Surgical Trial in Lobar Intracerebral Haemorrhage

Protocol

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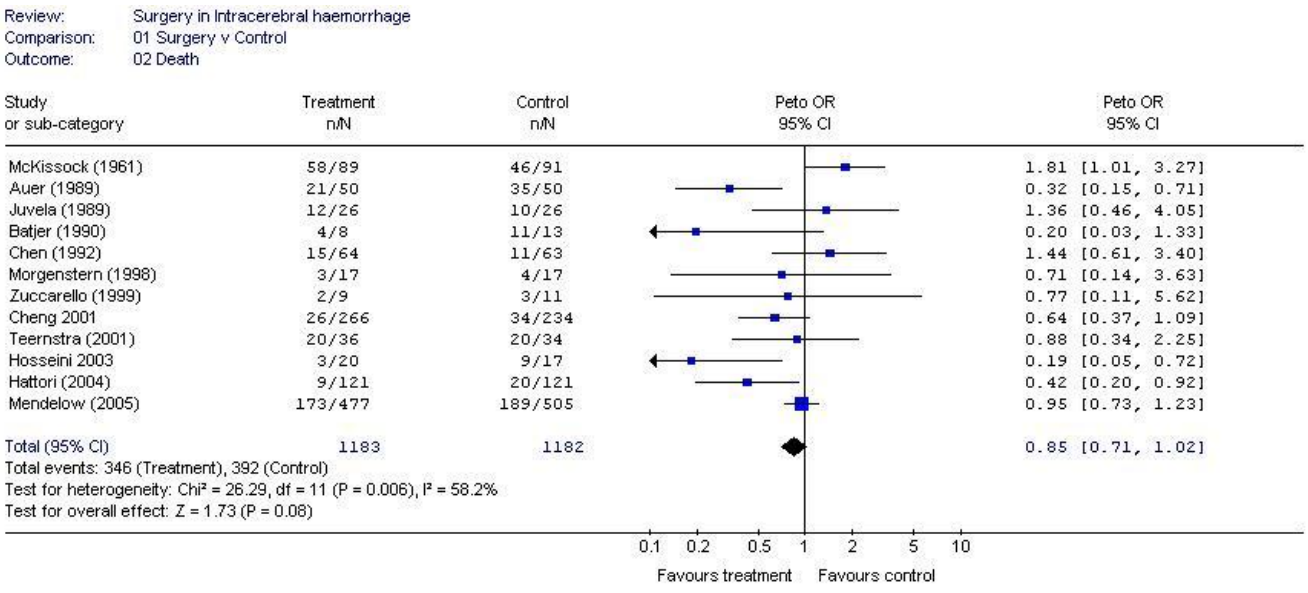
Background

Spontaneous intracerebral haemorrhage (ICH) accounts for 10% of all cases of stroke and is common in younger patients (Bamford et al., 1990). The morbidity and mortality exceed 60% and young disabled survivors are a significant burden to both Health and Social Services with only 12% of all ICH patients emerging with minor handicap (Broderick et al., 1994). The role of operative neurosurgical intervention is controversial and the practice continues to be haphazard (Fernandes et al., 1999; Gregson et al., 2003). Within the spectrum of ICH there are some patients (with large or space occupying ICH) who require surgery for neurological deterioration and others with small haematomas who should be managed conservatively. There is equipoise about the management of patients between these two extremes. Some patients have a penumbra of functionally impaired but potentially viable tissue around the ICH. Surgical removal of the clot may improve the function and recovery in this penumbra (Siddique et al., 2002).

The first randomised trial of Surgical Treatment of ICH, published in 1961 (McKissock et al.) did not show a significant advantage for either surgical or conservative treatment. However this trial was prior to CT and modern operative techniques and care facilities. Between 1989 and 1992 results from four small prospective randomised trials were published. Two trials showed a non-significant advantage for surgery (Auer et al., 1989; Batjer et al., 1990) and two favoured conservative treatment but the advantage was not significant (Juvela et al., 1989; Chen et al., 1992). Two further very small trials have been published both showing a non-significant advantage in favour of surgery (Morgenstern et al., 1998; Zuccarello et al., 1999). Each of these reported problems with recruiting sufficient patients from a single centre and argued for the importance of a large randomised multicentre trial. Further trials have reported since 2000: a large trial of 500 patients showing a non-significant advantage for surgery (Cheng et al., 2001); two smaller trials showing a significant advantage for surgery (Hosseini et al., 2003;Hattori et al., 2004) and a small trial suggesting an advantage for conservative treatment (Teernstra et al., 2001). The need to gain robust evidence to support clinical decision making led to the initiation of the Surgical Trial in Intracerebral Haemorrhage (STICH) funded by the MRC and the Stroke Association which was activated in 1998. This trial is the largest to date and successfully recruited 1033 patients from 87 centres around the world. It also suggested a small non-significant advantage for surgery (Mendelow et al., 2005).

A meta-analysis of the first four published randomised controlled trials was conducted by Prasad et al (2000) for the Cochrane Collaboration. We have updated this (see figure) to include all twelve trials. Including all twelve trials gives an odds ratio of 0.85(CI 0.71, 1.02) in favour of surgical treatment when the unfavourable outcome is death and an odds ratio of 0.86 (CI 0.72, 1.03) for the 11 trials with published data when the unfavourable outcome is severe disability or death.

