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ISRCTN97695350

TRANEXAMIC ACID FOR INTRACEREBRAL HAEMORRHAGE: TICH-3 TRIAL

Norway Investigators

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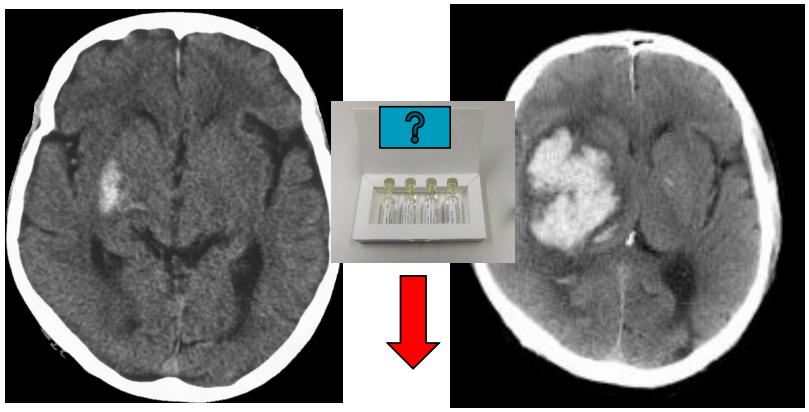
On behalf TICH-3 Trial Team

V1 15/02/24

Intracerebral Haemorrhage

Intracerebral haemorrhage can be devastating

- Haematoma expansion (HE) is common occurs early and is main cause of death
- Predictors – time, haematoma volume, anticoagulation and antiplatelets



- Drugs that stop bleeding (such as tranexamic acid), are effective in other bleeding conditions and could potentially reduce haematoma expansion

TICH-3: does giving tranexamic acid early after ICH prevent haematoma expansion and reduce death and disability

Tranexamic acid in other trials

- TXA acts through antifibrinolytic mechanisms
- CRASH-2 In patients with traumatic haemorrhage (including from head injuries), TXA significantly reduces death due to bleeding and all-cause mortality, with no increase in vascular occlusive events.
- Analysis of the CRASH-2 trial showed that because death due to bleeding occurred early after trauma, hyperacute administration of TXA was necessary for patients to receive any benefit.
- A meta-analysis of TXA in traumatic intracranial haemorrhage showed that it was associated with a significant reduction in subsequent intracranial bleeding.
- CRASH-3, reduced head injury related deaths in patients with traumatic brain injury, with early treatment more effective than later treatment.
- In TICH-2 (in 2325 patients with ICH within 8 hours of onset) TXA was safe, reduced haematoma expansion and early death. It did not significantly change outcome at 3 months
- Tranexamic acid is inexpensive, easy to administer, seems to be safe, and is widely available, so even a modest treatment effect could have an important impact on the global scale.

CRASH-2 https://doi.org/10.1016/S0140-6736(10)60835-5, CRASH-3 https://doi.org/10.1016/S0140-6736(19)32233-0 TICH-2 https://doi.org/10.1016/S0140-6736(18)31033-X

TICH-3 Synopsis

ICH emergency condition - facilitate rapid enrolment

Design: Double blind randomised clinical trial, pragmatic streamlined design

Participants: Inclusion: Adults (≥ 18 years) within < 4.5 hours of stroke onset

Exclusion: Massive ICH (Glasgow Coma Scale < 5 or Haematoma Volume > 60ml)

Consent: Rapid emergency process – oral consent followed by written consent

Intervention: Tranexamic 1g IV bolus added to 100ml sodium chloride over 10 mins then 1g added to 250ml sodium chloride infusion over 8hrs or saline by identical regime Given alongside standard ICH care, including BP lowering as per clinical guidelines[1]

Randomisation: Simple - use the lowest available treatment pack number

Primary Outcome: Early death (day 7)

Secondary outcome: Function-Shift analysis modified Rankin Scale day at 6 months

Sample size: 5500 (3900 UK and 1900 Internationally)

Cost/funder: UK NIHR plus others internationally

Duration: 7.25 years - Aim 5 yrs UK recruitment note STOP GO DECISION OCT 23

1: https://www.nice.org.uk/guidance/ng128/chapter/Recommendations

TICH-3 Eligibility Criteria

Inclusion criteria

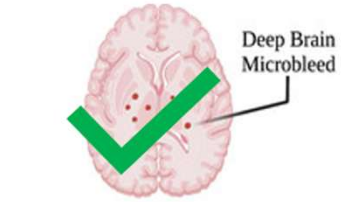
- Spontaneous ICH (confirmed on brain imaging) < 4.5 hours of onset

It is not necessary to exclude underlying vascular lesions – but if they are known please do not include.

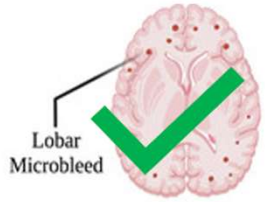
IMP treatment should be started within the 4.5 hours inclusion window.

Exclusion criteria

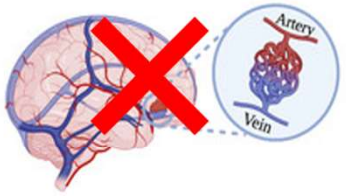
- Known indication for TXA treatment (e.g. traumatic brain injury) *or* contra-indication for TXA treatment (e.g. active seizures) *in view of treating physician*
- Patient known to be taking therapeutic anticoagulation with warfarin or low molecular weight heparin at time of enrolment. **(DOAC is permitted)**
- Massive ICH (usually when haematoma volume > 60ml HV – **only estimation is needed (+/- 10%)**
- Severe coma, Glasgow Coma Scale <5, palliative (end of life) care



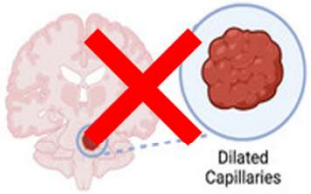
Hypertension Microangiopathy



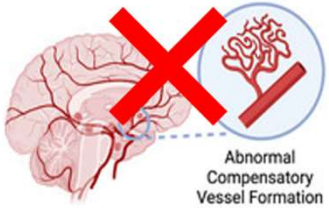
Cerebral Amyloid Angiopathy



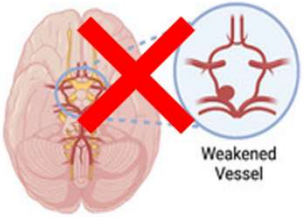
Arteriovenous Malformation



Cavernous Angioma



Moyamoya Disease



Aneurysm

TICH-3: Patients taking DOACs

Which DOACs can the patients be on to be recruited for TICH 3?

