NIHR HTA Programme

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The NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC), based at the University of Southampton, manages evaluation research programmes and activities for the NIHR

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Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH 2)

Final Version 2.0
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Short title:	**Tranexamic acid for IntraCerebral Haemorrhage TICH-2**
Acronym:	**TICH-2**
EudraCT number:	2012-004108-37
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SYNOPSIS

Title	Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH-2)
Acronym	TICH-2
Short title	Tranexamic acid for intracerebral haemorrhage (TICH-2)
Chief Investigator	Dr. Nikola Sprigg
Objectives	To assess whether tranexamic acid is safe and reduces death and dependency after hyperacute (within 8 hours of onset) primary intracerebral haemorrhage.
Trial Configuration	A phase III prospective pragmatic double blind randomised placebo controlled trial
Setting	Secondary care
Sample size estimate	With alpha=0.05, power=90%, assuming losses to follow up=5% and covariate adjustment reduces sample size by 20%, 2,000 participants will need to be recruited to detect a treatment effect of OR 0.74 by shift analysis of mRS outcome
Number of participants	2000
Eligibility criteria	Patients within 8 hours of acute primary intracerebral haemorrhagic stroke. Exclusion criteria will be one or more of: contra-indication to tranexamic acid, severe pre-morbid disability (modified rankin scale >4), Glasgow coma scale <5, or life expectancy < 3 months due to other disease (e.g. advanced metastatic cancer).
Description of interventions	Intravenous tranexamic acid: 1g loading dose given as 100 mls infusion over 10 minutes, followed by another 1g in 250 mls infused over 8 hours. Comparator – matching placebo (normal saline 0.9%) administered by identical regimen.
Duration of study	48 months. Participants will be followed up for 90 days.
Randomisation and blinding	Patients will be randomised (1:1) to receive either tranexamic acid or placebo (0.9 % saline). Randomisation will be performed by the Stroke Trials Unit (STU) and involve computerised minimisation on key prognostic factors: age; stroke severity; systolic blood pressure. Patients randomised to placebo will receive intravenous normal saline. Patients and outcome assessors will be blind to treatment allocation.

Outcome measures	**Primary outcome**: Death or dependency (modified Rankin Scale, mRS) day 90. **Secondary clinical outcomes:** At day 7 (or discharge if sooner), neurological impairment (NIHSS). At day 90, disability (Barthel index), Quality of Life (EuroQol), cognition, cognition and mood (TICS and ZDS). Safety: death, serious adverse events, thromboembolic events, seizures. Costs: length of stay in hospital, re-admission, institutionalisation. Radiological efficacy/safety (CT scan): change in haematoma volume from baseline to 24 hours, haematoma location, and new infarction.
Statistical methods	Death or dependency (ordinal shift on mRS) at day 90 will be analysed by intention-to-treat using ordinal logistic regression (OLR), with adjustment for minimisation factors. The assumption of proportional odds will be tested using the likelihood ratio test. Comparison of tranexamic acid versus control.

ABBREVIATIONS

AE	Adverse Event
ARSAC	The Administration of Radioactive Substances Advisory Committee
CI	Chief Investigator
CRF	Case Report Forms
CT	Computer Axial Tomographic
DSMC	Data Safety Monitoring Committee
HTA	Health Technology Assessment
ICH	Intracerebral haemorrhage
ICRP	International Commission on Radiological Protection
IMP	Investigational Medicinal Product
INTERACT	Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage-Trial
MHRA	Medicines and Health Care Products Regulatory Agency
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
NHS	National Health Service
NIHr	National Institute of Health Research
NIHSS	National Institute of Health Research Stroke Scale
OR	Odds Ratio
PAD	Peripheral artery disease
PICH	Primary Intracerebral Haemorrhage
R&D	Research and Development
REC	Research ethics Committee
SAE	Serious Adverse Event
STU	Stroke Trials Unit
SUSAR	Suspected Unexpected Serious Adverse Reaction
TIA	Transient Ischaemic Attach
TSC	Trial Steering Committee
VTE	Venous Thromboembolism

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TRIAL / STUDY BACKGROUND INFORMATION AND RATIONALE

Haemorrhagic stroke

Haemorrhagic stroke, or intracerebral haemorrhage caused by bleeding in the brain, can be devastating and is a common cause of death and disability, both in the UK and worldwide. Despite development of effective treatments for ischaemic stroke (thrombolysis, aspirin, hemicraniectomy) there is no proven effective treatment for primary intracerebral haemorrhage (PICH).

Haematoma expansion

Outcome after intracerebral haemorrhage is closely related to whether brain bleeding expands after onset, so called haematoma expansion, or whether re-bleeding occurs; both are associated with a bad outcome (death and disability).[1] Contrast extravasation during contrast-enhanced CT, and CT angiography, have been shown to predict haematoma expansion,[2-4] although there is currently wide variation in the use of these techniques in routine clinical practice.

Haematoma expansion is related to both haemostatic factors and blood pressure; furthermore, haematoma volume can be reduced surgically - all these approaches are potential targets for treatment in intracerebral haemorrhage.

Intensive blood pressure treatment

Lowering blood pressure in patients with intracerebral haemorrhage is a potential therapeutic option to limit haematoma expansion and improve outcome. INTERACT, the largest completed trial to date, assessed intensive blood pressure treatment in 404 intracerebral haemorrhage patients. The study showed that aggressively lowering blood pressure appears safe and may limit haematoma expansion, but did not change outcome.[5] A smaller trial using a different regime again showed a trend to reduction of haematoma expansion in patients randomised to aggressive blood pressure lowering strategies.[6] Some safety concerns remain regarding aggressively lowering blood pressure in acute stroke, and a larger on-going study INTERACT-2 is assessing this area further.[7] Other ongoing trials include ATACH-2 and ENOS (PICH subset).

Surgery for intracerebral haemorrhage

Surgical treatment for intracerebral haemorrhage has proved disappointing, the largest trial STICH [8] failing to show benefit of surgery over conservative treatment. However, patients

were only recruited when the surgeon was in equipoise and time to surgery was delayed (mean time 30 hours) and thus surgery was unlikely to be able to limit haematoma expansion. The on going STICH-2 [9] study is assessing the efficacy of surgery in patients with lobar haematomas.

Haemostatic therapy

Haemostatic drug therapies have been tested in spontaneous intracerebral haemorrhage, with recombinant factor VIIa being the most widely studied. In a phase IIb trial with 399 patients, rFVIIa restricted haematoma expansion, improved functional outcome and reduced mortality despite a significant increase in arterial thromboembolic events.[10] However in a larger phase III study in 816 patients, rFVIIa had no effect on functional outcome or mortality despite restricting haematoma expansion.[10] Meta-analysis of these and other haemostatic therapies for acute PICH, and containing data from 6 trials and 1398 patients, found no significant benefit on mortality, or death or dependency. There was a trend to improved outcome, but also a trend to increase in thromboembolic events.[11] In a small case series, platelet infusion therapy for patients with intracerebral haemorrhage whilst on anti-platelet therapy did not prevent death or improve outcome.[12]

Tranexamic acid

Tranexamic acid is a licensed anti-fibrinolytic drug that can be administered intravenously or orally and is used in a number of bleeding conditions to reduce bleeding.[13, 14] In a recent mega-trial (CRASH-2) in 20,000 patients with major bleeding following trauma, tranexamic acid significantly reduced mortality, OR 0.91 (0.85-0.97), with no increase in vascular occlusive events.[15] Treatment was most effective when given rapidly; delayed administration was associated with lack of efficacy and potential harm.[16] In a subgroup analysis of patients with traumatic ICH, tranexamic acid showed a non-significant trend to reduced mortality, OR 0.47 (0.21-1.04), and death of dependency, OR 0.66 (0.32-1.36).[17] However, patients in CRASH-2 were younger and had less co-morbidities than those with PICH. In another randomised controlled trial in traumatic intracerebral haemorrhage, tranexamic acid reduced death, OR 0.69 (0.35 -1.39), and death or dependency, 0.76 (0.46 – 1.27), without increased thromboembolic events.[18]

Tranexamic acid has been tested in aneurismal subarachnoid haemorrhage, where it reduced the risk of re-bleeding at the expense of increased risk of cerebral ischaemia.[19] However administration was for a week, conferring prolonged exposure to risk of ischaemic events.

Additionally, tranexamic acid has been found to restrict haematoma expansion in acute PICH in a small non randomised study, although this did not report on safety.[20] In another small study (n=156), rapid administration of a bolus of tranexamic acid within 24 hours of stroke was observed to reduce haematoma expansion (17.5% vs. 4.3%).[21] In this study, tranexamic acid was given in combination with intensive blood pressure control, suggesting that it may be possible to combine haemostatic and haemodynamic approaches.