Meta-analysis of all surgical intracerebral haemorrhage trials (Poor outcome = death)

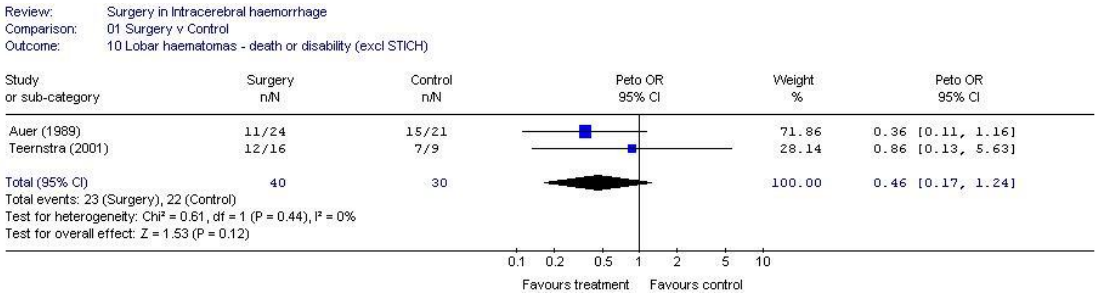


Further detailed analysis of the CT images has shown that 42% of patients included in STICH who had assessable scans also had an associated intraventricular haemorrhage (IVH). The prognosis

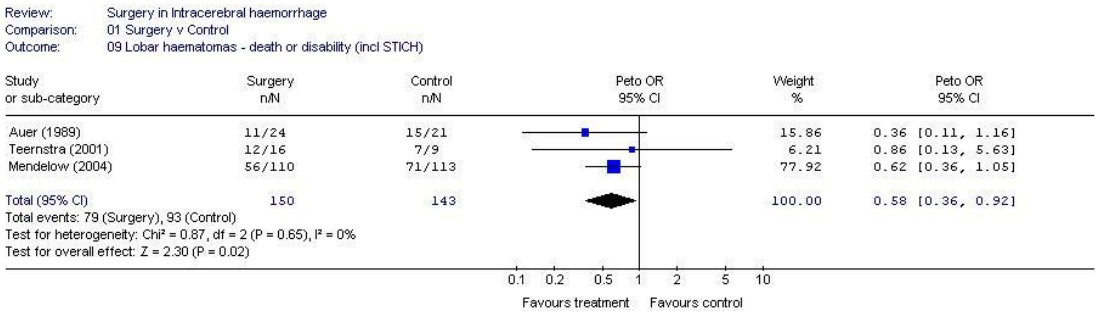
for patients with intraventricular haemorrhage with or without hydrocephalus is much worse than that for intracerebral haemorrhage alone. Removing these patients from the analysis and focusing on superficial haematomas presents a more encouraging picture for surgery. There were 223 patients in STICH with such haematomas and with initial conservative treatment 37% achieved a favourable outcome using the prognosis based outcome methodology used in STICH (Mendelow et al., 2003). By contrast 49% of patients achieved a favourable outcome with early surgery (p=0.080). Furthermore using prognosis based Rankin as the outcome variable a significant benefit was observed for surgical patients in this subgroup. (p = 0.013). Although this is a post hoc identified subgroup, the exclusion of IVH makes clinical sense in the context of debulking surgery for lobar haematomas. The treatment of IVH is different and does not involve craniotomy.

The majority of patients in the other trials reported in the meta-analysis had deep haematomas. Only in the trials by Auer et al. (45 patients) and Teernstra et al. (23 patients) did the numbers reach double figures. In the Auer et al. trial 54% of the 24 surgical patients had a favourable outcome compared to 29% of the 21 conservative patients. In the Teernstra trial 25% of the 16 surgical patients and 22% of the 9 conservative patients had a favourable outcome. Thus overall 42% of surgical patients and 27% of conservative patients had a favourable outcome.

Meta-analysis of lobar haematomas only from above trials (excluding STICH)



Meta-analysis of lobar haematomas only from above trials (including STICH)



Therefore the little randomised controlled data that do exist concerning lobar haematomas support the hypothesis that this subgroup might benefit from early surgery.

An unfortunate outcome of STICH has been that many people have misinterpreted the results to argue that there is no need to operate on patients with ICH at all. However neurosurgeons know that early removal of the ICH is highly effective postoperatively and in the context of trauma (Extradural haematoma - Mendelow et al., 1979, and Acute subdural haematoma - Seelig et al., 1981). It seems unlikely that surgery would be of benefit in one scenario and not in the other. To leave patients with lesions that should be removed (an unfortunate misinterpretation of STICH) would condemn such patients to non-operative treatment perhaps for evermore. Since STICH was not powered sufficiently to answer the question about this subgroup alone there is an urgent need to undertake STICH II.

This proposal (STICH II) is to evaluate the role of early surgery in superficial supratentorial haematomas without intraventricular haemorrhage.

Trial Objectives

To establish whether a policy of earlier surgical evacuation of the haematoma in selected patients with spontaneous lobar ICH will improve outcome compared to a policy of initial conservative treatment. The trial will also help to better define the indications for early surgery.

This will overcome two of the criticisms of STICH (timing was too late and sometimes location was too deep). The subgroup identified in STICH is clinically sensible and the hypothesis identified for STICH II is in line with current neurosurgical opinion.

