in a reasonable time span and to provide robust evidence it will be necessary to recruit patients from outside UK. In England and Wales there are only 30 neurosurgical units and only a third of these participate in randomised controlled trials. Experience with interested neurosurgical centres in previous studies has shown that about 25% of recruited centres fail to recruit any patients and a further 25% only recruit 1 or 2 patients. The best recruiting centres will recruit about 10 patients per year so to complete patient recruitment within the time scale we will approach at least 150 centres.

Loss to follow-up will be restricted as much as possible. In the STICH study the loss was about 5%. In STITCH(TRAUMA) the population will be a little younger and likely to be more mobile; however, we will carry out more checks and implement procedures that we have developed to minimise loss to follow-up. Methods of follow-up will be adapted to those most likely to be successful within each country and centre according to local population and care characteristics. Centres that achieve poor follow-up will be monitored closely and will be withdrawn from the study if they are unable to locate patients for 6 month follow up. We require residence in any study country as an eligibility criterion so patients who suffer a head injury whilst on holiday and might be lost to follow-up are not eligible and will not be included.

Statistical analysis

Analysis will be on an "intention to treat" basis. The primary analysis will be a simple categorical frequency comparison using the uncorrected chi-squared test for prognosis based [13, 15] favourable and unfavourable outcomes at six months. Patients with a good prognosis will be categorised as having a favourable outcome if they achieve good recovery or moderate disability on the Glasgow Outcome scale. Patients with a poor prognosis will be categorised as having a favourable outcome if they achieve good recovery, moderate disability or upper severe disability on the extended Glasgow outcome scale. Logistic regression analysis will be undertaken to adjust for covariates. Secondary outcomes will also be analysed using the prognosis based method as specified in STICH [3].

Given the likelihood of a proportion of crossovers, a secondary sensitivity analysis of per-treatment as well as an analysis considering crossovers to surgery as failed medical treatment will be undertaken. Further analyses of factors that drive crossovers as well as per-protocol and per-treatment analyses will be conducted to investigate the effect of crossovers.

Any subgroup analyses will be based on tests of interaction. The predefined subgroups (all of which will be considered exploratory, since the study is not powered for formal subgroup analyses) include the following:

- Age
- Haematoma volume
- Glasgow Coma Score
- Time from injury to randomisation
- Severity of neurological deficit
- Pupils equal and reacting or not
- Planned method of haematoma removal
- Patients with invasive monitoring (ICP/CPP)
- Anticoagulation status

Interim analyses will be conducted at intervals predetermined by the DMEC. The results of interim analyses will be strictly confidential and the trial will only be stopped early if one or other treatment policy shows an advantage at a very high significance level, or if recruitment rates fall below our pre-specified criteria (see under Pilot Study).

Deterministic and probabilistic sensitivity analyses will be conducted to consider the importance of individual parameters and assumptions in determining cost-effectiveness. This will include the effect of time horizon, variation in unit costs across centres, and quality of life values. Bootstrapped-generated differences in costs and effectiveness between strategies will be computed, and results presented using Cost Effectiveness Acceptability Curves (CEACs).

Receiver operating curves will be used to investigate appropriate thresholds of ICP and CPP for treatment as they have been used previously in paediatric studies. [16]

It is not possible to blind either patients or treating surgeons as to when the patient has had surgery or whether they have had surgery. To minimise possible sources of bias, randomisation will be undertaken centrally, thus ensuring concealment of allocation from the enrolling clinician, patient and relatives. All patients randomised, for whom outcome data can be collected, will be included in the analysis by intention to treat. The multidisciplinary team in the co-ordinating centre and the principal investigators will be blinded to the results until after the data set is locked following receipt of the final outcome questionnaire. Only the data manager will have access to 'unblinded' data.

Ethical Issues and research governance

Risks and anticipated benefits for trial participants and society

Risks and benefits for trial participants – the risks from undergoing surgery include risks of complications due to undergoing a general anaesthetic and surgery; however, the risks of undergoing early surgery may be equivalent to the risks of delaying surgery. Only those patients for whom the treating clinician, patient and relative are in equipoise regarding early surgery vs conservative management will be enrolled in the trial.