There have been recent calls in the literature for large clinical trials to examine the use of tranexamic acid in PICH.[22]

DETAILS OF INVESTIGATIONAL MEDICINAL PRODUCT(S)

Description and Manufacture

Intravenous tranexamic acid (Cyklokapron, 100mg/ml 5ml ampoules, Pfizer Manufacturing Authorisation: PL 00057/0952) or matched placebo of intravenous Sodium Chloride 0.9% 5ml ampoules (Hameln, Manufacturing Authorisation: 1502 / 0006R).

Tranexamic acid 100mg/ml 5ml ampoules are a licensed product and the summary of the product characteristics is available for investigator.

Packaging and labelling

Sharp Clinical Services Ltd (previously known as Bilcare GCS (Europe) Ltd) (MIA(IMP): 10284) will prepare blinded individual treatment packs containing four 5ml glass ampoules of tranexamic acid 500mg or sodium chloride 0.9% which will be identical in appearance by the addition of a heat shrink sleeving. Ampoules and the secondary carton will be labelled in accordance with Annex 13 of Volume 4 of The Rules Governing Medicinal Products in the EU: Good Manufacturing Practices, assuming that the primary and secondary packaging remain together throughout the trial. To facilitate identification the carton and the ampoules contained within it will be labelled with the same unique pack number.

Detailed prescribing and administration instructions will be provided in the treatment pack.

The final product will be QP released by the designated person at Sharp Clinical Services to provide blinded trial treatment packs for this trial.

Storage, dispensing and return

Sharp Clinical Services Ltd (previously known as Bilcare GCS (Europe) Ltd) (MIA(IMP): 10284) will store the treatment packs and distribute to pharmacies within trial sites using a web-based system control. Pharmacy at each participating site will take receipt of numbered supplies from Sharp Clinical Services.

The web-based system operates as follows. Participating centres will be allocated a batch of trial treatment. The container numbers for these batches are tracked by the web-based system to the participating site and once receipt has been confirmed they are released for use in the trial. When the supplies at the participating centre reach a pre-determined level then a re-order is triggered and a further supply of trial treatment is sent to the corresponding participating site.

The packs will be stored at room temperature and protected from excessive heat and freezing in a restricted access area. The IMP will be clearly labelled for clinical trial use only. Each pack will be a numbered box containing either tranexamic acid or placebo according to a computer-defined sequence.

The local site investigator is responsible for ensuring trial treatment accountability, including reconciliation of trial treatment and maintenance of trial treatment records, throughout the course of the study in accordance with UK regulatory requirements. Responsibility can be delegated to the site pharmacy clinical trials staff.

Following randomisation the participant will be allocated a treatment pack number. Specifically authorised personnel will retrieve the appropriate pack number and complete the participant name, date of randomisation and participant number. Pack number allocation will be checked and countersigned by the research staff and the nursing staff administering the treatment. The treatment will be prescribed on the participant's treatment chart as trial medication.

Dispensing will be recorded on the appropriate trial specific accountability forms. Trial treatment must not be used for any other purpose than the present study. Returned trial treatment that has been dispensed to a participant must not be re-dispensed to a different participant. Any unused drug will be returned to pharmacy.

Placebo

The placebo will be supplied, packaged, labelled, QP released and distributed as for the active IMP.

Known Side Effects

Gastrointestinal disorders (nausea, vomiting, diarrhoea) may occur but disappear when the dosage is reduced. Hypotension has occasionally been reported after rapid intravenous infusion. Rare instances of colour vision disturbances have been reported following long-term use. Rare cases of thromboembolic events have been reported. Rare cases of allergic skin reactions have also been reported (see Appendix A).

Tranexamic acid will counteract the thrombolytic effect of fibrinolytic preparations but these would be contra-indicated in patients with haemorrhagic stroke.

TRIAL / STUDY OBJECTIVES AND PURPOSE

PURPOSE

To assess in a pragmatic phase III prospective double blind randomised placebo-controlled trial whether tranexamic acid is safe and reduces death or dependency after primary intracerebral haemorrhage (PICH). The results will determine whether tranexamic acid should be used to treat PICH, which currently has no proven therapy.

PRIMARY OBJECTIVE

To assess whether tranexamic acid is safe and reduces death or dependency after primary intracerebral haemorrhage (PICH).

SECONDARY OBJECTIVES

To assess the effect of tranexamic acid on secondary outcomes: clinical outcomes, safety outcomes, costs and radiological efficacy.

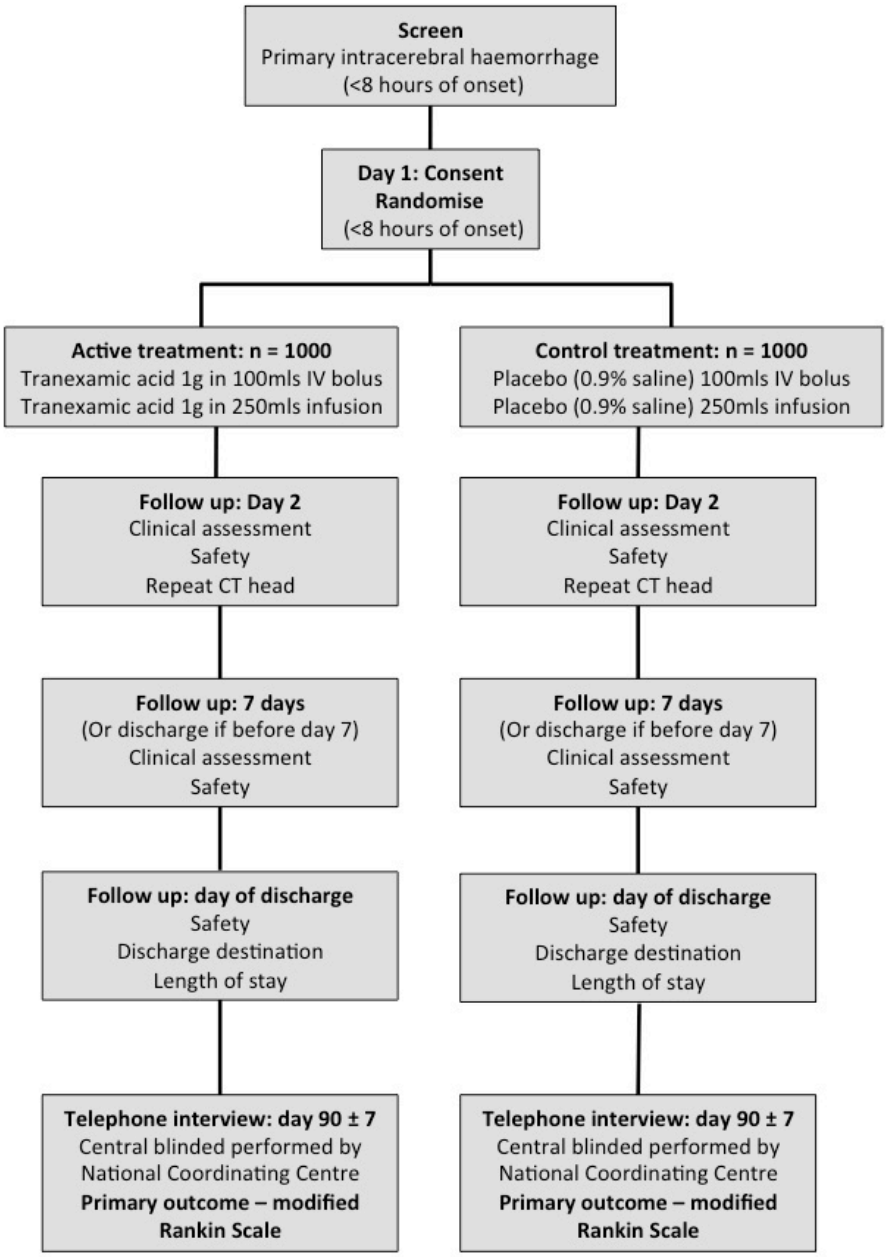
TRIAL / STUDY DESIGN

TRIAL / STUDY CONFIGURATION

Pragmatic, phase III, prospective double blind randomised placebo-controlled trial performed in two phases: 18 month start up phase (activate 30 centres, recruit a minimum of 300

participants) then main phase (120 centres recruit to a total of 2,000 participants). There will be no break in recruitment as the trial proceeds from the start-up phase to the main phase provided the stopping criteria are not met.

See trial flow chart



The trial will consist of a UK base with UK participating sites and an international element involving a number of international sites. Separate local approvals will be sought for the international sites, all applicable local regulations will be adhered to and a contract will be in place between the University of Nottingham and those sites apportioning liabilities and responsibilities for the conduct of the study.

Assessments:

Clinical assessment; Baseline (Day 1), end of treatment (day 2) and day 7 (or earlier if discharged). Day 90 – telephone interview.
Radiological – Day 2 CT brain scan to assess for haematoma expansion.

Primary endpoint

Death or dependency (modified Rankin Scale, mRS) at day 90.