- **Direct thrombin inhibitor** – Dabigatran
- **Factor 10a inhibitor** – Apixaban, rivaroxaban, edoxaban

If patients on DOAC with ICH are enrolled to TICH-3 can they still have reversal agents?

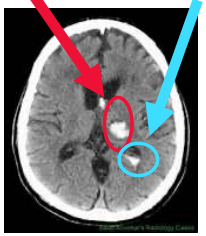
- Yes, all patients should receive standard care, and be treated as per local DOAC ICH guidelines and given anticoagulation reversal agent in accordance with local guidance i.e Idarucizumab or PCC.
  Please ensure you document which reversal agents were given in eCRF
- **Can a reversal agent/PCC be administered at the same time as TICH-3 treatment?**
  Yes - do not delay starting the TICH-3 trial treatment, reversal agent/PCC can be administered at the same time as the TICH-3 trial treatment as long as through separate IV cannula.
- **Types of anticoagulation (blood thinners) that cannot be included:**

1. warfarin - exclude if INR shows levels high (>1.5). Cannot include unless the INR is sub therapeutic
2. LWMH - low molecular weight heparins at treatment dose eg for treating a DVT or PE. Note if LMWH is being used prophylactically at low dose to prevent DVT and PE these patients can be included in TICH-3

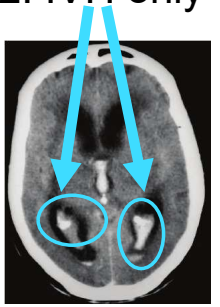
Eligibility: Frequently asked questions

- If time of stroke onset is unknown?
  Patient can be enrolled if presenting within 4.5 hours of discovery if HV < 60mls on CT scan.
- Can patients with intraventricular haemorrhage (IVH) be enrolled?
  Yes, so long as they have intracerebral haemorrhage, (fig 1) do not have other exclusion criteria. Isolated IVH (fig 2) should not be included.
- Can patient be enrolled if they are a candidate for neurosurgery?
  Yes, neurosurgery is not an exclusion.
- Can patient be enrolled if they have a DNAR/from care home/already dependent?
  Yes, so long as they are still for active care and consent is obtained
- Can patients with recurrent bleeds be enrolled? Yes, it is likely that most patients will have an arteriopathy due to hypertension or cerebral amyloid angiopathy.
- Can a nurse consultant assess eligibility? Confirming eligibility is defined as a medical decision, so must be undertake by a medically qualified doctor under the clinical trials regulations.

1. ICH and IVH



2. IVH only



Final decision on eligibility rests with treating physician

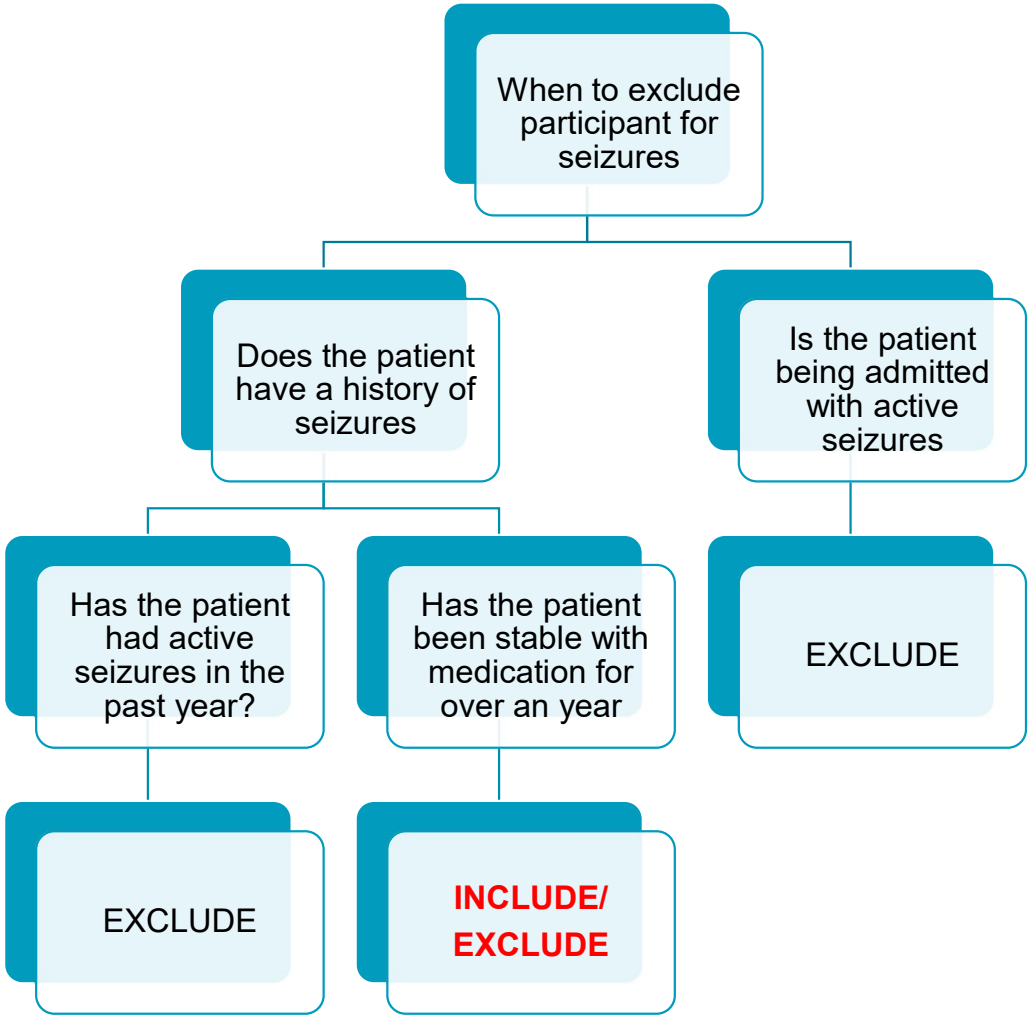
Eligibility: seizures

- Eligibility for TICH 3 in patients with a history of seizures is at the discretion of the treating physician