Trial Design

STICH II is an international multicentre randomised parallel group trial comparing early craniotomy to evacuate the haematoma with initial conservative treatment, following spontaneous superficial intracerebral haemorrhage affecting the lobar region only. Only patients for whom the treating neurosurgeon is in equipoise about the benefits of early craniotomy compared to initial conservative treatment are eligible for the trial. Outcome is measured at six months via a postal questionnaire including the Glasgow Outcome scale, Modified Rankin Scale, EuroQol and Barthel. Six hundred patients will be recruited to the trial over thirty months. Follow-up will take six months with analysis and reporting taking one year.

Trial interventions

The trial intervention is early evacuation of the haematoma usually by craniotomy, combined with appropriate best medical treatment versus best medical treatment, combined with delayed evacuation only if it becomes necessary later. In STICH 26% of patients crossed over from conservative treatment to surgery but we have little information about the reasons for crossover. This is a major problem with surgical trials and crossovers of this size are common (Fairbank et al 2005). We aim to have fewer crossovers in STICH II. We will collect further information about the status (GCS and focal signs) of all patients through the first five days of their trial progress in order to be able to monitor the change in status that leads to a change in equipoise for the treating neurosurgeon. 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 whether surgery has removed the clot or not.

Allocation of patients

All appropriate patients who are considered for STICH II 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. Written witnessed informed consent of the patient must be obtained prior to randomisation by trained neurosurgical staff. If the patient is unable to give consent themselves due to the nature of the haemorrhage a personal representative will be approached to give assent on behalf of the patient. The personal representative will be the person with the closest personal relationship with the patient who is themselves capable and willing to assent 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.)* 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/assent form will be given to the patient, one will be filed in the patient notes and one will be filed with the trial documentation. (Consent from the patient or assent from a relative will be obtained prior to randomisation. This study does not permit assent from a professional representative or randomisation without prior consent/assent).

Randomisation must take place within 48 hours of ictus. Randomising clinicians will complete a one-page randomisation form. Stratified randomisation will be undertaken using a central 24 hour randomisation service accessed by telephone. Stratification will be by prognostic group, type of procedure and country. Best medical treatment must begin as soon as possible and continue throughout follow-up, if required. If the patient is randomised to early surgery this should be undertaken within 12 hours of randomisation.

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

It is not possible to blind either patients or treating surgeons to when the patient has had surgery or whether they have had surgery. To minimise possible sources of bias randomisation will be undertaken centrally. All patients randomised 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. All computerised data will be password protected. Outcome will be assessed by postal questionnaire to the patient or a relative.

Inclusion Criteria

- Evidence of a spontaneous lobar ICH on CT scan (1 cm or less from the cortex surface of the brain)
- Patient within 48 hours of ictus
- Best MOTOR score on the GCS of 5 or 6 and best EYE score on the GCS of 2 or more.
- Volume of haematoma between 10 and 100ml [Calculated using (a x b x c)/2 method]

Exclusion Criteria

- Clear evidence that the haemorrhage is due to an aneurysm or angiographically proven arteriovenous malformation.
- Intraventricular haemorrhage of any sort
- ICH secondary to tumour or trauma.
- Basal ganglia, thalamic, cerebellar or brainstem haemorrhage or extension of a lobar haemorrhage into any of these regions.
- Severe pre-existing physical or mental disability or severe co-morbidity which might interfere with assessment of outcome.
- If surgery cannot be performed within 12 hours.
- If the haematological effects of any previous anticoagulants are not completely reversed.

Follow-up

The patients' Glasgow Coma Score and Glasgow Outcome Scale will be recorded at discharge from the neurosurgical unit or at two weeks whichever is earlier. These data will be used by the DMC to monitor progress of the trial.

Postal follow-up will occur at six months. The patient's GP (in the UK) or consultant (outside the UK) will be contacted at four months to confirm that the patient is alive and to confirm his/her place of residence and to request completion of the adverse events form. The six-month outcome questionnaire will be mailed to the patient at five months and followed with a reminder at six months if necessary and telephone follow-up at seven months by "blinded" clerical or nursing staff, if necessary. The methodology developed for use in STICH will be used in STICH II.

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 (Mendelow et al 2003, 2005).

SECONDARY: Mortality, Rankin, Barthel, EuroQol, Survival

Structured postal questionnaires will be used. Versions containing the extended Glasgow Outcome Scale, Rankin and Barthel already exist and have been translated into the necessary languages. In Europe they will be sent to the patient at five months for completion by the patient or carer if necessary. In countries where the postal system is problematic the patients will be asked to attend a follow-up clinic where the questionnaires will be distributed and collected by an independent researcher. In countries where literacy or language/dialect is problematic an independent blinded interviewer will administer the questionnaire. This same methodology was used successfully in STICH.

The aim will be to achieve 100% follow-up and this can be achieved with the full cooperation of the centre investigators. 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.

Economic issues

An economic analysis was undertaken in STICH in the UK only. This showed that hospital stay costs, allied service costs and total costs were non significantly higher in the initial conservative treatment group (Mendelow et al 2005). Because of the different health service systems used in the different countries, the costs of collecting health service data, and the indication from STICH that there is no evidence for a difference in costs when the sample is larger than that planned in STICH II we do not propose to recollect cost data. We will however include EuroQol in our outcome measures.