Secondary endpoint

1. Neurological impairment (NIHSS) at day 7 or discharge if sooner.
2. Disability (Barthel index) at day 90,
3. Quality of Life (EuroQol) at day 90,
4. Cognition and mood at day 90 (TICS and ZDS).
5. Costs: length of stay in hospital, re-admission, institutionalisation.
6. Radiological efficacy/safety (CT scan): change in haematoma volume from baseline to day 2, haematoma location and new infarction.

Safety endpoints

Recorded until end of follow-up (day 90):

1. Death (cause);
2. VTE; ischaemic events (stroke/TIA/MI/PAD);
3. Seizures;
4. Serious adverse events in first 7 days

Stopping rules and discontinuation

Participants may withdraw consent at any time. Study medication maybe stopped at any time by the investigator or treating physician if deemed advisable.

RANDOMIZATION AND BLINDING

All participants eligible for inclusion will be randomised centrally using a secure internet site in real-time. Randomisation involves minimisation on key prognostic factors: age; sex; time since onset; systolic blood pressure; stroke severity (NIHSS); presence of intraventricular haemorrhage; known history antiplatelet treatment used immediately prior to stroke onset. This approach ensures concealment of allocation, minimises differences in key baseline prognostic variables, and slightly improves statistical power.[23]
Randomisation will allocate a number corresponding to a treatment pack and the participant will receive treatment from the allocated numbered pack.
In the event of computer failure (for example: server failure), investigators will follow the working practice document for computer system disaster recovery, which will allow the participant to be randomised following standardised operating procedure.

Maintenance of randomisation codes and procedures for breaking code

Clinicians, patients and outcome assessors (research nurse and radiologist) will be blinded to treatment allocation.

In general there should be no need to unblind the allocated treatment. If some contra-indication to antifibrinolytic therapy develops after randomisation (e.g. clinical evidence of thrombosis), the trial treatment should simply be stopped. Unblinding should be done only in those rare cases when the doctor believes that clinical management depends importantly upon knowledge of whether the patient received antifibrinolytic or placebo. In those few cases when urgent unblinding is considered necessary, the emergency telephone number should be telephoned, giving the name of the doctor authorising unblinding and the treatment pack number. The caller will then be told whether the patient received antifibrinolytic or placebo The rate of unblinding will be monitored and audited.

In the event of breaking the treatment code this will normally be recorded as part of managing a SAE (see below for more details) and such actions will be reported in a timely manner. The Chief Investigator (delegated the sponsor's responsibilities) shall be informed

immediately (within 24 hours) of any serious adverse events and shall determine seriousness and causality in conjunction with any treating medical practitioners

TRIAL MANAGEMENT

Day-to-day management of the trial will be the responsibility of the Trial Management Group. The Trial Management Group will report to the independent Trial Steering Committee. An independent Data Safety Monitoring Committee will monitor safety of participants, and will report to the Trial Steering Committee. Trial co-ordination will be through the Stroke Trials Unit, in conjunction with the Nottingham Clinical Trials Unit (NCTU).

The Chief Investigator is the data custodian and has overall responsibility for the study and shall oversee all study management.

Trial Management Group

The Trial Management Group (TMG) will include the Chief Investigator, Study Trial Manager, Trial Statistician, and other project staff. This group, based at the Stroke Trials Unit, will meet regularly, at least every four weeks.

Trial Steering Committee

The independent Trial Steering Committee (TSC) will provide oversight of the trial. It will meet (in person or by telephone conference) prior to commencement of the trial, and then at regular intervals until completion (at least annually). Specific tasks of the TSC are:

- to approve the trial protocol
- to approve necessary changes to the protocol based on considerations of feasibility and practicability
- to receive reports from the Data Monitoring Committee
- to resolve problems brought to it by the co-ordinating centre and TMG
- to ensure publication of the trial results
- to advise on whether the main phase of the trial is feasible

Data Safety Monitoring Committee

An independent Data Monitoring Committee (DSMC) will be established. The DSMC will receive safety reports every six months, or more frequently if requested and perform

unblinded reviews of efficacy and safety data. The DSMC will perform a formal interim analyses after 800 participants have been recruited (comprising both trial phases) and followed-up at 90 days.
A DSMC Charter will be prepared containing details of membership, terms and conditions and full details of stopping guidelines. The DSMC will report their assessment to the independent chair of the TSC who will report to the HTA.

Collaborators, and all others associated with the trial, may write through the trial office to the DSMC, to draw attention to any concern they may have about the trial interventions, or any other relevant issues.

DURATION OF THE TRIAL / STUDY AND PARTICIPANT INVOLVEMENT

The study will be run in two phases: an 18 month start-up phase (activate a minimum of 30 centres, recruit a minimum of 300 participants) then main phase (25 months, 120 centres. recruit to a total of 2,000 participants). There will be no break in recruitment as the trial proceeds from the start-up phase to the main phase unless the TSC and funder consider the trial no longer feasible or stopping criteria are met.

The participant's involvement in the trial will last 90 days, from randomisation (day 1) until final follow up at 90 days. Treatment period will be for 1 day (approximately 8 hours).
Enrolment will begin when the study has obtained full regulatory approval and cease when the final participant has been recruited.

End of the Trial

The trial will end when the final participant has completed the treatment period and follow up (Day 90).

SELECTION AND WITHDRAWAL OF PARTICIPANTS

Recruitment

The trial setting is in secondary care, in acute stroke services across the UK and worldwide; 30 in the start up phase, 120 in the main phase. Estimated 80 UK sites, 40 non-UK sites. UK participants will be recruited from NIHR Stroke Research Network sites (adoption will be

sought from the NIHR Stroke Research Network). These sites have dedicated Stroke Research Network Local Research Network nurses to facilitate recruitment and follow-up.

Participants will be recruited from the acute stroke unit or emergency admissions department. The initial approach will be from a member of the patient's usual care team (which may include investigators).

The investigator or their nominee will inform the participant or their legal representative, of all aspects pertaining to participation in the study.

If needed, the usual hospital interpreter and translator services will be available to assist with discussion of the trial, the participant information sheets, and consent forms, but the consent forms and information sheets will not be available in other languages.

It will be explained to the potential participant or their legal representative that entry into the trial is entirely voluntary and that their treatment and care will not be affected by their decision. It will also be explained that they can withdraw at any time but attempts will be made to avoid this occurrence. In the event of their withdrawal it will be explained that their data collected so far cannot be erased and we will seek consent to use the data in the final analyses where appropriate.

Inclusion criteria

Adult (≥18 years) patients with acute PICH within 8 hours of stroke onset. (Where stroke onset time is unknown, the time of when last known well will be used.)

Exclusion criteria

1) Patients with intracerebral haemorrhage secondary to anticoagulation, thrombolysis or known underlying structural abnormality such as arterial venous malformation, aneurysm, tumour, venous thrombosis as cause for the intracerebral haemorrhage.. Note it is not necessary for investigators to exclude underlying structural abnormality prior to enrolment, but where an underlying structural abnormality is already known, these patients should not be recruited.
2) Patients for whom tranexamic acid is thought to be contraindicated.
3) Patients with pre-morbid dependency (mRS>4).
4) Participation in another drug trial concurrently.
5) Pre-stroke life expectancy <3 months (eg. advanced metastatic cancer).

6) Coma – Glasgow coma scale <5

Expected duration of participant participation

Study participants will be participating in the study for 90 days.