- If you have an eligibility query please call the emergency phone number

+44 (0)7725 580 092 +44 (0)7736 843 592

+44 (0)7798 670 726 +44 (0)7810 540 604

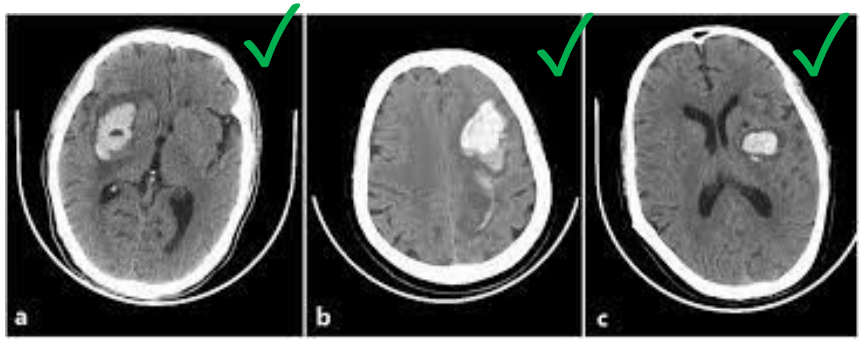


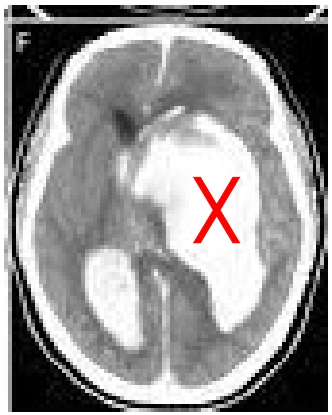
Size matters – but estimates are ok!

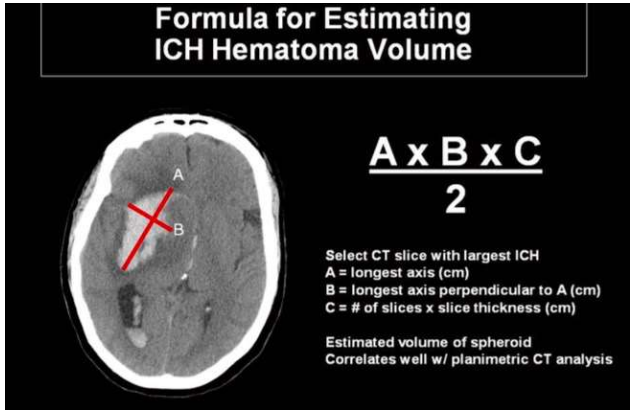
Exclude patients with massive haematoma (usually > 60ml)

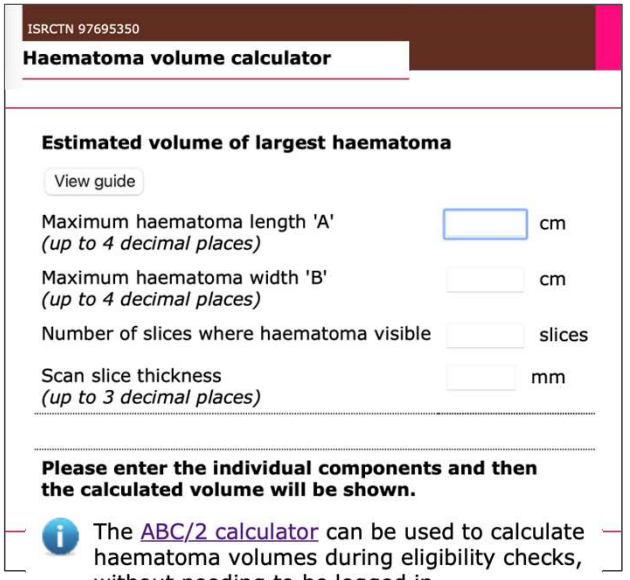
1. If CT scan uses automated haematoma volume software – patient can be enrolled if HV not greater than 60mls (+/- 10%)
2. Calculate HV manually using TICH-3 HV=ABC/2 calculator on the website[1] or alternatives e.g. mdcalc app[2] *(ignore 25 – 75% calculator and count all slices where ICH visable due to time critical nature)*
3. If ABC/2 not possible: measure the maximum length of the haematoma. Exclude - if max length A > 5cm

- ❖Do not include IVH volume in calculation
- ❖HV can be estimated by anyone trained to do so









Emergency Consent Process

Rapid consent process, participants or relatives provide verbal consent

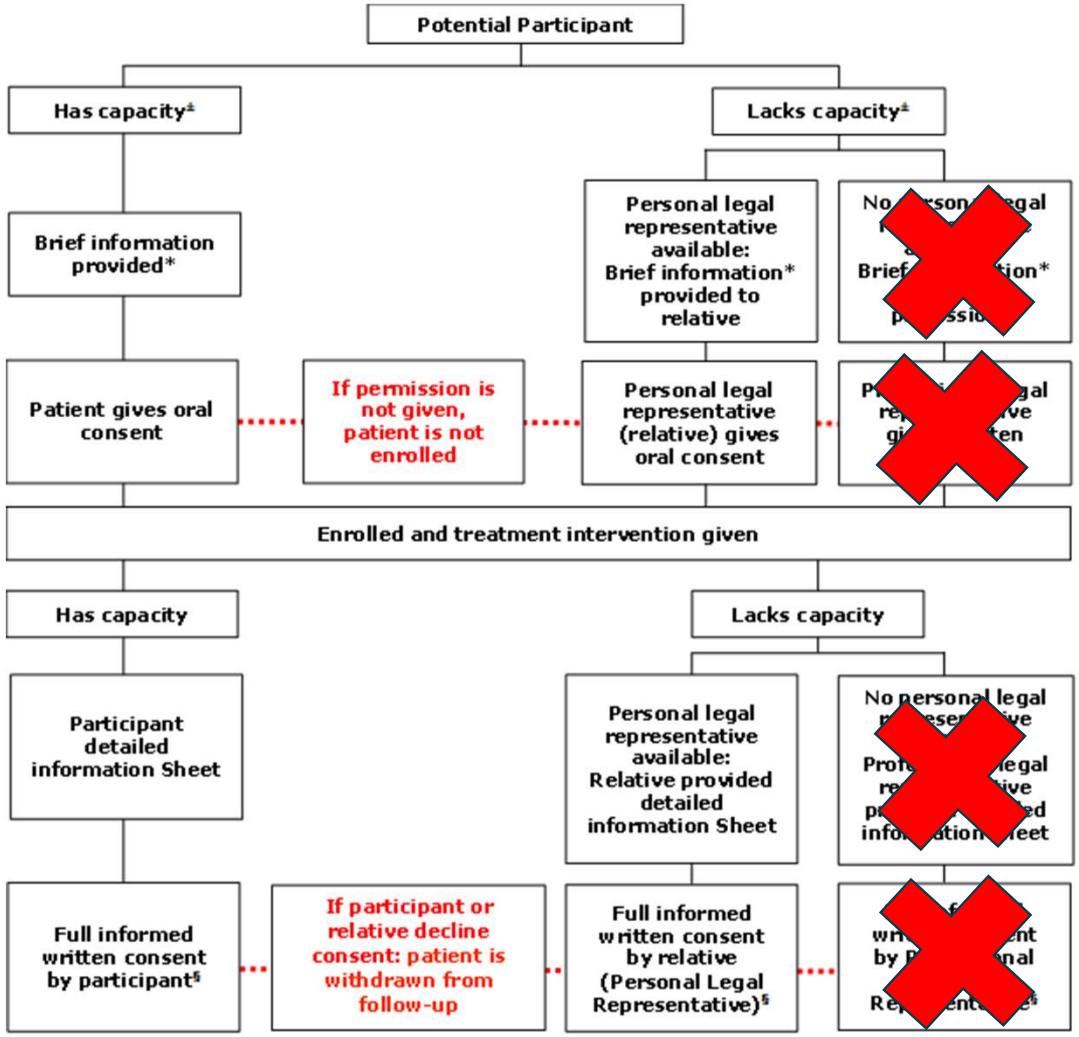
Full informed written consent to be obtained later after administration of IMP