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

Subgroup analysis of the STICH trial has demonstrated that for patients with only a lobar haematoma without an intraventricular extension 37% had a favourable outcome with initial conservative treatment and 49% had a favourable outcome with early surgery. With a 37% favourable outcome from conservative treatment a sample size of 566 would be required to show a 12% benefit from surgery ($2p<0.05$) with 80% power. We therefore propose a sample size of 600.

Centre eligibility

We plan to include 40 centres from UK, USA, Argentina, Belgium, Czech Republic, France, Germany, Greece, India, Latvia, Lithuania, Macedonia, Netherlands, Poland, Russia, South Africa, Spain, and Ukraine. 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.

Data collection

Before randomisation a form will be completed by the responsible neurosurgeon recording demographic and clot characteristics and status at randomisation. This information will be required in order to randomise the patient. During the randomisation phone call the neurosurgeon will be informed of the treatment group the patient is allocated to plus the patient identifier number for the trial. The neurosurgeon will record this information on the randomisation form and then fax the form to the STICH Office. 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.

At two weeks after randomisation or at discharge or at death whichever occurs first the discharge/2 week form will be completed by the responsible neurosurgeon. This form will record 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 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 will be sent to the STICH office within two weeks. The data manager will enter the data into the anonymised password protected database.

At four months the patient's GP or consultant will be asked to complete an adverse events form detailing whether the patient has suffered any adverse events since the discharge/2 week form and from five months outcome data will be collected as detailed under Follow-up and Outcome Measures above.

All paper copies will be kept in locked filing cabinets in a locked office.

CT scans
Copies of the randomisation CT scan and the 5-day post randomisation CT scan should be sent to the STICH office. The 5-day scan should be performed between 3 and 7 days after randomisation. The preferred method of sending CT scans will be in Dicom compatible format. Dicom images (on separate CDs for the two time points) should be sent anonymised with patient identifier. They will be analysed by trained readers blinded to treatment group and patient identity.

Statistical analysis
Analysis will be on an "intention to treat" basis. The primary analysis will be a simple categorical frequency comparison using the chi-squared test for prognosis based (Mendelow et al., 2003; Murray et al., 2005) 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 (Mendelow et al., 2005).

Any subgroup analyses will be based on tests of interaction. The predefined subgroups include the following:

Age
Volume
Glasgow Coma Score
Time from ictus to randomisation
Severity of neurological deficit
Planned method of haematoma removal

The main trial will evaluate craniotomy but patients receiving other forma of surgery will be entered into the trial and analysed separately.

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.

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 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 MRC and Ethics committees, for communication and dissemination of information to centres, for monitoring centres, for data analysis and for writing up of results.

Professor G D Murray is responsible for overall statistical validity of the trial.

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

Dr A R Gholkar is responsible for the central reading of CT scans.

Dr Elise Rowan, trial/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.

Miss Gillian Kenyon, trial secretary, is responsible for all trial correspondence in relation to the trial, for sending postal questionnaires and reminders, for the organisation of investigator

meetings and travel for monitoring, maintaining telephone and fax communications, preparing quarterly newsletters and publications, and reimbursing centres.

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, 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 STICH 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,
disseminating information about the trial within the centre,
maintaining local trial documentation
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 STICH office in Newcastle expeditiously
ensuring follow-up is obtained in the centre
attending investigator meetings
facilitating centre monitoring
commenting on the final report.

Each centre will normally receive at least one monitoring visit after recruiting at least six patients.

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.

Trial Steering Committee

The Trial Steering Committee will meet four times during the study. The Trial Steering Committee will provide overall supervision of the trial on behalf of the MRC. It will consider progress of the trial, 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.

Data Monitoring Committee

A data monitoring committee will be established to consider data from interim analyses and report to the Trial Steering Committee. At their first meeting they will determine the 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.