Removal of participants from therapy or assessments

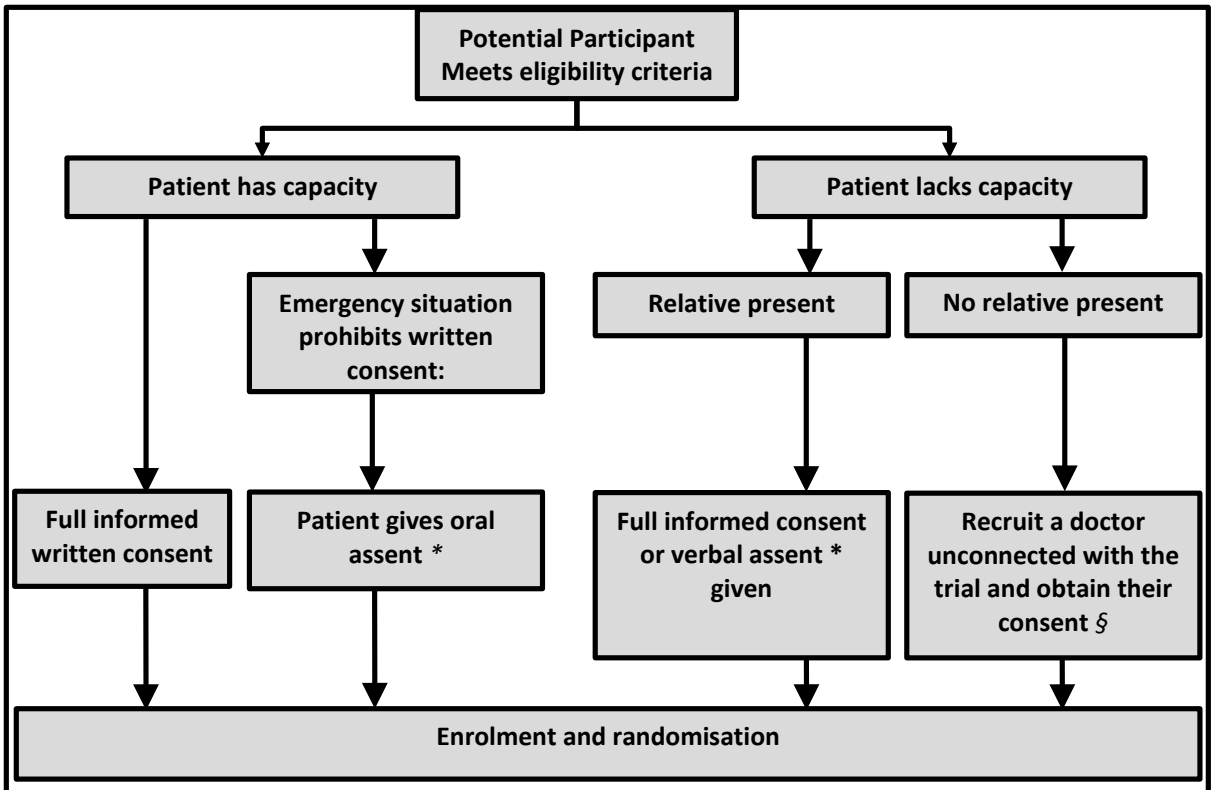
Participation in the trial is voluntary and patients are free to withdraw from the trial at any stage without giving a reason. Study medication may be stopped at any time by the investigators or any treating clinician if deemed in the patient's best interest. Treatment (with tranexamic acid/placebo) will be given on top of 'best medical care'.

Participants may be withdrawn from the trial either at their own request or at the discretion of the Investigator. The participants will be made aware that this will not affect their future care. Participants will be made aware (via the information sheet and consent form) that should they withdraw the data collected to date cannot be erased and may still be used in the final analysis.
Enrolled participants who withdraw before randomisation can be replaced (though keeping their trial ID), but participants who withdraw after randomisation will not be replaced.

Informed consent

Intracerebral haemorrhage is a medical emergency, for which there is no proven effective treatment and rapid deterioration can occur early, leading to brain damage, long term disability or death. Intracerebral haemorrhage can cause significant brain injury and many patients may not be physically or mentally capable of giving informed consent to participate in a clinical trial. There is evidence from trials in traumatic bleeding that 2g of tranexamic acid (the regime being utilised in TICH-2) is safe (with no significant increase in harm in 20,000 patients), and improves survival. In addition, tranexamic acid is more effective when given early[16]. The need for urgent treatment, in an attempt to prevent potentially fatal deterioration, means that it would be inappropriate to delay treatment until fully informed consent can be obtained from an incapacitated patient.

Therefore the following procedure will be used for giving information and obtaining informed consent for the TICH-2 trial



*** Patients or relatives will be approached to give oral assent in circumstances where the therapeutic time window does not allow investigators to seek full informed written consent, and only if the attending clinicians consider it appropriate. Patients or relatives will not be approached if there is insufficient time to give a brief oral summary of the trial, or they do not speak fluent English and no translator is available. How long will be required for oral assent will depend on factors such time window for treatment efficacy before brain damage. If the patient or relative does not give oral assent they will not be recruited.**

If oral assent for recruitment is given:

- **Participants (or relatives if the participant lacks capacity) will be approached as soon as possible after recruitment to give written consent to participation in follow up and access to their data**
- **Oral assent will be monitoring by Trial Steering Committee**

***§* Patients who lack capacity to consent (e.g. unconscious) with no relative present will be discussed with a doctor unconnected to the trial. Information relating to the trial is provided verbally and their verbal consent for the patient's inclusion in the trial is obtained. If a doctor unconnected with the trial is not available, patients will not be entered**

Patient has capacity to provide consent:

All participants who are able to will provide written informed consent. The Informed Consent Form will be signed and dated by the participant before they enter the trial. The Investigator (or nominee) will explain the details of the trial and provide a Participant Information Sheet. The Investigator will answer any questions that the participant has concerning study

participation. Potential participants will be given as long as they need to consider whether to consent, however we recommend that a maximum of 15 minutes should be taken obtaining consent. It will be explained to the potential participant that as this is an emergency treatment, with a small therapeutic time window before permanent brain damage occurs, previous work suggests that the earlier the treatment is commenced the greater the potential for benefit.

If the participant is unable to write (e.g. in the presence of dominant hand weakness, ataxia or dyspraxia), witnessed verbal consent may be recorded on the consent form.

Patient has capacity but time prohibits written consent:

If the therapeutic time window before brain damage occurs does not allow investigators to seek informed written consent and the attending clinician considers it appropriate, the potential participant will be asked if they are willing to be recruited.

Specifically, the responsible doctor will explain to the patient that they will receive the usual care for haemorrhagic stroke but that in addition to this, the patient can be enrolled in a research study that aims to improve the treatment of patients with this condition. It will be explained that the study is being done to see whether using a drug called tranexamic acid will help patients with haemorrhagic stroke by reducing the amount of bleeding into the brain therefore preventing further brain damage. If enrolled the patient will be given an infusion into a vein over 8 hours of either the tranexamic acid or a dummy medicine (a salt water liquid which does not contain tranexamic acid). The doctor will explain that tranexamic acid has been shown to improve outcome in patients with other types of severe injury and that whilst we hope that it will also improve recovery after haemorrhagic stroke, at present we cannot be sure about this. Further information will be provided on request. If requested, an information sheet will be provided. If they say yes, the potential participant will be randomised. Written informed consent will be sought later for access to medical notes and for participation in the trial follow up, including additional CT scan. The participant information sheet will be provided to the participant at this time if not already provided.

Patient lacks capacity to give consent:

Lack of capacity will be determined by the participant's attending stroke physician.

If the potential participant lacks capacity to give meaningful consent (e.g. in cases of dysphasia, confusion, or reduced conscious level) the following procedure will be employed.

Relatives present: If relatives (or other legal representative such as partner or close friend, able to represents the patients views and wishes) are present, bearing in mind the clinical

situation and their level of distress, they will be provided with brief information about the trial. Specifically, the responsible doctor will explain to the relatives that the patient will receive the usual care for haemorrhagic stroke but that in addition to this, the patient can be enrolled in a research study that aims to improve the treatment of patients with this condition. It will be explained that the study is being done to see whether using a drug called tranexamic acid will help patients with haemorrhagic stroke by reducing the amount of bleeding into the brain therefore preventing further brain damage. The relative will be informed that the patient will be given an infusion into a vein over 8 hours of either the tranexamic acid or a dummy medicine (a salt water liquid which does not contain tranexamic acid). The doctor will explain that tranexamic acid has been shown to improve outcome in patients with other types of severe injury and that whilst we hope that it will also improve recovery after haemorrhagic stroke, at present we cannot be sure about this. Further information will only be provided on request. If requested, a brief information sheet will be provided. If relatives object to the inclusion of the patient in the trial, their views will be respected and the patient will not be enrolled. Full informed written consent will be obtained from the patient or legal representative afterwards as soon as practicable.

Relatives not present: If no relatives are present, we intend to recruit a doctor, wherever possible unconnected with the trial, provide them with verbal information relating to the trial and obtain their verbal consent for the patient's inclusion in the trial. If a doctor unconnected with the trial is not available patients will not be entered into the trial.

If enrolled, full informed written consent will be obtained from the patient or their legal representative afterwards as soon as practicable.

Participants who originally lacked capacity (and were entered into the study following agreement from a legal representative) but then regain capacity will need to give informed written consent to continue in the study. The participants' decision to withdraw would overrule the decision of the legal representative.

Participants may discontinue treatment either at their own request or if it is felt in their best interest by the attending physician. Participants who discontinue treatment (for whatever reason) will not be withdrawn from the trial unless the participant specifically withdraws consent for further follow-up. Participants maybe withdrawn from the trial either at their own request (if they regain capacity) or at the request of the legal representative. The participants and the legal representative will be made aware that this will not affect the participant's future

care. Participants who withdraw from the trial will be informed that data already collected prior to withdrawal cannot be deleted.

The requirements of the relevant ethics committee will be adhered to at all times.
Should there be any subsequent amendment to the final protocol, which might affect a participant's participation in the trial, continuing consent will be obtained using an amended consent form which will be signed by the participant.