Hierarchy approach

Patient has capacity – gives oral consent

1. Patient does not have capacity – relative or close friend likely to know patient wishes provides oral consent
2. Patient does not have capacity and no relatives available – contact relatives via telephone to obtain consent.
3. *Patient does not have capacity and no relatives available – independent doctor provides written consent*

The person taking consent must be appropriately trained and on the delegation log



Remote recruitment

Eligibility

Confirming eligibility is defined as a medical decision, so must be undertake by a medically qualified doctor under the clinical trials regulations.

- The clinician does not need to be on the TICH-3 delegation log to confirm eligibility however they must be on the delegation log to take enrolment consent (code J).

Consent

Verbal consent is taken in the first instance, to receive the trial treatment, there would not be a consent form to sign if the patient has capacity to give consent or there is a relative giving consent on behalf of the patient.

- Oral consent can be taken remotely if the enrolling investigator is not on site either on the phone or via telemedicine.

- Oral consent can be given remotely by a relative, if the patient does not have capacity.

Eligibility assessment and method of obtaining consent must be documented in the patients' medical notes.

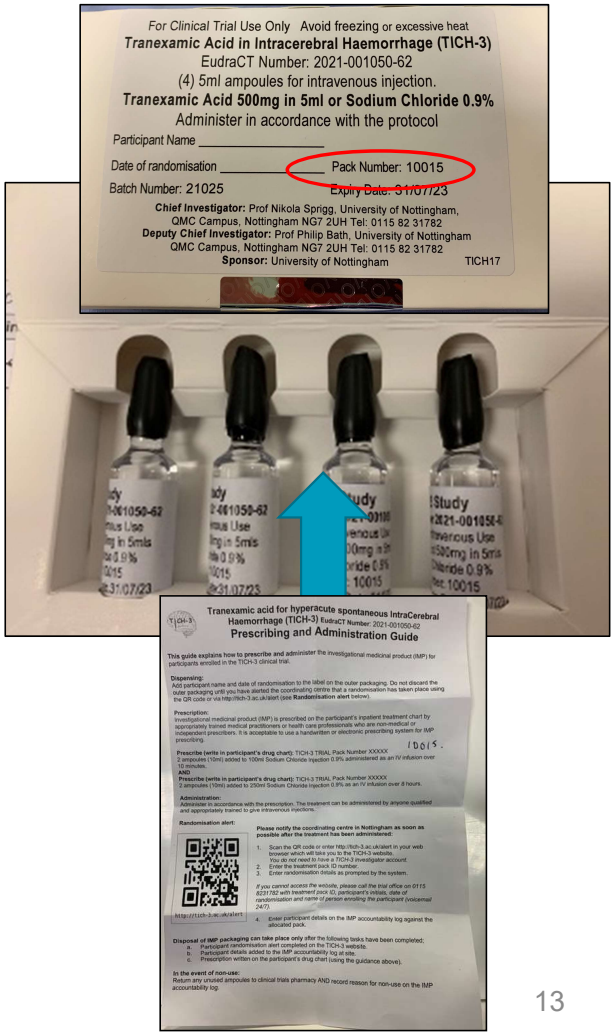
Out of hours recruitment

The process is very simple for out of hours recruitment

1. **Confirm eligibility** – can be completed by any clinician they do not need to be on the TICH-3 delegation log
2. **Take initial oral enrolment consent** – consent process just needs to be documented in the medical record. We also allow remote recruitment over phone/telemedicine. If no relatives, then ask an independent doctor and use brief consent form to document.
   - Person taking consent must be appropriately trained and authorised on the TICH-3 deleagtion log with code J applied (enrolment consent for CTIMPs)
3. **Prescribing and administration of the IMP** can be completed by anyone appropriately trained to do so, they do not need to be GCP trained or on the TICH-3 delegation log
4. **Complete QR code recruitment alert** – this is within each treatment pack and can be completed by anyone (do not need to be on delegation log, no logins required to complete the form to alert the team a recruitment has taken place)
5. **When the research team is next on site** you will see the recruitment alert in your emails to know a participant was recruited and then you would find the participant to take the follow-on written consent, add participant to website and begin data entry

Randomisation: open lowest pack number

- Blinded treatment packs will be randomly assigned to sites in blocks of 6 treatment packs
- TICH-3 will use simple randomisation
- After confirming eligibility and obtaining consent the investigator **randomises the patient by selecting and opening the treatment pack with the lowest pack number.**
- The prescribing and administration guide can be found inside each treatment pack.
- Due to emergency nature of trial randomisation is notified to the coordinating centre after the IMP has been administered by completing the randomisation alert (guidance for this is within the prescribing and administration guide).