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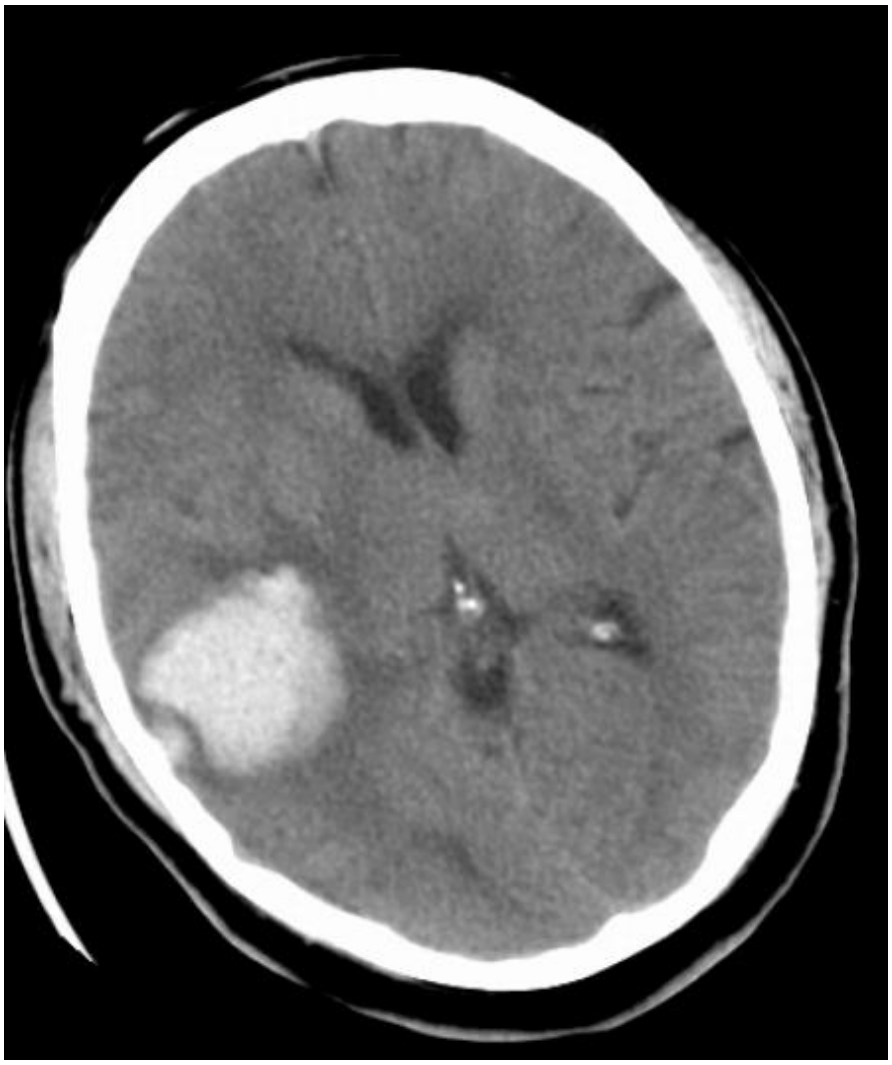
Example CT scans of patients with intracerebral haematomas that would and would not be eligible for STICH II

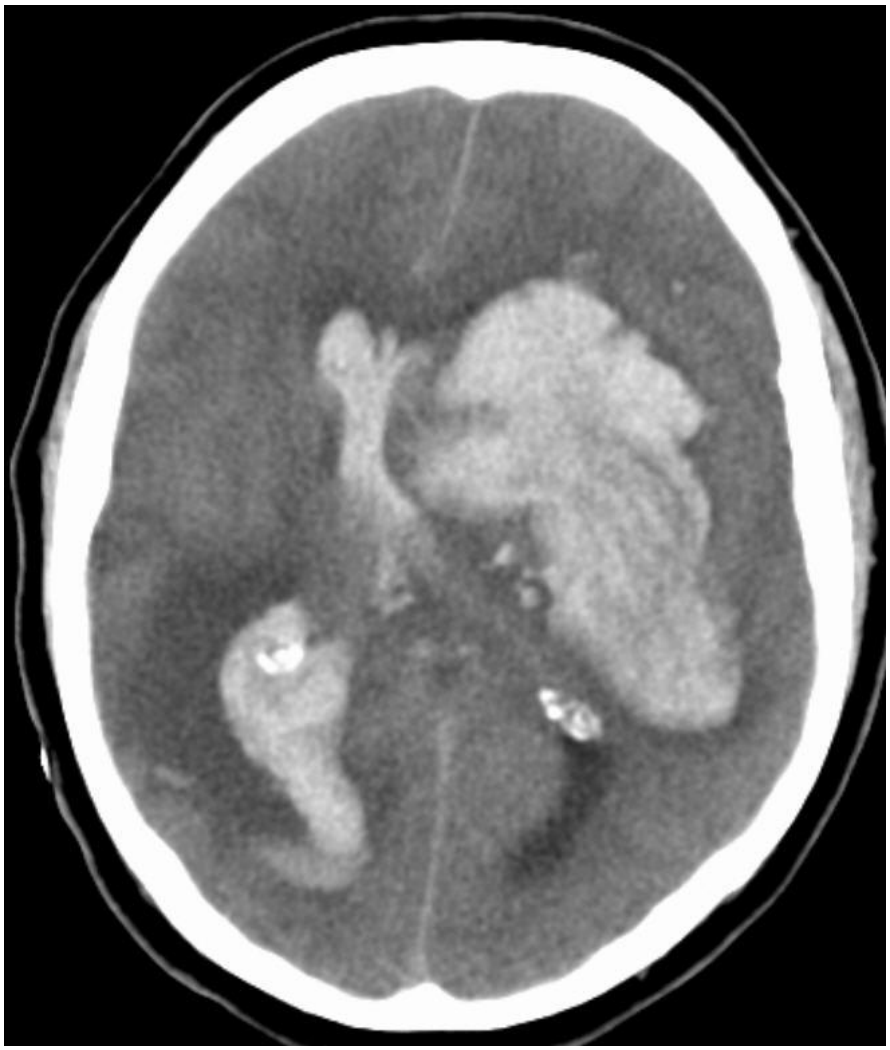
Example 1

This picture shows a scan of a patient who would be eligible for STICH II. The patient has a lobar intracerebral haematoma, close to the cortical surface. The volume of the haematoma is within the 10 – 100 ml criterion. There is no evidence of hydrocephalus or intraventricular haemorrhage and the haematoma does not extend into the basal ganglia, and is not associated with trauma, tumour or aneurysm.



Example 2

In contrast this picture shows the scan of a patient who has a haematoma that would exclude them from STICH II. The haematoma is not within 1cm of the cortical surface of the brain. It extends from the lobar region into the basal ganglia. There is evidence also of intraventricular haemorrhage.