TRIAL / STUDY TREATMENT AND REGIMEN

Trial treatment is administered as tranexamic acid 1g (10ml in 100ml sodium chloride 0.9% infusion bag) through a venous cannula with a loading dose infusion over 10 minutes followed by 1g infusion (10ml in 250ml sodium chloride 0.9% infusion bag) over 8 hours. Placebo treatment replaces tranexamic acid 100mg/ml with sodium chloride 0.9%

Participants will be assessed before treatment (day 1), after treatment (day 2) and after 7 and 90 days. See flow chart for more details.

Patients will be assessed clinically at baseline, in line with local clinical practice pre-inclusion (day 1), end of treatment (day 2) and day 7. Follow up at day 90 will be via a telephone interview as is standard practice in clinical stroke trials.

Brain imaging (CT head scan) will be performed as part of routine clinical management prior to enrolment (all acute stroke patients have a CT head scan performed on admission to hospital). For the purpose of the study the CT head scan will be repeated after treatment, day 2, (tranexamic acid/placebo) to assess haematoma expansion.

Participant measures

Assessments	Screening	Day 1	Day 2	Day 7 (or discharge if sooner)	Day 90 (telephone interview)
CT Scan	X*		X^		
Clinical Assessment	X**		X	X	
Consent	X				
Eligibility screening		X			
Randomisation		X			
Administer Intervention		X			
NIHSS	X*		X	X	
mRS		X			X
Barthel Index					X
EuroQOL (EQ5D)					X
Cognition (TICS)					X
Mood (ZDS)					X
SAEs		X	X	X	X

mRS modified rankin scale; NIHSS National institute of Health Stroke Score; SAEs: serious adverse events; TICS Telephone Interview Cognitive Status; ZDS Zung Depression Score

* Routine clinical scan for index stroke

** Routine clinical assessment

^ Additional scan to assess for hematoma expansion

Follow Up

Face to face assessment at the end of treatment (day 2) and day 7 with telephone follow up at day 90.

Researchers will not contact the participant or their family directly at Day 90, they will first contact the participants general practitioner (GP) or obtain information through the Medical Research Information Service, at the NHS Information Centre to check their health status. Permission to contact the GP at day 90 will be sought at the time of consent.

Concomitant and Rescue Medications and Treatments

The intervention (tranexamic acid or placebo) will be given in addition to routine care. There are no prohibited concomitant treatments.

Compliance

Compliance will be assessed by examining the participant's drug chart and recording evidence of treatment administration. Compliance will also be assessed by recording, and returns of residual/unused trial medications. Compliance will be recorded on the case report forms at end of treatment (day 2).

Accountability for drugs & placebos

The pharmacist will maintain records of the dispensing of the drug and the research nurse will record administration of the drug to the patient. Dispensing details will be recorded on each participant's CRF. Unused and partially used supplies will be returned to pharmacy. This will be recorded in the pharmacy study log.

Management of study drug overdose

No specific antidotes are available. The study drug will be administered by slow intravenous injection by qualified nursing staff so the potential for overdose is not anticipated.

Criteria for terminating trial

The trial may be terminated by either the TSC, the sponsor or the funders as a result of a formal or informal interim analysis and based on overwhelming evidence of major safety concerns, new information, or issues with trial conduct (e.g. poor recruitment, loss of resources). Any decision to stop the study prematurely will be based on asymmetric stopping rules.

The trial may be stopped at one centre due to unacceptable performance in recruitment and/or failure to comply with protocol.

RADIATION EXPOSURE

Details of diagnostic or therapeutic ionising radiation

The participant will receive a routine clinical non-contrast single run CT head scan at the time of presentation with stroke and an additional non-contrast single run CT head scan at the end of the treatment. The CT head scan at the time of stroke is part of routine clinical care whether or not the patient goes on to participate in the trial. For patients who are randomised into the trial the results will be used as baseline data.

Trial Procedures

Single run non-contrast CT head scan 1 day post recruitment (day 2).

Details of radioactive materials and dose

From NRPB –W67 'Doses from computed tomography (CT) examinations in the UK (2003 review), the doses from CT scans will vary between sites with different models of equipment and between different sizes of patient.

A CT of the brain will give an average of 1.5mSv but this could be up to a maximum of 5mSv. So a typical dose from CT due to research exposures would be 1.5mSv, but could be as high as 5mSv.

A 1.5mSv dose would be roughly equivalent to 8 months of exposure to natural background radiation to a member of the public resident in the UK. A 5mSv dose is roughly equivalent to 2¼ years of background received by a member of the public resident in the UK.

Risk Assessment (induction of fatal cancer)

Based on a risk coefficient for developing fatal radiation induced cancer (all ages) of 5%/Sv (ICRP), this would lead to a risk of radiation exposure incurred as part of the trial. similar to the annual risk of dying from an accident in the home.

This is classed as an intermediate risk and the required benefit should be aimed directly at diagnosis, cure or prevention of disease.

Clinical Assessment

The scan itself takes about half a minute and does not involve any injections. The scan uses x-rays, which in large amounts can be harmful, but for this extra CT head scan the additional risk to the participant from the scan has been judged to be extremely small.

The objective of the exposure is to assess the extent of the bleeding (haematoma) in the brain to see if it has got worse (larger) or better (smaller) following treatment.

An alternative would be MRI brain scan but this takes longer and many patients are unsuitable or unable to tolerate it due to claustrophobia.

The procedure for CT and any doses in lay terms are explained in the participant information sheet.

STATISTICS

Sample size and justification

The null hypothesis (H_0) is that tranexamic acid does not alter death or dependency in participants with acute PICH. The alternative hypothesis (H_A) is that death or dependency differ between those participants randomised to tranexamic acid versus saline. A total sample size of 2,000 (1,000 per group) participants with acute primary intracerebral haemorrhage are required, assuming overall *significance (alpha) = 0.05*; *power (1-beta) = 0.90*; distribution in mRS (mRS 0=4%, 1=17% 2=16% 3=19% 4=24% 5=7% 6(death)=13% based on data from participants with primary intracerebral haemorrhage in the ENOS trial); *ordinal odds ratio of 0.79*; increases due to *losses to follow-up* of 5%; and a reduction of 20% for *baseline covariate adjustment*.[24] In summary, a trial of 2,000 participants (1,700 from main phase and 300 from start-up phase) will have 90% power to detect an ordinal shift of mRS outcome with odds ratio 0.79.

Assessment of efficacy

Detailed information regarding analyses will be provided in a separate statistical analysis plan to be prepared and finalised prior to database lock.

Primary outcome: Death or dependency (ordinal shift on mRS) at day 90 will be compared between tranexamic acid and saline by intention-to-treat using ordinal logistic regression (OLR), with adjustment for minimisation factors. The assumption of proportional odds will be tested using the likelihood ratio test.

Sub-group analyses: The comparison of tranexamic acid and saline on the primary outcome will be performed in pre-specified subgroups, including the minimisation criteria, and: start of treatment (≤3, >3 hours), spot positive (yes,no) and intraventricular haemorrhage (yes, no). Analysis of the primary outcome in these pre-specified sub-groups does not comprise the primary analysis and has not informed the sample size calculation.

The interpretation of any subgroup effects will be based on interaction tests (i.e. evidence of differential treatment effects in the different subgroups).

Secondary analyses: Binary logistic regression will be used for binary outcomes, including death, SAEs and thromboembolic events. ANCOVA will be used for continuous measures, including hematoma expansion. Wilcoxon rank sum test will be used for continuous measures which are not normally distributed, including Barthel Index. Regression analyses will be performed with adjustment for minimisation factors. As it is likely that haematoma volumes will be skewed, potential transformations of the data will be explored to permit an analysis based on ANCOVA, so as to exploit the baseline haematoma volumes and maximise statistical power. The impact of tranexamic acid on quality of life will be assessed using the EuroQoL. A full health-economic analysis will only be performed after completion of the main phase of the trial.

DSMC Analyses: The DSMC will perform a formal interim analyses after 800 participants have been recruited (comprising both trial phases) and followed-up at 90 days. Safety analyses will be performed 6 monthly.

Decision to proceed to main phase – stopping criteria: The decision to recommend proceeding from start-up to main phase will be made by the Trial Steering Committee at 17 months on the basis of information on feasibility (at least 27 active sites and 270 recruited participants, i.e. at least 90% of target of both measures) and safety (as assessed by the independent Data safety Monitoring Committee). The recommendation will be given to HTA for ratification.

The DSMC will recommend to the TSC that the trial be stopped if there is 'proof beyond reasonable doubt' of overall benefit with the active treatment or if there is a lower level of evidence suggesting overall hazard. Evidence of hazard will include effect on the primary outcome (shift analysis of mRS) and analysis of safety endpoints, as specified in the protocol (death, VTE, ischaemic events, seizures, serious adverse events).