Prescribing and Administering the IMP

Prescribing the IMP

Investigational medicinal product (IMP) is prescribed on the participant's inpatient treatment chart by appropriately trained medical practitioners or health care professionals who are non-medical or independent prescribers. It is acceptable to use a handwritten or electronic prescribing system for IMP prescribing.
Do not need to be on delegation log or GCP trained to prescribe.

Prescribe (write in participants drug chart):

TICH-3 - TRIAL Pack Number XXXXX

TRANEXAMIC ACID OR PLACEBO

2 ampoules (10ml) added to 100ml Sodium Chloride Injection 0.9% administered as an IV infusion over 10 minutes.

AND

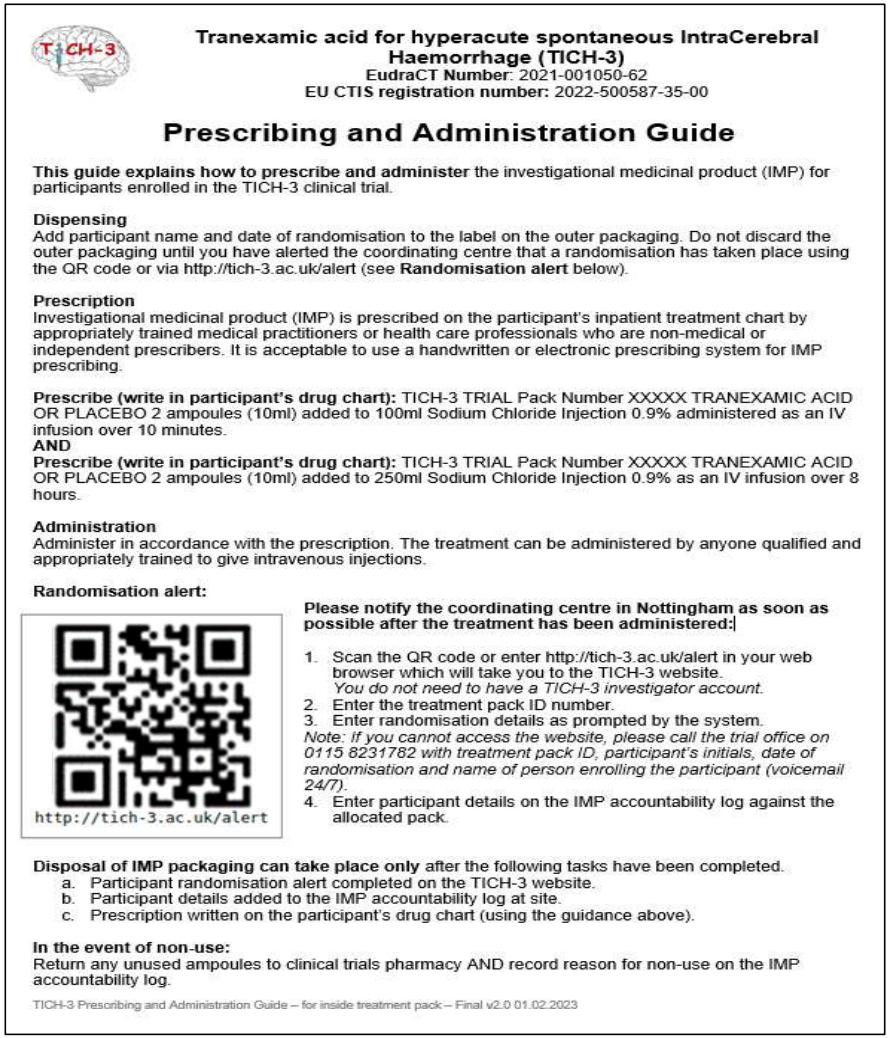
TICH-3 TRIAL Pack Number XXXXX

TRANEXAMIC ACID OR PLACEBO

2 ampoules (10ml) added to 250ml Sodium Chloride Injection 0.9% as an IV infusion over 8 hours.

Administering the IMP

Administer in accordance with the prescription. The treatment can be administered by anyone qualified and appropriately trained to give intravenous injections. ***Do not need to be on delegation log or GCP trained to administer.***



Tranexamic acid for hyperacute spontaneous IntraCerebral Haemorrhage (TICH-3)
EudraCT Number: 2021-001050-62
EU CTIS registration number: 2022-500587-35-00

Prescribing and Administration Guide

This guide explains how to prescribe and administer the investigational medicinal product (IMP) for participants enrolled in the TICH-3 clinical trial.

Dispensing
Add participant name and date of randomisation to the label on the outer packaging. Do not discard the outer packaging until you have alerted the coordinating centre that a randomisation has taken place using the QR code or via http://tich-3.ac.uk/alert (see **Randomisation alert** below).

Prescription
Investigational medicinal product (IMP) is prescribed on the participant's inpatient treatment chart by appropriately trained medical practitioners or health care professionals who are non-medical or independent prescribers. It is acceptable to use a handwritten or electronic prescribing system for IMP prescribing.

Prescribe (write in participant's drug chart): TICH-3 TRIAL Pack Number XXXXX TRANEXAMIC ACID OR PLACEBO 2 ampoules (10ml) added to 100ml Sodium Chloride Injection 0.9% administered as an IV infusion over 10 minutes.
AND
Prescribe (write in participant's drug chart): TICH-3 TRIAL Pack Number XXXXX TRANEXAMIC ACID OR PLACEBO 2 ampoules (10ml) added to 250ml Sodium Chloride Injection 0.9% as an IV infusion over 8 hours.

Administration
Administer in accordance with the prescription. The treatment can be administered by anyone qualified and appropriately trained to give intravenous injections.

Randomisation alert:

http://tich-3.ac.uk/alert

Please notify the coordinating centre in Nottingham as soon as possible after the treatment has been administered:

1. Scan the QR code or enter http://tich-3.ac.uk/alert in your web browser which will take you to the TICH-3 website.
   You do not need to have a TICH-3 investigator account.
2. Enter the treatment pack ID number.
3. Enter randomisation details as prompted by the system.
   Note: If you cannot access the website, please call the trial office on 0115 8231782 with treatment pack ID, participant's initials, date of randomisation and name of person enrolling the participant (voicemail 24/7).
4. Enter participant details on the IMP accountability log against the allocated pack.

Disposal of IMP packaging can take place only after the following tasks have been completed.
a. Participant randomisation alert completed on the TICH-3 website.
b. Participant details added to the IMP accountability log at site.
c. Prescription written on the participant's drug chart (using the guidance above).

