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ISRCTN97695350

TRANEXAMIC ACID FOR INTRACEREBRAL HAEMORRHAGE: TICH-3 TRIAL

ENROLLING INVESTIGATORS & EMERGENCY DEPARTMENT STAFF

Professor Nikola Sprigg and
Brittany Dutton

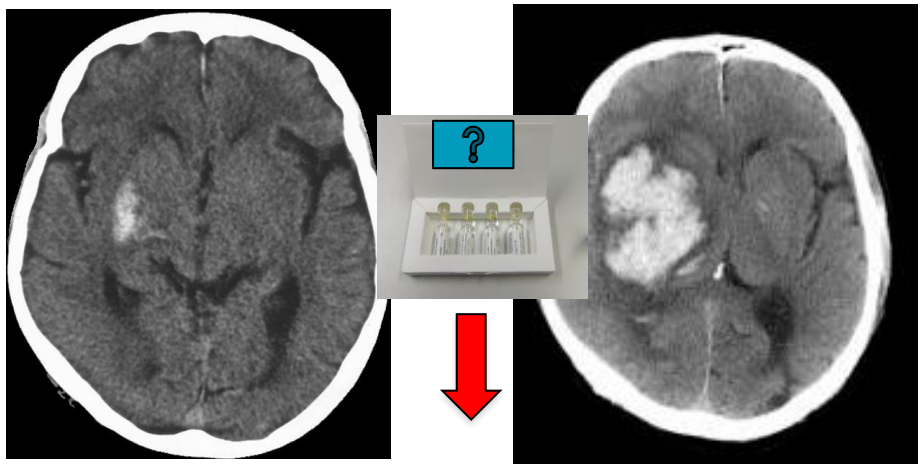
On behalf TICH-3 Trial Team

Final 3.1 17/12/2024

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

PROTOCOL

Final version 3.1 25/04/2024

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

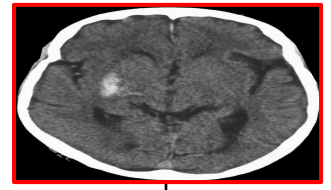
Primary Outcome: Early death (day 7)

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

Sample size: 5500 (3900 UK and 1900 Internationally)

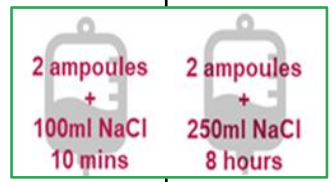
Cost/funder: UK NIHR plus others internationally

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



Verbal permission

Randomise - open lowest numbered treatment pack



Recruitment Alert

Written consent

Primary outcome:
Mortality day 7

Secondary:
mRS day 180

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

TICH-3 Eligibility Criteria

Inclusion criteria

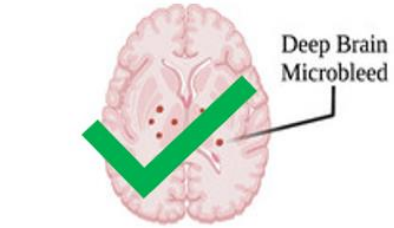
- Spontaneous ICH (confirmed on brain imaging) < 4.5 hours of onset

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

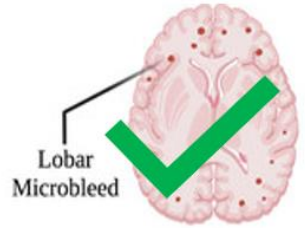
IMP treatment should be started within the 4.5 hours inclusion window.

Exclusion criteria

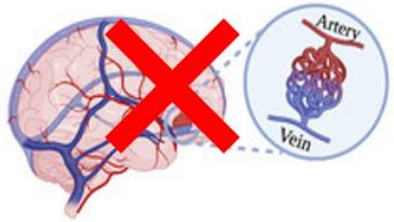
- Known indication for TXA treatment (e.g. traumatic brain injury) *or* contra-indication for TXA treatment (e.g. active seizures) *in view of treating physician*
- Patient known to be taking therapeutic anticoagulation with warfarin or low molecular weight heparin at time of enrolment. **(DOAC is permitted)**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