To guide the DSMC in their deliberations the following guidelines are included in the protocol to illustrate the corresponding levels of evidence:

- Shift analysis of mRS favours the active (benefit) with P<0.001 (2-sided). The significance level of P<0.001 amounts to 'proof beyond reasonable doubt'.
- Shift analysis of mRS favours the control (hazard) with P<0.02 (2-sided)
- Analysis of death favours the control (hazard) with P<0.02 (2-sided)

Procedures for missing, unused and spurious data

Missing data will be reported, rules/methods for handling missing data will be detailed in the statistical analysis plan.

Definition of populations analysed

Safety population: All randomised participants.

Intention-to-treat population: All randomised participants, who receive any study medication. The intention-to-treat population will be defined in a blinded review prior to database lock.

Per protocol population: All participants in the intention-to-treat population who are deemed to have no major protocol violations that could interfere with the objectives of the study. The per-protocol population will be defined in a blinded review prior to database lock.

Analyses

All efficacy analyses will be performed on the intention-to-treat population; the robustness of the primary and key secondary analyses will be assessed in the per-protocol population. Safety analyses will be performed on the safety population.

Protocol Violations and Deviations

The study should be conducted in accordance with the approved protocol and changes to the protocol will only be made to protect the safety, rights, or welfare of the subject.

Protocol Violation

A protocol violation is a major deviation from the trial protocol where a participant is enrolled in spite of not fulfilling all the inclusion and exclusion criteria, or where deviations from the protocol could affect the trial delivery or interpretation significantly.

The following baseline characteristics constitute a protocol violation:

1. Randomisation > 8 hours from onset of symptoms
2. Participant less than 18 years of age
3. Failure to obtain appropriate consent
4. Pre-morbid dependency (mRS) >4

5. Baseline cranial imaging shows underlying structural abnormality such as tumour or arterial venous malformation
6. On anticoagulation
7. Randomising event was secondary to trauma
8. Glasgow Coma Score < 5
9. Known probable life expectancy of less than 3 months
10. Female patient of childbearing potential, pregnant or breastfeeding at randomisation

The following practice during the trial constitutes a protocol violation:

1. Subsequent randomisation into another drug or devices trial
2. Patient does not receive randomised treatment
3. Failure to complete SAEs where appropriate
4. Failure to complete outcomes where appropriate
5. Follow-up assessments are performed (as opposed to submitted) outside the specified time as shown below:

a. 2-day follow-up: >2 days past the due date
b. 7-day follow-up: >7 days past the due date
c. Hospital event form: >30 days past the due date
d. 90-day follow up: >30 days past the due date

Protocol Deviation

A Protocol Deviation is a minor deviation from the protocol that affects the conduct of the trial in a minor way. This includes any deviation from the trial protocol that is not listed as a Protocol Violation. Examples of Deviations are given below but this is not exhaustive.

Follow-up assessments are performed (as opposed to submitted) outside the specified time as shown below:

a. 2-day follow-up: >1day past the due date
b. 7-day follow-up: >3days past the due date
c. Hospital event form: >7days past the due date
d. 90-day follow-up: >7 days past the due date

Review of Protocol Violations and Deviations

Protocol Violations will be reviewed annually by both the Data Safety Monitoring Committee (using unblinded data) and the Trial Steering Committee (with blinding to treatment assignment).

The list of protocol violations and deviations will be updated, as necessary, in a working practice document which will be uploaded and available on the trial website.

ADVERSE EVENTS

Definitions

An adverse event is any unfavourable and unintended sign, symptom, syndrome or illness that develops or worsens during the period of observation in the study.

An AE does include a / an:

1. Exacerbation of a pre-existing illness.
2. Increase in frequency or intensity of a pre-existing episodic event or condition.
3. Condition detected or diagnosed after medicinal product administration even though it may have been present prior to the start of the study.
4. Continuous persistent disease or symptoms present at baseline that worsen following the start of the study.

An AE does not include a / an:

1. Medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion); but the condition that lead to the procedure is an AE.
2. Pre-existing disease or conditions present or detected at the start of the study that did not worsen.
3. Situations where an untoward medical occurrence has not occurred (e.g., hospitalisations for cosmetic elective surgery, social and / or convenience admissions).
4. Disease or disorder being studied or sign or symptom associated with the disease or disorder unless more severe than expected for the participant's condition.
5. Overdose of concurrent medication without any signs or symptoms.

A Serious Adverse Event (SAE) is any adverse event occurring following study mandated procedures, having received the IMP or placebo that results in any of the following outcomes:

1. Death
2. A life-threatening adverse event
3. Inpatient hospitalisation or prolongation of existing hospitalisation
4. A disability / incapacity
5. A congenital anomaly in the offspring of a participant

Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined using the criteria above. Hence, a severe AE need not necessarily be serious.

Serious adverse events are common in haemorrhagic stroke, for a full list of expected SAE that are not subject to expedited reporting, investigators should refer to Appendix A.
As the IMP is administered once and has a short half life, serious adverse events occurring within the first 7 days will be assessed for seriousness, expectedness and causality. In addition fatal SAEs and safety outcome events (VTE, recurrent stroke, TIA, MI, PAD and seizures) will be reported until day 90.

Causality

Not related or improbable: a clinical event including laboratory test abnormality with temporal relationship to trial treatment administration which makes a causal relationship incompatible or for which other drugs, chemicals or disease provide a plausible explanation**.** This will be counted as “unrelated” for notification purposes.

Possible: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, but which could also be explained by other drugs, chemicals or concurrent disease. This will be counted as “related” for notification purposes.

Probable: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, and is unlikely to be due to other drugs, chemicals or concurrent disease. This will be counted as "related" for notification purposes.

Definite: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, and which can definitely not be attributed to other causes. This will be counted as "related" for notification purposes.

An AE whose causal relationship to the study IMP is assessed by the Chief Investigator as "possible", "probable", or "definite" is an Adverse Drug Reaction.

With regard to the criteria above, medical and scientific judgment shall be used in deciding whether prompt reporting is appropriate in that situation.

Reporting of adverse events

Participants will be asked to contact the study site immediately in the event of any serious adverse event. All adverse events will be recorded and closely monitored until resolution, stabilisation, or until it has been shown that the study medication or treatment is not the cause. The Chief Investigator (delegated the sponsor's responsibilities) shall be informed immediately (within 24 hours) of any serious adverse events, occurring within the first 7 days and shall determine seriousness and causality in conjunction with any treating medical practitioners.

In the event of a pregnancy occurring in a trial participant or the partner of a trial participant monitoring shall occur during the pregnancy and after delivery to ascertain any trial related adverse events in the mother or the offspring. Where it is the partner of trial participant consent will be obtained for this observation from both the partner and her medical practitioner.

All serious adverse events occurring within the first 7 days will be recorded and reported to the MHRA and REC as part of the annual reports. SUSARs will be reported within the statutory timeframes to the MHRA and REC as stated below. The Chief Investigator shall be responsible for all adverse event reporting.

SUSARs

A serious adverse event that is either sudden in its onset, unexpected in its severity and seriousness or not a known side effect of the IMP *and* related or suspected to be related to the IMP is classed as Suspected Unexpected Serious Adverse Reaction and requires expedited reporting as per the clinical trials regulations.

All serious adverse events that fall or are suspected to fall within these criteria shall be treated as a SUSAR until deemed otherwise.

The event shall be reported immediately (within 24 hours) of knowledge of its occurrence to the Chief Investigator.

The Chief Investigator will:

- Assess the event for seriousness, expectedness and relatedness to the study IMP
- Take appropriate medical action, which may include halting the trial and inform the Sponsor of such action
- If the event is deemed a SUSAR, shall, within seven days, enter the required data on the MHRA's eSUSAR web site.
- Shall inform the REC using the reporting form found on the NRES web page within 7 days of knowledge of the event
- Shall, within a further eight days send any follow-up information and reports to the MHRA and REC.
- Make any amendments as required to the study protocol and inform the ethics and regulatory authorities as required

Trial Treatment Related SAEs

A serious adverse event that is unexpected in its severity and seriousness *and* deemed directly related to or suspected to be related to the trial treatment but not the IMP shall be reported to the ethics committee that gave a favourable opinion as stated below.

The event shall be reported immediately of knowledge of its occurrence to the Chief Investigator.

The Chief Investigator will:

- Assess the event for seriousness, expectedness and relatedness to the trial treatment.
- Take appropriate medical action, which may include halting the trial and inform the Sponsor of such action.
- If the event is deemed related to the trial treatment shall inform the REC using the reporting form found on the NRES web page within 7 days of knowledge of the event.
- Shall, within a further eight days send any follow-up information and reports to the REC.
- Make any amendments as required to the study protocol and inform the REC as required

Participant removal from the study due to adverse events

Any participant who experiences an adverse event may be withdrawn from the study at the discretion of the Investigator. Should the participant not receive the complete intervention due to, for example, an adverse event, they will remain in the study until the end of the trial at day 90 (±7), as completeness of follow-up is essential. However, should they wish to do so, any participant is free to withdraw from the trial at any time and without giving reason.