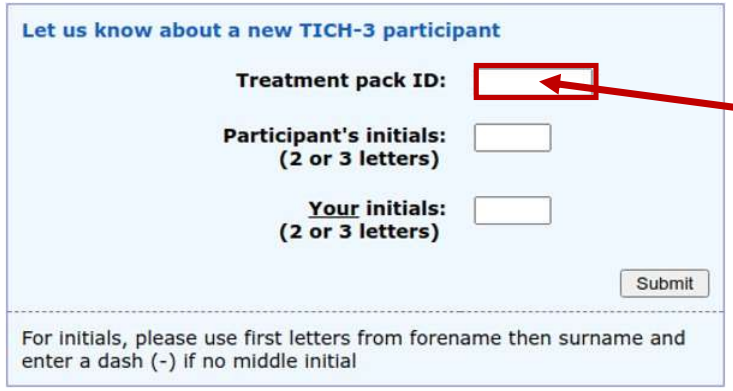
In the event of non-use:
Return any unused ampoules to clinical trials pharmacy AND record reason for non-use on the IMP accountability log.

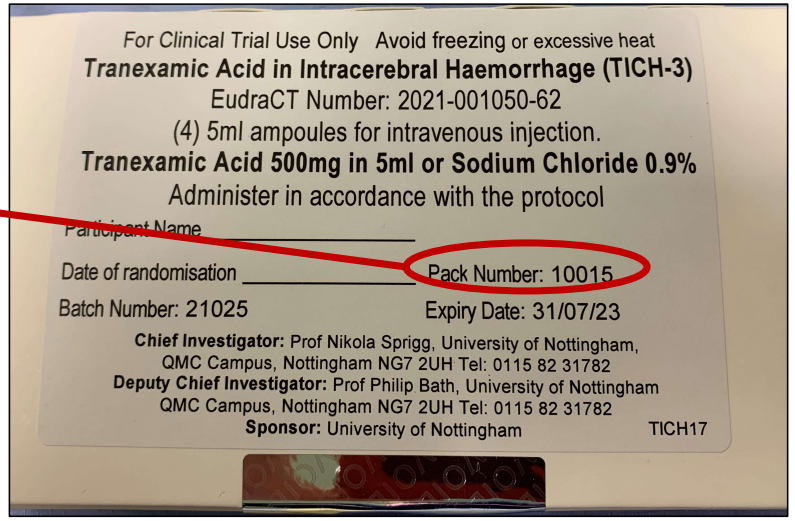
Randomisation Alert

1. Investigator will enter the treatment pack ID (pack number), participant initials and their own initials to alert the coordinating centre to a new randomisation.

SCAN
QR CODE

http://tich-3.ac.uk/





2. Investigator will then confirm that the participant was randomised at the hospital shown in the alert box.

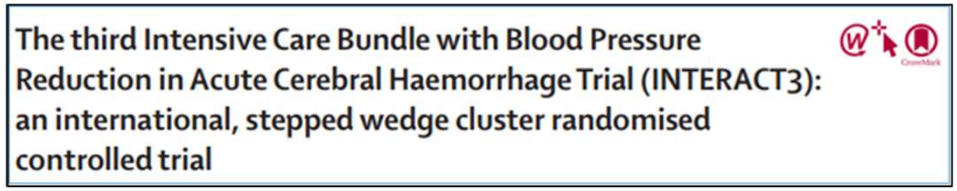
Standard of care for ICH

- All participants should receive standard care for ICH as per the local clinical pathway and guidelines. This is likely to include:

✓ Referral to stroke unit

✓ **Blood pressure lowering as per clinical guidelines[1] target**
For patients with BP 150-220mmHg aim for BP 130-140mmg
x Do not use the same cannula for study drug infusion and blood pressure lowering infusions– need separate IV access line

aiming for a target of BP< 140mmHg as per clinical guidelines, supported by the recent INTERACT -3 Results https://doi.org/10.1016/S0140-6736(23)00806-1


The third Intensive Care Bundle with Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT3): an international, stepped wedge cluster randomised controlled trial

✓ Consideration of referral to neurosurgery or critical care if appropriate

✓ Prophylaxis of venous thromboembolism with intermittent compression stockings

Please note tranexamic acid is not standard of care for spontaneous ICH

1: https://www.nice.org.uk/guidance/ng128/chapter/Recommendations

Broken vials:

Broken prior to randomisation e.g. upon receipt in pharmacy

✓Inform the Nottingham coordinating centre and dispose of the pack(s) in accordance with WPD020 (Destruction of IMP).

Broken after randomisation, **before treatment**:

✓Disregard this pack and use the lowest treatment pack ID that is available at your centre

Broken during treatment i.e. Bolus given but infusion vial breaks:

✓Administer as much drug as possible

✓Record on day 7 form that participant does not receive all of the randomised treatment as per protocol and explain why