Anticipated benefit for society is that of improved outcome for patients in the future. The results will inform decision making, permitting evidence-based policies to be developed for the management of traumatic ICH. If surgery is shown to be ineffective, then cost savings can be made by avoiding surgery. If surgery is shown to be effective, then better outcomes will be achieved for the patient together with reduced rehabilitation and recovery costs to the NHS and the patient and their families.

The study requires CT scans. All patients will have undergone a diagnostic CT scan as is standard practice. The study also requires a CT scan at 5 days post randomisation in order to measure changes in the size of the TICH. Most patients will receive this as part

of standard treatment and the study will be able to use any scan taken for clinical purposes between 3 and 7 days post randomisation. Only those patients who do not receive such a scan during this period will require an additional scan. We will appoint a Clinical Radiation Expert (CRE) and a Medical Physics Expert (MPE) to advise on exposure to radiation. The protocol specifies above the type of scan, its settings, how they should be submitted to the centre and how they will be stored and analysed.

Informing patients of possible benefits and risks

Patients and relatives will receive detailed information sheets and will have the opportunity to discuss the study with site investigators and their staff prior to deciding whether or not to participate.

Data collection and retention

To preserve confidentiality all patients will be allocated a unique study identifier, which will be used on all data collection forms and questionnaires; names or addresses will not appear on completed questionnaires or case report forms. Only a limited number of members of the research team will be able to link this identifier to patient-identifiable details (name & address) which will be held on a password protected database. All study documentation will be held in secure offices, and the research team will operate to a signed code of confidentiality. A full audit trail of any alterations made to the data post entry will be kept.

Trial documentation will be kept for 15 years after publication of the final paper/report from this study.

Proposed actions for compliance with Medicines for Human Use Regulations

This study is not a drug trial and the Medicines for Human Use (Clinical Trials) Regulations 2004 do not apply.

Research governance

In conformance with the Research Governance Framework for Health and Social Care, the role of Sponsor for this study will be taken on by the Newcastle upon Tyne Hospitals Foundation NHS Trust. On a day-to-day basis, sponsor-level activities will be carried out by the Newcastle Clinical Trials Unit. The study will be conducted in accordance with NCTU-wide and study-specific Standard Operating Procedures (SOPs) and Work Instructions. All study-attached staff will be appropriately qualified and will be trained in those aspects of Good Clinical Practice (GCP) appropriate to their role in the study. Country-specific procedures in respect of ethical approval, and other permissions required, will be observed. Within the UK, a favourable opinion will be obtained via the Integrated Research Approval Service (IRAS) from a Research Ethics Committee appropriate to multi-domain research. Site-specific assessments will be obtained in respect of each participating centre within the UK. Also within the UK, R&D approval will be sought in respect of all participating centres and the study will be open to audit by the appropriate research governance teams in the Trusts (either as part of their 10% routine audit, or 'for cause'). A member of the study team will also visit centres with high volume recruitment or where there are concerns about patient eligibility identified by central monitoring to confirm patient existence and carry out a site monitoring visit against pre-defined risk-based criteria.

Trial Steering Committee:

Independent oversight of the study will be provided by a Trial Steering Committee (TSC). The TSC will meet at least annually during the study. The Trial Steering Committee will provide overall supervision of the trial on behalf of the HTA. It will consider progress of the trial (in particular, success in site and patient recruitment), adherence to the protocol, patient safety and consideration of new information. The trial will be conducted according to the standards set out in the MRC Guidelines for Good Clinical Practice. A

written charter will be developed and agreed prior to the first TSC meeting. TSC members are listed on page 2.

Data Monitoring and Ethics Committee:

In order to monitor accumulating data on patient safety and treatment benefit an independent data monitoring and ethics committee (DMEC) will be established. The DMEC will consider data from interim analyses and report to the Trial Steering Committee. A written charter will be developed and agreed prior to the first DMEC meeting. At their first meeting the DMEC will determine the nature and frequency of interim analyses. Interim analyses will be strictly confidential and the committee will only recommend stopping the trial early if one or other treatment shows an advantage at a very high significance level.

Management committee:

This group will meet weekly to monitor progress and compliance.

Roles and responsibilities

Principal Investigators and trial team

Professor A D Mendelow has overall responsibility for the trial. He is also responsible for disseminating information about the trial, recruiting centres and for writing and publication of the results.