Appendix 1

Timelines for Surgical Trial in Lobar Intracerebral Haemorrhage (STICH II)

	Baseline (<48 hrs from ictus)		Day 1	Day 2	Day 3	Day 4	Day 5	Discharge	Day 182 (+/- 30 dys)
	Pre randomisation	Post randomisation							
Eligibility Consent Demography Medical History Haematoma characteristics	X								
GCS Neurological status	X		X	X	X	X	X		
CT	X						X		
Surgery		Within 12 hrs (if randomised to early surgery)	If it becomes necessary due to change in status (if randomised to initial conservative treatment)						
Treatment details								X	
Where living								X	X
GOS								X	
eGOS									X
Rankin	X								X
Barthel									X
EuroQol									X

Appendix 2

Surgical Trial in Lobar Intracerebral Haemorrhage (STICH II)

A Study of the Treatment of Brain Haemorrhages

Information for Patients

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with relatives and friends if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

What is the purpose of the study?
You have suffered a form of stroke called a Brain Haemorrhage where bleeding has taken place inside the brain. This form of stroke is frequently life threatening and the best policy for treatment is not yet known. It is clear that some patients do benefit from an early operation to remove the blood clot with earlier recovery. Others do not benefit from an early operation because the risks associated with having an operation are greater than the damage caused by the clot. In these patients it is best to treat them “conservatively” with close monitoring. If they then get worse it may become necessary to operate. At present in the patients with your type of haemorrhage there is uncertainty about which of these two options is of greater benefit. This study is trying to find out exactly which patients would benefit from early surgery and which would benefit from initial conservative treatment.

Why have I been chosen?
You have been chosen because at this moment in time the consultant in charge of your care is "uncertain" whether you will benefit most from surgery or "conservative treatment".

Do I have to take part?
It is up to you whether or not you decide to take part. If you do not wish to take part in the study your treatment will not be compromised in any way and a decision about operation will be taken by the Consultant in charge according to how the situation develops. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time without giving a reason. This will not affect the standard of care you receive. If you withdraw from the study we will need to keep all the data collected up to your withdrawal and we will ask for permission to send you a six-month follow-up questionnaire.

What will happen to me if I take part?
If you agree to take part in the study you will be randomly allocated, by computer, to one of two groups. One group of patients will receive an immediate operation; the other group of patients will be kept under close observation. If you are in the ‘early operation’ group, your Consultant will undertake a craniotomy and closely monitor your condition. If you are in the ‘non-operation’ group, your condition will be closely monitored and you can still receive an operation later, should this become necessary. Whichever group you are allocated to you will receive the best available medical treatment. In total we hope to recruit 600 patients to this study.

What do I have to do?
Once you are included in this study details will be collected from your medical notes regarding the treatment you receive and your response to that treatment. You will be sent a questionnaire in six months time asking how you are managing and about your health generally. This questionnaire will take approximately 15 minutes to complete and you will be supplied with a stamped addressed

envelope to return it to the project office in Newcastle. Before sending the questionnaire we will confirm with your consultant and your GP whether you have experienced any complications and where you are living.

What is the procedure being tested?
No new procedure is being tested during this study. Both methods of treatment are used routinely.

What are the alternative treatments?
Early surgery and initial conservative management are the two methods used to treat lobar brain haemorrhages. At present there are no other treatments available. There is a drug treatment under investigation for use within a few hours of a brain haemorrhage to prevent further bleeding called Factor VIIa. If this drug treatment is appropriate for you, then taking part in this study does not prevent you from receiving the drug

What are the risks or benefits of taking part?
The usual possible risks associated with having an operation or being managed "conservatively" apply to this study. Your doctor will be able to discuss these with you. We cannot promise that the study will help you, but the information we get might improve treatment of future patients with brain haemorrhage.

What if something goes wrong?
If you participate in this study your hospital consultant remains in charge of your medical care. If you wish to complain about any aspect of the way you have been approached or treated during the course of this study you should ask to speak to the researchers who will do their best to answer your questions. If you remain unhappy and wish to complain formally the normal National Health Service complaints mechanisms is available to you. Details can be obtained from this hospital.

Will my taking part in this study be kept confidential?
All information collected about you or from you will be treated as strictly confidential. All the data is stored by the co-ordinating centre at Newcastle University. The staff at Newcastle will maintain the confidentiality of all the data they store. With your permission they will inform your GP that you are taking part in the study. All data entered on computer for analysis will be coded. The data will be retained for 15 years and then destroyed securely. Identifiable data may be viewed by authorised persons such as researchers and Newcastle NHS Trust to check the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and nothing that could reveal your identity will be disclosed outside the research site or the STICH Office at Newcastle University.

What will happen to the results of the study?
It is anticipated that the data from this study will be published in medical journals. When this happens it will be presented anonymously and it will not be possible to identify any individual patient.

Who is funding and organising this study?
This study is funded by the Medical Research Council and is being carried out in other countries around the world as well as in the UK. The study is being co-ordinated by the STICH Office, Newcastle University

Who has reviewed this study?
This study has been reviewed by the Multi-Centre Research Ethics Committee for Scotland.

Appendix 2

Contact for further details.

If you have any questions about the study please speak to the Local Co-ordinator

Please retain this sheet for your future information.