ETHICAL AND REGULATORY ASPECTS

ETHICS COMMITTEE AND REGULATORY APPROVALS

The trial will not be initiated before the protocol, informed consent forms and participant and GP information sheets have received approval / favourable opinion from the Medicines and Healthcare products Regulatory Agency (MHRA), Research Ethics Committee (REC), and the respective National Health Service (NHS) Research & Development (R&D) department. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant and GP information sheets (if appropriate) have been reviewed and received approval / favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the MHRA, R&D and REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, in accordance with the Medicines for Human Use Regulations, Statutory Instrument 2004, 1031 and its subsequent amendments and the Department of Health Research Governance Framework for Health and Social care, 2005.

INFORMED CONSENT AND PARTICIPANT INFORMATION

The process for obtaining participant informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The investigator or their nominee and the participant or other legal representative shall both sign and date the Consent Form, if possible this will be before enrolment into the study. If this is not possible, where permission for enrolment is given verbally or by a relative or legal representative, written consent will be obtained as soon as practicable.

The participant will receive a copy of the signed and dated forms and the original will be retained in the Trial Master File. A second copy will be filed in the participant's medical notes and a signed and dated note made in the notes that informed consent was obtained for the trial.

The decision regarding participation in the study is entirely voluntary. The investigator or their nominee shall emphasize to them that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. No trial-specific interventions will be done before informed consent has been obtained.

The investigator will inform the participant of any relevant information that becomes available during the course of the study, and will discuss with them, whether they wish to continue with the study. If applicable they will be asked to sign revised consent forms.

If the Informed Consent Form is amended during the study, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Informed Consent Form by the REC and use of the amended form (including for ongoing participants).

RECORDS

Drug accountability

Drug supplies will be kept in a secure, limited access storage area under the storage conditions specified by Pharmacy.

The investigator and the local site pharmacist shall maintain records of the study drug's delivery to the pharmacy, an inventory at the site, the distribution to each participant, and the return to the pharmacy or alternative disposition of unused study drugs. These records will include dates, quantities received, batch / serial numbers, expiration dates, and the unique code numbers (patient trial number) assigned to the trial participant. Investigators and /or the local site pharmacists will maintain records that document adequately that the participants were provided with the correct study medication. These records will be part of each patient's Case Report Form (CRF). All study medication packs and bottles received by the pharmacy shall be accounted for.

Case Report Forms

Each participant will be assigned a trial identity code number (country number, centre number and randomisation number), allocated at randomisation, for use on CRFs other trial documents and the electronic database. The documents and database will also use their initials (of first and last names separated by a hyphen or a middle name initial when available). The date of birth (dd/mm/yy) is entered into the database once for the use of data verification and is not visible when entering study data.

CRFs will be treated as confidential documents and held securely in accordance with regulations. The investigator will make a separate confidential record of the participant's name, date of birth, local hospital number or NHS number, and Participant Trial Number (the Trial Recruitment Log), to permit identification of all participants enrolled in the trial, in case additional follow-up is required.

CRFs shall be restricted to those personnel approved by the Chief or local Principal Investigator and recorded on the 'Trial Delegation Log.'

All paper forms shall be filled in using black ballpoint pen. Errors shall be lined out but not obliterated by using correction fluid and the correction inserted, initialled and dated.

The Chief or local Principal Investigator shall sign a declaration ensuring accuracy of data recorded in the CRF.

Source documents

Source documents shall be filed at the investigator's site and may include but are not limited to, consent forms, current medical records, laboratory results and pharmacy records. A CRF may also completely serve as its own source data. Only trial staff as listed on the Delegation Log shall have access to trial documentation other than the regulatory requirements listed below.

Direct access to source data / documents

The CRF and all source documents, including progress notes and copies of laboratory and medical test results shall made be available at all times for review by the Chief Investigator, Sponsor's designee and inspection by relevant regulatory authorities (MHRA).

DATA PROTECTION

All trial staff and investigators will endeavour to protect the rights of the trial's participants to privacy and informed consent, and will adhere to the Data Protection Act, 1998. The CRF will only collect the minimum required information for the purposes of the trial. CRFs will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the trial staff and investigators and relevant regulatory authorities (see above). Computer held data including the trial database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method).
Information about the trial in the participant's medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information.

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

QUALITY ASSURANCE & AUDIT

INSURANCE AND INDEMNITY

Insurance and indemnity for trial participants and trial staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but trial participants may have recourse through the NHS complaints procedures.

The University of Nottingham as research Sponsor indemnifies its staff, research participants and research protocols with both public liability insurance and clinical trials insurance. These policies include provision for indemnity in the event of a successful litigious claim for proven non-negligent harm.

TRIAL CONDUCT

Trial conduct will be subject to systems audit of the Trial Master File for inclusion of essential documents; permissions to conduct the trial; Trial Delegation Log; CVs of trial staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, correct randomisation, timeliness of visits); adverse event recording and reporting; drug accountability, pharmacy records and equipment calibration logs.
The Trial Coordinator, or where required, a nominated designee of the Sponsor, shall carry out a site systems audit at least yearly and an audit report shall be made to the Trial Steering Committee.

TRIAL DATA

Monitoring of trial data shall include confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. The Trial Coordinator, or where required, a nominated designee of the Sponsor, shall carry out monitoring of trial data as an ongoing activity.

Entries on CRFs will be verified by inspection against the source data. A sample of CRFs (10% or as per the trial risk assessment) will be checked on a regular basis for verification of all entries made. In addition the subsequent capture of the data on the trial database will be checked. Where corrections are required these will carry a full audit trail and justification.

Trial data and evidence of monitoring and systems audits will be made available for inspection by the regulatory authority as required.

RECORD RETENTION AND ARCHIVING

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Code of Research Conduct and Research Ethics, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The Trial Master File and trial documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at the University of Nottingham. This archive shall include all trial databases and associated meta-data encryption codes.

DISCONTINUATION OF THE TRIAL BY THE SPONSOR

The Sponsor reserves the right to discontinue this trial at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice from the Trial Steering Committee and Data Monitoring Committee as appropriate in making this decision.

STATEMENT OF CONFIDENTIALITY

Individual participant medical information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted above.

Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

Data generated as a result of this trial will be available for inspection on request by the participating physicians, the University of Nottingham representatives, the REC, local R&D Departments and the regulatory authorities.

PUBLICATION AND DISSEMINATION POLICY

Reporting, dissemination and notification of the results

Trial results will be published in a peer reviewed academic journal. Reporting will be in compliance with CONSORT [25, 26] recommendations. The focus of that article will be to discuss the effectiveness and safety of tranexamic acid in haemorrhagic stroke. When the study is complete summary findings will post on the support group website. Findings will also be presented at conferences such as UK Stroke Forum, European Stroke Conference and World Stroke Congress.

Policy for publication and authorship

The trial results will be published by named members of the trial team, on behalf of the TICH 2 Trial Collaborative Group. Members of the collaborative group will be listed in the publication, based on contributorship. Any secondary publication may be published by named individuals, but with appropriate acknowledgement of the collaborative group.

USER AND PUBLIC INVOLVEMENT

The project and protocol was discussed at the Nottingham Stroke Survivor Consumer Group meeting on January 30th 2012. The group reviewed the trial design and were highly supportive of the project. A member of the Group (Malcolm Jarvis) was involved in the subsequent designing of the definitive study and is a lay member of the Trial Steering Committee. The Stroke Consumer Group will also help with dissemination of the results via the user group website. The consent proceedure was reviewed and disucssed with the group on July 30th 2012, the group feel strongly that potential participants should not be denied access to the study because they lack capacity, have no relative present or an independent doctor cannot be accessed. The group, all of whom are stroke survivors, would like the treating stroke physician to be able enroll patients if the stroke physician feels it is in the patients best interest.

STUDY FINANCES

Funding source

This study is funded by NIHR HTA project code 11_129_109.

Participant stipends and payments

Participants will not be paid to participate in the trial. Travel expenses will be offered for any hospital visits in excess of usual care.

SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator: (name)_____

Signature:_____

Date: _____

Trial Statistician: (name)_____

Signature:_____

Date: _____

Trial Pharmacist: (name)_____

Signature:_____

Date: _____

REFERENCES

1. Steiner T, Bosel J. Options to restrict hematoma expansion after spontaneous intracerebral hemorrhage. Stroke. 2010;41:402-409
2. Delgado Almandoz JE, Yoo AJ, Stone MJ, Schaefer PW, Goldstein JN, Rosand J, Oleinik A, Lev MH, Gonzalez RG, Romero JM. Systematic characterization of the computed tomography angiography spot sign in primary intracerebral hemorrhage identifies patients at highest risk for hematoma expansion. Stroke. 2009;40:2994-3000
3. Delgado Almandoz JE, Yoo AJ, Stone MJ, Schaefer PW, Oleinik A, Brouwers HB, Goldstein JN, Rosand J, Lev MH, Gonzalez RG, Romero JM. The spot sign score in primary intracerebral hemorrhage identifies patients at highest risk of in-hospital mortality and poor outcome among survivors. Stroke. 2010;41:54-60
4. Ederies A, Demchuk A, Chia T, Gladstone DJ, Dowlatshahi D, BenDavit G, Wong K, Symons SP, Aviv RI. Postcontrast ct extravasation is associated with hematoma expansion in cta spot negative patients. Stroke. 2009;40:1672-1676
5. Anderson CS, Huang Y, Arima H, Heeley E, Skulina C, Parsons MW, Peng B, Li Q, Su S, Tao QL, Li YC, Jiang JD, Tai LW, Zhang JL, Xu E, Cheng Y, Morgenstern LB, Chalmers J, Wang JG, for the INTERACT Investigators. Effects of early intensive blood pressure-lowering treatment on the growth of hematoma and perihematomal edema in acute intracerebral hemorrhage: The intensive blood pressure reduction in acute cerebral haemorrhage trial (interact). Stroke. 2010;41:307-312
6. Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) investigators. Antihypertensive treatment of acute cerebral hemorrhage. Critical Care Medicine. 2010;38:637-648
7. Delcourt C, Huang Y, Wang J, Heeley E, Lindley R, Stapf C, Tzourio C, Arima H, Parsons M, Sun J, Neal B, Chalmers J, C; A, Investigators. I. The second (main) phase of an open, randomised, multicentre study to investigate the effectiveness of an intensive blood pressure reduction in acute cerebral haemorrhage trial (interact2). International Journal of Stroke. 2010;5:110-116
8. Mendelow AD GB, Fernandes HM, Murray GD, Teasdale GM, Hope DT, Karimi A, Shaw MD, Barer DH; STICH investigators. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the international surgical trial in intracerebral haemorrhage (stich): A randomised trial. Lancet. 2005;365:387-397
9. Mendelow A, STICH2 investigators. Http://research.Ncl.Ac.Uk/stich2/.
10. Mayer SA, Brun NC, Begtrup K, Broderick JP, Davis S, Diringer MN, Skolnick BE, Steiner T, for the Recombinant Activated Factor VII intracerebral Hemorrhage Trial Investigators. Recombinant activated factor vii for acute intracerebral hemorrhage. New Engl J Med. 2005;352:777-785
11. Al-Shahi Salman R. Haemostatic drug therapies for acute spontaneous intracerebral haemorrhage. Cochrane Database of Systematic Reviews 2009 Issue 4.
12. Creutzfeldt CJ WJ, Longstreth WT Jr, Becker KJ, McPharlin TO, Tirschwell DL. Prior antiplatelet therapy, platelet infusion therapy, and outcome after intracerebral hemorrhage. J Stroke Cerebrovasc Dis. 2009 18:22108
13. Dunn CJ GK. Tranexamic acid: A review of its use in surgery and other indications. Drugs. 1999;57:1005-1032

14. Roberts I, Shakur H, Ker K, Coats T, on behalf of the CRASH-2 Trial collaborators. Antifibrinolytic drugs for acute traumatic injury. Cochrane Database of Systematic Reviews. 2011;Issue 1. Art. No.: CD004896
15. CRASH-2 trial collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (crash-2): A randomised, placebo-controlled trial. Lancet. 2010;Epub Jun 14
16. The CRASH-2 collaborators. The importance of early treatment with tranexamic acid in bleeding trauma patients: An exploratory analysis of the crash-2 randomised controlled trial. Lancet. 2011;377
17. CRASH-2 Collaborators (Intracranial Bleeding Study). Effect of tranexamic acid in traumatic brain injury: A nested randomised, placebo controlled trial (crash-2 intracranial bleeding study). BMJ. 2011;343
18. Surakrant Y. Warawut K PP, Bandit T, Nakornchai P, Pisake L. Tranexamic acid for preventing progressive intracranial hemorrage in adults with traumatic brain injury. National Neurotrauma Symposium 2010
19. Yvo Roos GR, Marinus Vermeulen, Ale Algra, and Jan van Gijn. Antifibrinolytic therapy for aneurysmal subarachnoid hemorrhage: A major update of a cochrane review Stroke. 2003;34:2308-2309
20. Ojacastro MF TM, Dulos ID, Tabuena RP. . Efficacy of tranexamic acid in reducing hematoma volume in patients with hypertensive intracerebral hemorrhage.2008;3 suppl 1:197-8. International Journal of Stroke. 2008;3(Suppl):197-198
21. Sorimachi T FY, Morita K, Tanaka R. . Rapid administration of antifibrinolytics and strict blood pressure control for intracerebral hemorrhage. 2005;57(5):837-44. Neurosurgery. 2005;57:837-844
22. Roos Y. Editorial:Tranexamic acid for traumatic brain injury. BMJ. 2011;343:d3958
23. Weir CJ, Lees KR. Comparison of stratification and adaptive methods for treatment allocation in an acute stroke clinical trial. Stat.Med. 2003;22:705-726
24. The Optimising Analysis of Stroke Trials (OAST) Collaboration. Should stroke trials adjust functional outcome for baseline prognostic factors? Stroke. 2009;40:888-894
25. Moher D, Hopewell S, Schulz KF, Montori V, Gotzsche PC, Devereaux PJ, Elbourne D, Egger M, Altman DG. Consort 2010 explanation and elaboration: Updated guidelines for reporting parallel group randomised trials. BMJ. 2010;340:c869
26. Schulz KF, Altman DG, Moher D. Consort 2010 statement: Updated guidelines for reporting parallel group randomised trials. BMJ. 2010;340:c332

Appendix A: Expected events not subject to expedited reporting

After tranexamic acid the following events are expected and therefore not subject to expedited reporting:

== Gastro-intestinal ==
Abdominal pain
Diarrhoea
Gastrointestinal disturbance
Nausea
Vomiting
== Cardiovascular ==
Arterial thrombosis any site
Deep vein thrombosis (DVT)
Collapse
Hypotension
Ischaemic stroke
Peripheral artery embolism
Pulmonary embolism (PE)
Tachycardia
Venous thrombosis any site

== Central nervous system ==
Convulsions
Disturbance in colour vision
Dizziness
Headache
Seizure

== General ==
Anaphylaxis
Fatigue
Flushing
Hypersensitivity including oropharangeal swelling, urticaria, angiodema
Musculoskeletal pains
Rash

After haemorrhagic stroke the following events are expected and therefore not subject to expedited reporting:

== Cardiovascular ==
Acute coronary syndrome (ACS)
Atrial fibrillation (AF)
Bradycardia
Cardiac arrest
Cardiac failure
Cardiac dysrhythmia
Carotid endarterectomy
Chest pain
Collapse
Deep vein thrombosis (DVT)
Hypertension

Hypotension
Myocardial infarction (MI)
Pulmonary embolism (PE)
Sudden cardiac death
Systemic embolism
Tachycardia
Unstable angina

== Central nervous system ==
Agitation
Anxiety
Cerebral oedema
Complication of initial stroke
Dementia
Depression
Dysphagia
Extension of initial haemorrhagic stroke – haematoma expansion
Extension of initial ischaemic stroke –infarct expansion
Haemorrhagic transformation of infarct (HTI)
Headache
Intracerebral bleed
Recurrent stroke - ischamaemic
Sedation
Seizure
Sensory loss
Transient ischaemic attack (TIA)
Vertigo
Visual loss
Weakness

== Gastro-intestinal ==
Abdominal pain
Cholecystitis
Constipation
Diarrhoea
Dysphagia
Feeding tube insertion and/or complication
Gall Stones
Gastrointestinal bleed
Gastrointestinal disturbance
Incontinence, faecal
Heartburn
Hepatitis
Maelena
Nausea
Oral ulceration
Pancreatitis
Vomiting
Weight loss

== Genito-urinary ==
Sexual dysfunction

Incontinence, urinary
Renal impairment
Urinary retention
Urinary tract infection (UTI)

== Haematological ==
Anaemia
Leukopenia
Thrombocytopenia

== Miscellaneous ==
Acid base disturbance
Bacteraemia
Diaphoresis
Electrolyte disturbance
Fall
Fatigue
Hyperglycaemia
Hyperuricaemia
Hypoglycaemia
Lymphadenopathy
Malignancy/Cancer –new diagnosis
Muscle twitching
Osteoarthritis

== Respiratory ==
Asthma
Bronchitis
Bronchospasm
Chest infection
Chronic obstructive pulmonary disease (COPD)
Emphysema
Exacerbation of COPD
Hypoxia
Pleural effusions
Pneumonia
Pulmonary embolism (PE)
Shortness of breath