Dr B A Gregson is responsible for the overall statistical validity of the trial and day-to-day conduct of the trial including availability of co-ordinating advice in Newcastle. She is also be responsible for preparation of protocols and questionnaires, for MREC application, for preparing annual reports to HTA and Ethics committees, for communication and dissemination of information to centres, for monitoring centres, for data analysis and for writing up of results.

Mr P Mitchell is responsible for recruiting centres and for analysis and publication of results.

Professor Elaine McColl is responsible for ensuring that the trial is run according to GCP guidelines and will supervise and advise on overall trial conduct and project management.

Dr Iain Chambers is responsible for ensuring the quality of ICP and CPP data collected and for the analysis of this data.

Dr Paul McNamee is responsible for the economic validity of the trial; he will be responsible for the design of the economic component of the trial and will over see the economic data collection and analysis.

The trial manager is responsible for ensuring ethics approvals and agreements are in place in all centres, negotiating as required between contracts personnel, to run the pilot, to maintain a website to encourage site and patient recruitment, to provide reports to trial management and steering committees, to the funder and to the research ethics committees as required, to monitor compliance and to communicate with the centres.

The data manager is responsible for maintaining computerised databases containing all data related to the trial, for the quality of computerised information, for conducting preliminary analyses and preparing reports for the DMEC, for providing information to the applicants and for preparing monthly newsletters.

The trial secretary will be responsible for all trial correspondence in relation to the trial, for sending postal questionnaires and reminders, to aid in establishing the pilot, for the organisation of investigator meetings and travel for monitoring, maintaining telephone and fax communications, preparing quarterly newsletters and publications, and reimbursing centres.

The health economist is responsible for undertaking the collection and analysis of economic data.

Responsibilities of National Investigators

In countries with multiple centres one centre investigator will be required to fulfil the role of National Investigator. National investigators will be responsible for obtaining national ethical approval and other permissions as required, for ensuring that documentation is translated from English as required, for identifying suitable centres within their country, for encouraging recruitment and acting as a liaison person between the STITCH(TRAUMA) team and the centre if required.

Responsibilities of Centre Investigators

Each centre will agree to follow the protocol. They will provide and update when necessary full address and contact details. Within each centre there will be at least one named collaborator who is responsible for the conduct of the trial in his/her centre and in particular for:

local ethical applications and applications for other permissions as required,
disseminating information about the trial within the centre,
maintaining local trial documentation, including site files, delegation logs etc
identifying suitable patients,
ensuring all case report forms are completed and returned to the STICH office in Newcastle expeditiously,
ensuring copies of CT scans are provided to STITCH office in Newcastle expeditiously
ensuring follow-up is obtained in the centre
attending investigator meetings (in person or via video- or teleconference)
facilitating centre monitoring
commenting on the final report.

Centres will receive a monitoring visit as required either after recruiting at least ten patients or if there is a perceived need.

Two funded Investigator Meetings will be held in year 1 and year 4 of the study. Additional meetings will be held during international neurosurgical conferences if possible.

Payments to participating Centres

Payments are detailed in the site agreements of registered centres.

Participating centres will receive pre-determined fixed per patient payments upon receipt of payment claims forms and completed data collection forms/scans by the STITCH(Trauma) Office. The payments are a contribution towards research related expenses, including IRB expenses, the cost of randomisation phone calls, CT scans, staff time for completing paperwork, data collection, postal and fax costs and travel expenses to attend STITCH(Trauma) investigator meetings. Per patient payments can only be made to institutions and not personally to individual investigators.

In order for centres to claim the first per patient payment, they should send back:

Randomisation form
Randomisation CT
Discharge/2 week form
5 day CT
1st payment claims form

In order for investigators to claim the second per patient payment, the STITCH(Trauma) office should have received:

3 month form (a postal questionnaire completed in UK only)
Major adverse event form (completed and returned by investigator)
6 month form (a postal questionnaire completed and returned by patients)
2nd payment claims form (completed and returned by investigator)

To claim the third per patient payment, the STITCH(Trauma) office should have received:

Major adverse event form (completed and returned by investigator)
12 month form (a postal questionnaire completed and returned by patients)
3rd payment claim form (completed and returned by investigator)

Please note, the STITCH(Trauma) Office will usually send postal questionnaires to patients unless site specific arrangements are in place in countries where postal follow up is problematic.

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