Date: 1 August 2006
Protocol STICH II Version 1.3 Date 10 August 2006

Consumers for Ethics in Research (CERES) publish a leaflet entitled ‘Medical Research and You’. This leaflet gives more information about medical research and looks at some questions you may want to ask. A copy may be obtained from CERES, PO Box 1365, London N16 0BW.

Appendix 3

Surgical Trial in Lobar Intracerebral Haemorrhage (STICH II)
A Study of the Treatment of Brain Haemorrhage

PATIENT CONSENT FORM

Patient Name:

I freely consent to my participation in the above clinical study, the nature of which has been explained by: ☐

Name of Consultant/Doctor

I have read and understand the Information Sheet dated 01 August 2006 (version 1.2) for the above study. I have had the opportunity to consider the information and any questions I had relating to the study have been answered to my satisfaction. ☐

I have discussed the possible benefits and risks from participation. I understand that my participation is voluntary, and that I am free to withdraw at any time, without giving a reason and without my medical care or legal rights being affected. ☐

I agree to my General Practitioner being informed that I am participating in the study. ☐

I understand that any personal information collected about me for the trial will be treated as strictly confidential, and that my medical records will be consulted and data from the study will be presented anonymously to medical journals and meetings. ☐

Signature of Patient:

Witnessed by: (eg., Senior Nurse)

Position:

Date:

Appendix 4

Surgical Trial in Lobar Intracerebral Haemorrhage (STICH II)

A Study of the Treatment of Brain Haemorrhage

Information for Relatives

You are being invited to assent to your relative taking part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with relatives and friends if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

What is the purpose of the study?
Your relative has suffered a form of stroke called a Brain Haemorrhage where bleeding has taken place inside the brain. This form of stroke is frequently life threatening and the best policy for treatment is not yet known. It is clear that some patients do benefit from an early operation to remove the blood clot with earlier recovery. Others do not benefit from an early operation because the risks associated with having an operation are greater than the damage caused by the clot. In these patients it is best to treat them “conservatively” with close monitoring. If they then get worse it may become necessary to operate. At present in the patients with your relative’s type of haemorrhage there is uncertainty about which of these two options is of greater benefit. This study is trying to find out exactly which patients would benefit from early surgery and which would benefit from initial conservative treatment.

Why has your relative chosen?
Your relative has been chosen because at this moment in time the consultant in charge of their care is "uncertain" whether they will benefit most from surgery or "conservative treatment".

Do I have to take part?
It is up to you to decide whether or not your relative would choose to take part. If you believe they would not wish to take part in the study their treatment will not be compromised in any way and a decision about operation will be taken by the Consultant in charge according to how the situation develops. If you do believe they would wish to take part you will be given this information sheet to keep and be asked to sign an assent form. If you decide to take part you are still free to withdraw at any time without giving a reason. This will not affect the standard of care your relative will receive. If you withdraw from the study we will need to keep all the data collected up to your withdrawal and we will ask for permission to send your relative a six-month follow-up questionnaire.

What will happen to my relative if he/she takes part?
If you agree to your relative taking part in the study they will be randomly allocated, by computer, to one of two groups. One group of patients will receive an immediate operation; the other group of patients will be kept under close observation. If your relative is in the ‘early operation’ group, their Consultant will undertake a craniotomy and closely monitor your condition. If your relative is in the ‘non-operation’ group, their condition will be closely monitored and they can still receive an operation later, should this become necessary. Whichever group your relative is allocated to they will receive the best available medical treatment. In total we hope to recruit 600 patients to this study.

Appendix 4

What does my relative have to do?
Once your relative is included in this study details will be collected from their medical notes regarding the treatment they receive and their response to that treatment. Your relative will be sent a questionnaire in six months time asking how they are managing and about their health generally. This questionnaire will take approximately 15 minutes to complete and you will be supplied with a stamped addressed envelope to return it to the project office in Newcastle. Before sending the questionnaire we will confirm with your relative's consultant and GP whether your relative has experienced any complications and where they are living.

What is the procedure being tested?
No new procedure is being tested during this study. Both methods of treatment are used routinely.

What are the alternative treatments?
Early surgery and initial conservative management are the two methods used to treat lobar brain haemorrhages. At present there are no other treatments available. There is a drug treatment under investigation for use within a few hours of a brain haemorrhage to prevent further bleeding called Factor VIIa. If this drug is appropriate for your relative, then taking part in this study does not prevent them from receiving the drug.

What are the risks or benefits of taking part?
The usual possible risks associated with having an operation or being managed "conservatively" apply to this study. Your relative's doctor will be able to discuss these with you. We cannot promise that the study will help your relative, but the information we get might improve treatment of future patients with brain haemorrhage.

What if something goes wrong?
If your relative participates in this study their hospital consultant remains in charge of their medical care. If you wish to complain about any aspect of the way your relative has been approached or treated during the course of this study you should ask to speak to the researchers who will do their best to answer your questions. If you remain unhappy and wish to complain formally the normal National Health Service complaints mechanism is available to you. Details can be obtained from this hospital.

Will my relative's taking part in this study be kept confidential?
All information collected about your relative or from you will be treated as strictly confidential. All the data is stored by the co-ordinating centre at Newcastle University. The staff at Newcastle will maintain the confidentiality of all the data they store. With your permission they will inform your relative's GP that your relative is taking part in the study. All data entered on computer for analysis will be coded. The data will be retained for 15 years and then destroyed securely. Identifiable data may be viewed by authorised persons such as researchers and Newcastle NHS Trust to check the study is being carried out correctly. All will have a duty of confidentiality to your relative as a research participant and nothing that could reveal your relative's identity will be disclosed outside the research site or the STICH Office at Newcastle University.