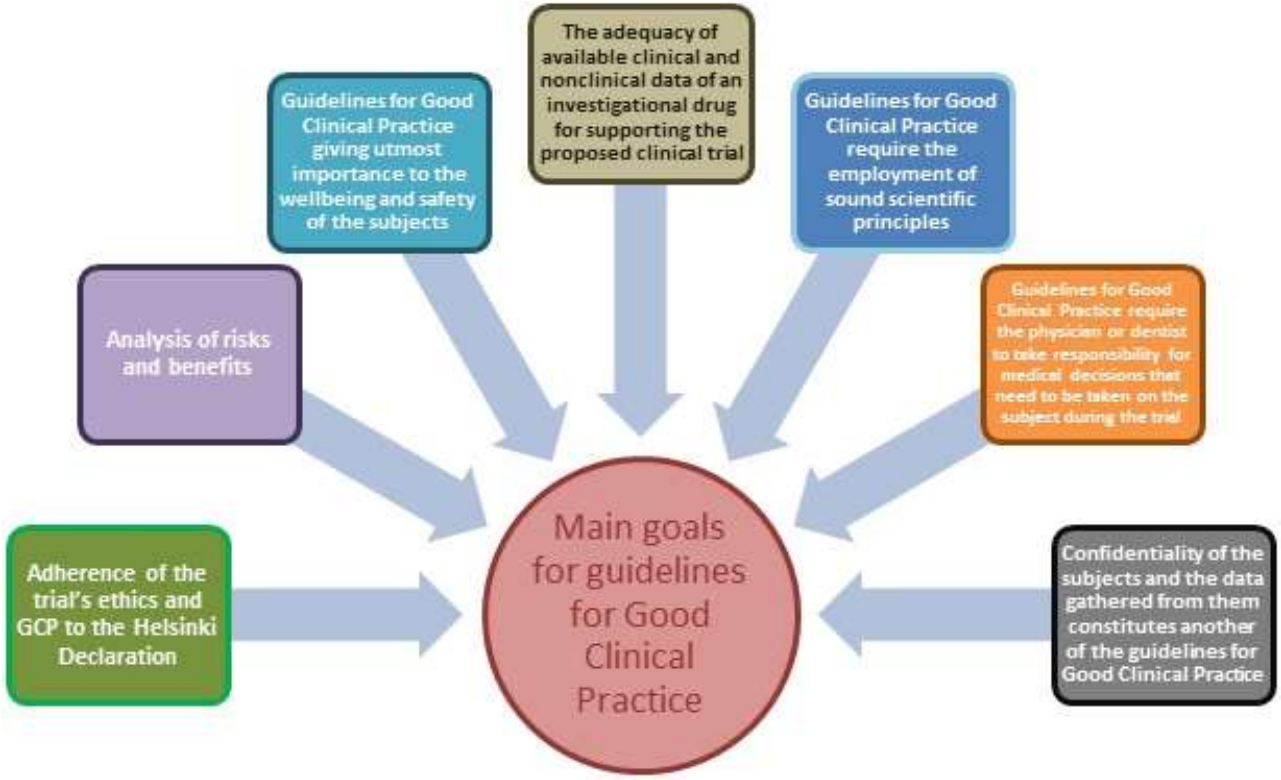
x Do not open another treatment pack

Always record broken vials on the inventory or accountability log as appropriate

Good Clinical Practice (GCP)

- TICH-3 is to be performed in line with all the principles of good clinical practice
- Investigators must adhere to the protocol at all times
- The safety and rights of the participant are paramount
- Training for investigators should be in proportion to their role within the trial and in accordance with their experience and skills
- The participant has the right to withdraw at any time without giving a reason, without it affecting their medical care
- Investigators eligible for NIHR GCP online training learn account

https://portal.nihr.ac.uk/register



- **Sponsors SOPS can be found on the document page; see TA016 GCP Breach Reporting**

GCP training

Free GCP training - In English, French and Spainish

https://globalhealthtrainingcentre.tghn.org/ich-good-clinical-practice/

Safety Events, SARS and SUSARS

TXA has an established safety record – we only collect data on focused **safety outcomes** occurring within the **first 7 days or events suspected to be related to the IMP (SAR or SUSAR):**

Safety outcomes: **If a safety outcome (e.g. seizure) occurs during infusion, the infusion must be stopped immediately**

1. Venous occlusive events: VTE (Pulmonary embolism, Deep vein thrombosis)
2. Ischaemic events (arterial thrombosis at any site, ischaemic stroke, transient ischaemic attack peripheral artery embolism, myocardial infarction, acute coronary syndrome)
3. Seizures
4. Fatal events up to discharge from hospital

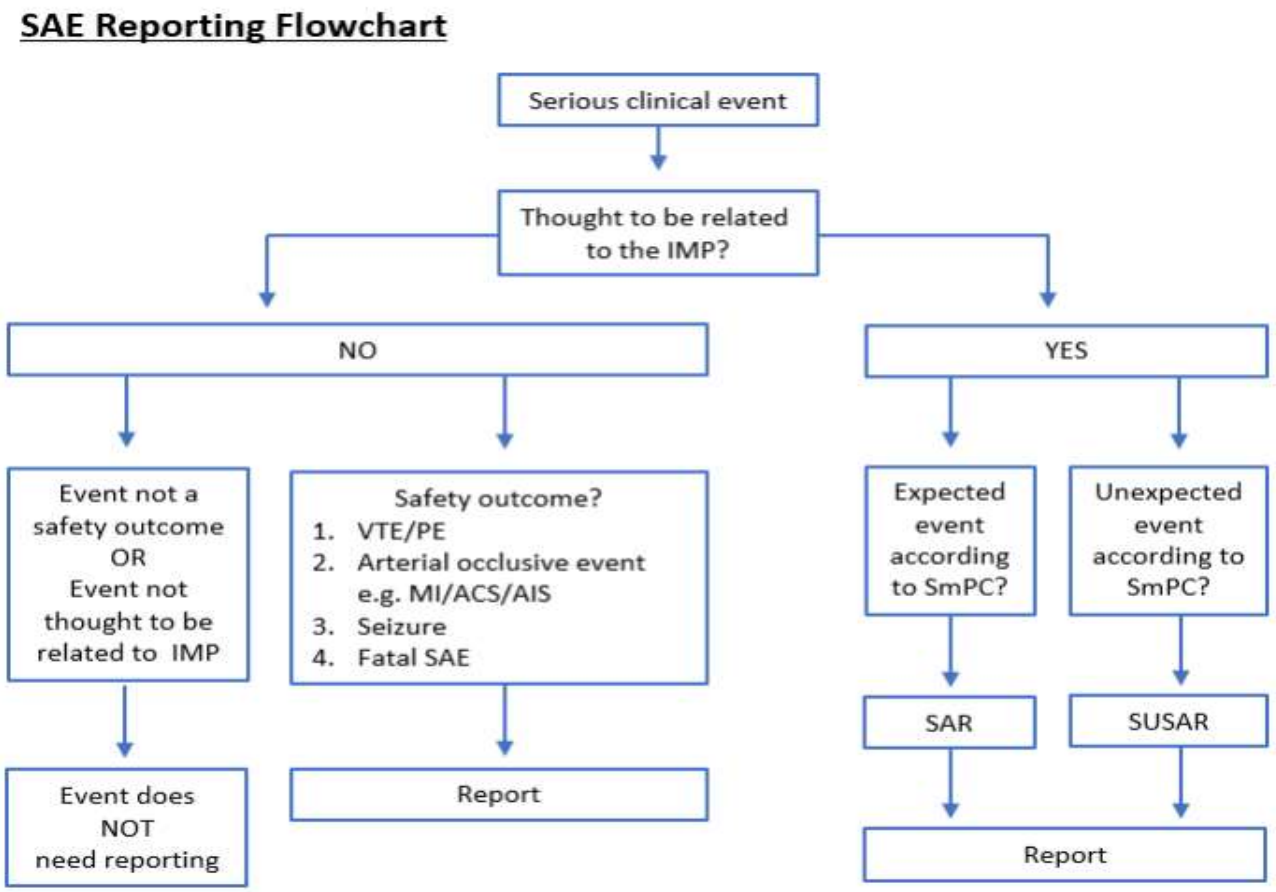
Serious adverse reactions (SAR) or Suspected Unexpected Serious Adverse Reactions (SUSAR):