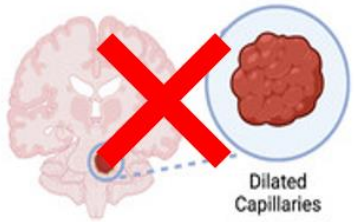
Hypertension Microangiopathy



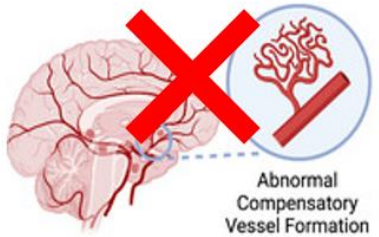
Cerebral Amyloid Angiopathy



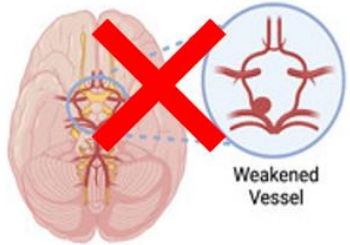
Arteriovenous Malformation



Cavernous Angioma

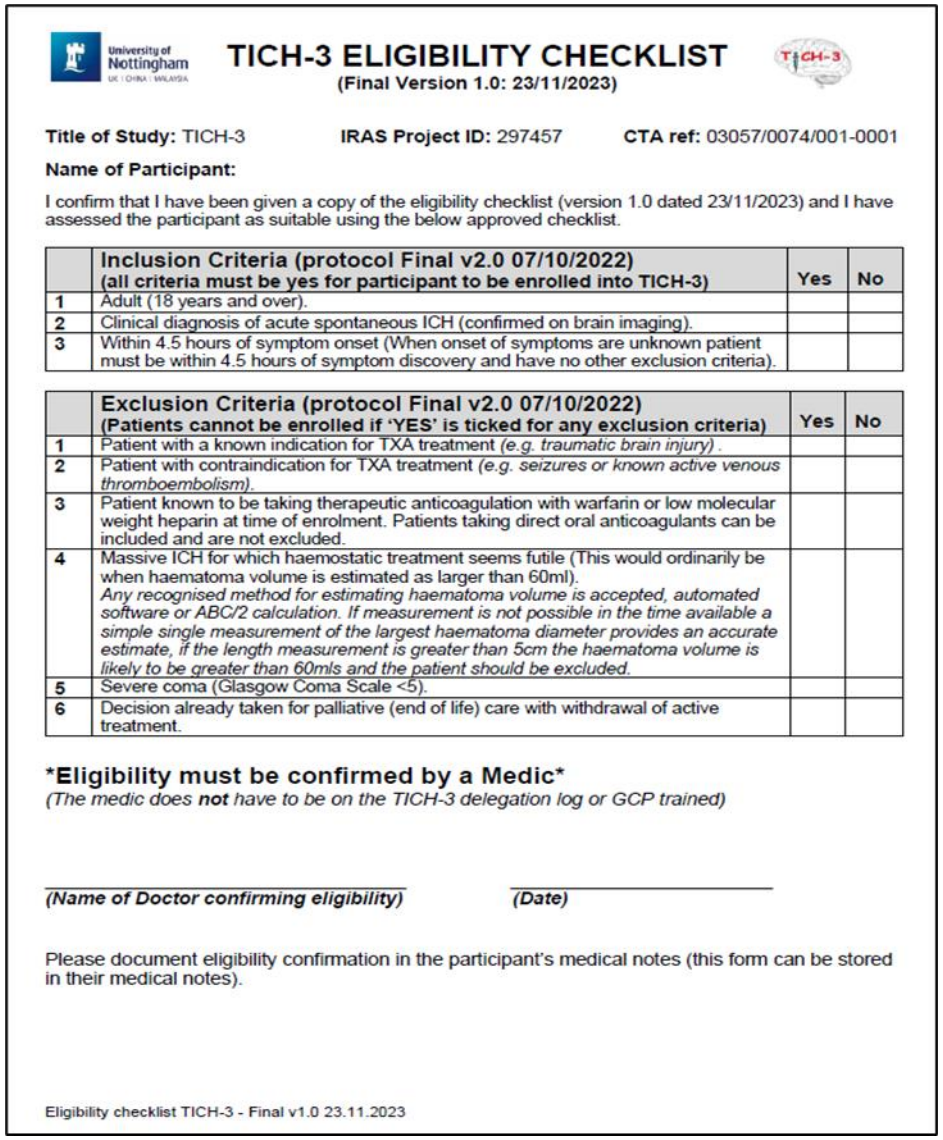


Moyamoya Disease



Aneurysm

Eligibility checklist (optional document)