What will happen to the results of the study?
It is anticipated that the data from this study will be published in medical journals. When this happens it will be presented anonymously and it will not be possible to identify any individual patient.

Who is funding and organising this study?
This study is funded by the Medical Research Council and is being carried out in other countries around the world as well as in the UK. The study is being co-ordinated by the STICH Office, Newcastle University

Appendix 4

Who has reviewed this study?
This study has been reviewed by the Multi-Centre Research Ethics Committee for Scotland.

Contact for further details.
If you have any questions about the study please speak to the Local Co-ordinator

Please retain this sheet for your future information.

Date: 10 August 2006
Protocol STICH II Version 1.3 Date 10 August 2006

Consumers for Ethics in Research (CERES) publish a leaflet entitled 'Medical Research and You'. This leaflet gives more information about medical research and looks at some questions you may want to ask. A copy may be obtained from CERES, PO Box 1365, London N16 0BW.

Appendix 5

Surgical Trial in Lobar Intracerebral Haemorrhage (STICH II)
A Study of the Treatment of Brain Haemorrhage

RELATIVE ASSENT FORM

Patient Name:

I freely consent to my relative participating in the above clinical study, the nature of which has been explained by: ☐

Name of Consultant/Doctor

I have received, read and understand the Information Sheet dated 10 August 2006 (version 1.2) and any questions I had relating to the study have been answered to my satisfaction. ☐

I have discussed the possible benefits and risks from participation. I understand that my relative's participation is voluntary, and that he/she is free to withdraw at any time, without reason and without prejudice to his/her further treatment. ☐

I agree to my relative's General Practitioner being informed that my relative is participating in the study. ☐

I understand that any personal information collected about my relative for the trial will be treated as strictly confidential, and that his/her medical records will be consulted and data from the study will be presented anonymously to medical journals and meetings. ☐

Signature of Relative:

Name of Relative:

Witnessed by: (eg., Senior Nurse)

Position:

Date:

Appendix 6

Randomisation Form

(PLEASE COMPLETE PRIOR TO TELEPHONING)

1. Country _____ **2**. Hospital Name _____

3. Centre Number _____ **4.** Name of Consultant Neurosurgeon _____

5. Patient's Name (Given name/Family name) _____ /

6. Date of Birth: (DD/ MM/YYYY) ___ / ___ /19 **7.** Gender: ___ *1 = male, 2 = female*

8. Consent or assent obtained ?.....*1 = yes, 2 = no* …… ___ **YES**

Clinical Details

9. Date of first symptoms.....*(DD/MM/YYYY)* ___ / ___ /20

10. Time of first symptoms ……*(24 hour clock)* ___ :
(Time from first symptoms to randomisation in hours should be < 48 hours)

Record the following details at time of randomisation. (If patient sedated/ventilated please record GCS and localising features immediately prior to intubation)

(please use appropriate number score)

11. Glasgow Coma Score: Best Eye Response (1-4): ..... ___ **2 – 4**

12. Best Verbal Response (1-5): ..... ___ **1 – 5**

13. Best Motor Response (1-6): *(non plegic limb)* ..... ___ **5 localising or 6 obeying commands**

14. Localising features: Affected arm: ...*1= normal, 2= weak, 3= paralysed …* …… ___

15. Affected leg: .....*1= normal, 2= weak, 3= paralysed ..* ……. ___

CT Scan: ___

16. Side of haemorrhage: ……...*1 = right, 2 = left* …….. ___

17. Maximum length of haematoma (**mm**): ……. ___

18. Width of haematoma {at 90 degrees} (**mm**): …… ___

19. Height of haematoma (**mm**): …… ___

} **Volume = (a x b x c)/2000 = 10 – 100 ml**

20. Minimum depth from nearest cortical surface (**mm**): …… ___ **0– 10 mm**

21. Are other inclusion and exclusion criteria fulfilled?

a). Site of haemorrhage is lobar only

b). There is no intraventricular haemorrhage

c). There is no evidence of hydrocephalus

d). Haemorrhage is not associated with aneurysm, angiographically proven AVM, tumour or trauma

e). There is no severe pre-existing physical or mental disability or comorbidity

f). Surgery can be performed within 12 hours of randomisation ***….1 = all yes, 2 =any no ….*** ___ **All Yes**

22. Please state intended method of surgical evacuation ___
1=craniotomy, 2=other (specify)……..

Now with all details ready please telephone for randomisation +44 (0) 1224 273 661

Once the above details have been given the automated system will inform you which treatment arm has been allocated to your patient and the randomisation number. Please enter the randomisation number and the present date and time and tick the treatment arm allocated,:

Randomisation Number _____ **Date** *(DD/MM/YYYY)* ___ / ___ /20 **Time** ___ :

Randomised to: Early Surgery ___ **Initial Conservative Treatment** ___

Please Fax and return a copy of this form to:
Neurosurgical Trials Unit, 3-4 Claremont Terrace, Newcastle University, Newcastle upon Tyne, NE2 4AE, U. K.
Fax +44 191 222 5762,
Tel +44 191 222 5761

Appendix 6