- All events suspected to be related to the IMP will be assessed for seriousness, expectedness and causality by local investigator. Section 4.8 of the SmPC, date of last revision 02 February 2021, will act as the **Reference Safety Information:** Tranexamic Acid https://Tranexamic Acid_SmPC_20210202_REVISION.pdf

Serious Adverse Events (SAEs) that are not safety outcomes, SARS or SUSARS should not be reported
E.g. Neurological deterioration, haematoma expansion, cerebral oedema that is NOT thought to be related to the IMP, and does not result in death does not need to be reported as an SAE

The PI must review and sign off SAE's – recommend print off and file SAE form in site file after sign off by PI

SAE Reporting Flowchart



What to do in Case of Emergency

Safety events during the infusion

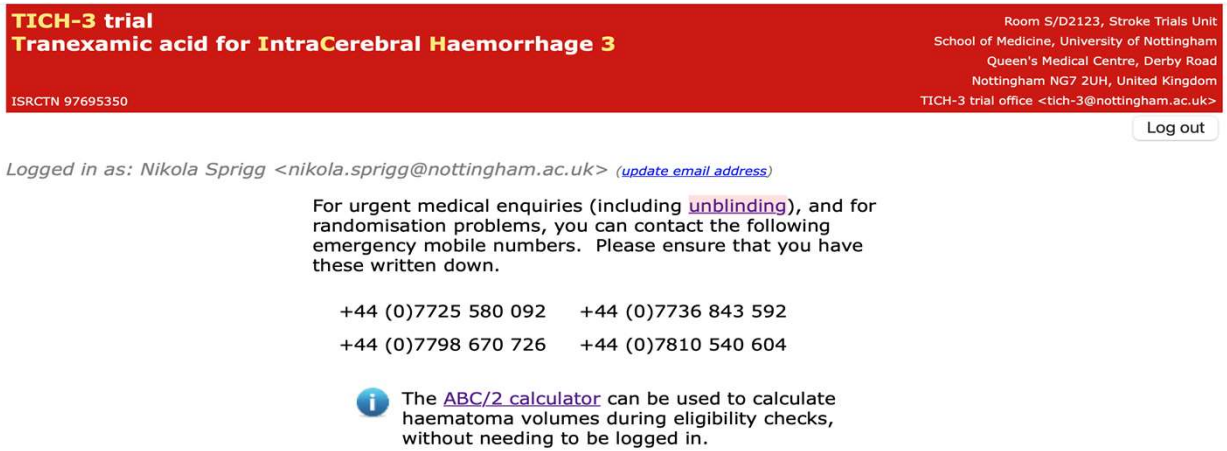
If seizure, thrombosis or arterial occlusion occurs during infusion, the infusion must be stopped immediately. This will be recorded as part of the trial documentation and safety monitoring.

Emergency Unblinding

In general there should be no need to unblind the allocated treatment. If some contraindication to tranexamic acid 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 TXA 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 TXA or placebo.

Eligibility query or any other emergency query

Call the emergency contact number
listed on TICH-3 website.



ACTION – Return Training Log

- Please use the self referral form to create your account for the TICH-3 website after training has been completed, this also adds you to the online delegation log for PI approval: http://tich-3.ac.uk/?ZSelfRef

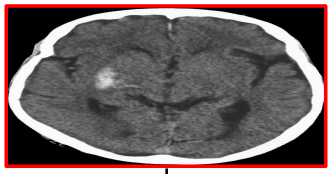
- Team members who could not attend live training can access training slides from TICH-3 website https://stroke.nottingham.ac.uk/tich-3/docs/#UK_site_training

  There are 3 versions of the training slides

  1. Investigator training which gives a detailed description of the whole trial process, intended for the PI and research nurses/coordinators. There is also a video of this training.
  2. Enrolling investigator training this streamlined training is intended for team members who will only be taking enrolment consent i.e. consultants
  3. Pharmacy training this streamlined training is intended for members of pharmacy team

- A short 3 ½ minute video is available to introduce team members to the TICH-3 trial http://tich-3.ac.uk/docs/#Videos

TICH-3 Key Points



Verbal permission

Randomise - open lowest numbered treatment pack

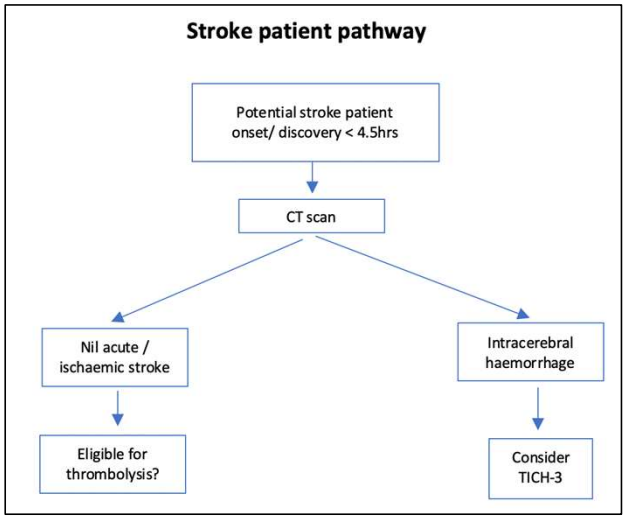
Recruitment Alert

Written consent

Primary outcome: Mortality day 7

Secondary: mRS day 180

- Pragmatic design and methods
- Inclusion criteria – ICH < 4.5 hours, Exclusion - massive ICH (low GCS < 5, HV > 60mls), contraindication to tranexamic acid (e.g. seizures)
- Emergency consent – initially oral followed by written consent
- Simple randomisation – use the lowest available treatment pack number
- QR code randomisation alert – inform trial office of enrolment
- Safety monitoring – safety events for 7 days, SAR and SUSAR Venous and arterial occlusive events and seizures
- Central postal/telephone follow up at 6 months



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THANK YOU!

Any questions?

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PLEASE SIGN UP TO THE TRAINING LOG ON THE SELF REFERRAL FORM