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TICH-3 ELIGIBILITY CHECKLIST

(Final Version 1.0: 23/11/2023)

Title of Study: TICH-3 **IRAS Project ID:** 297457 **CTA ref:** 03057/0074/001-0001

Name of Participant:

I confirm that I have been given a copy of the eligibility checklist (version 1.0 dated 23/11/2023) and I have assessed the participant as suitable using the below approved checklist.

	Inclusion Criteria (protocol Final v2.0 07/10/2022) (all criteria must be yes for participant to be enrolled into TICH-3)	Yes	No
1	Adult (18 years and over).		
2	Clinical diagnosis of acute spontaneous ICH (confirmed on brain imaging).		
3	Within 4.5 hours of symptom onset (When onset of symptoms are unknown patient must be within 4.5 hours of symptom discovery and have no other exclusion criteria).		

	Exclusion Criteria (protocol Final v2.0 07/10/2022) (Patients cannot be enrolled if 'YES' is ticked for any exclusion criteria)	Yes	No
1	Patient with a known indication for TXA treatment *(e.g. traumatic brain injury)*.		
2	Patient with contraindication for TXA treatment *(e.g. seizures or known active venous thromboembolism)*.		
3	Patient known to be taking therapeutic anticoagulation with warfarin or low molecular weight heparin at time of enrolment. Patients taking direct oral anticoagulants can be included and are not excluded.		
4	Massive ICH for which haemostatic treatment seems futile (This would ordinarily be when haematoma volume is estimated as larger than 60ml). *Any recognised method for estimating haematoma volume is accepted, automated software or ABC/2 calculation. If measurement is not possible in the time available a simple single measurement of the largest haematoma diameter provides an accurate estimate, if the length measurement is greater than 5cm the haematoma volume is likely to be greater than 60mls and the patient should be excluded.*		
5	Severe coma (Glasgow Coma Scale <5).		
6	Decision already taken for palliative (end of life) care with withdrawal of active treatment.		

Eligibility must be confirmed by a Medic

*(The medic does **not** have to be on the TICH-3 delegation log or GCP trained)*

_____ _____

(Name of Doctor confirming eligibility) ***(Date)***

Please document eligibility confirmation in the participant's medical notes (this form can be stored in their medical notes).

Eligibility checklist TICH-3 - Final v1.0 23.11.2023

Eligibility can be confirmed by a medic that is not on the TICH-3 delegation log. An appropriate research team member on the delegation will then take oral enrolment consent, this can be completed remotely.

There is an eligibility checklist on the TICH-3 documents page that can be used to document participants eligibility whether this was completed remotely or on site.

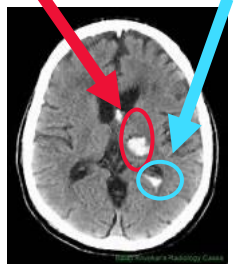
This is an optional document that is not required to be completed but is available if you wish to use this.

All processes off eligibility assessment and consent must be documented in the participants medical notes.

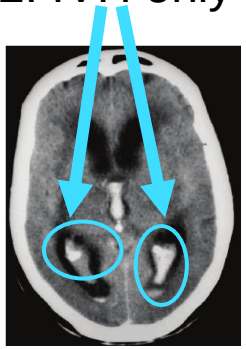
Eligibility: Frequently asked questions

- 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 UNLESS the patient is being given TXA as part of standard neurosurgical care
- 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

For additional FAQs please see TICH-3 documents page https://stroke.nottingham.ac.uk/sif/docs/?sid=TICH-3

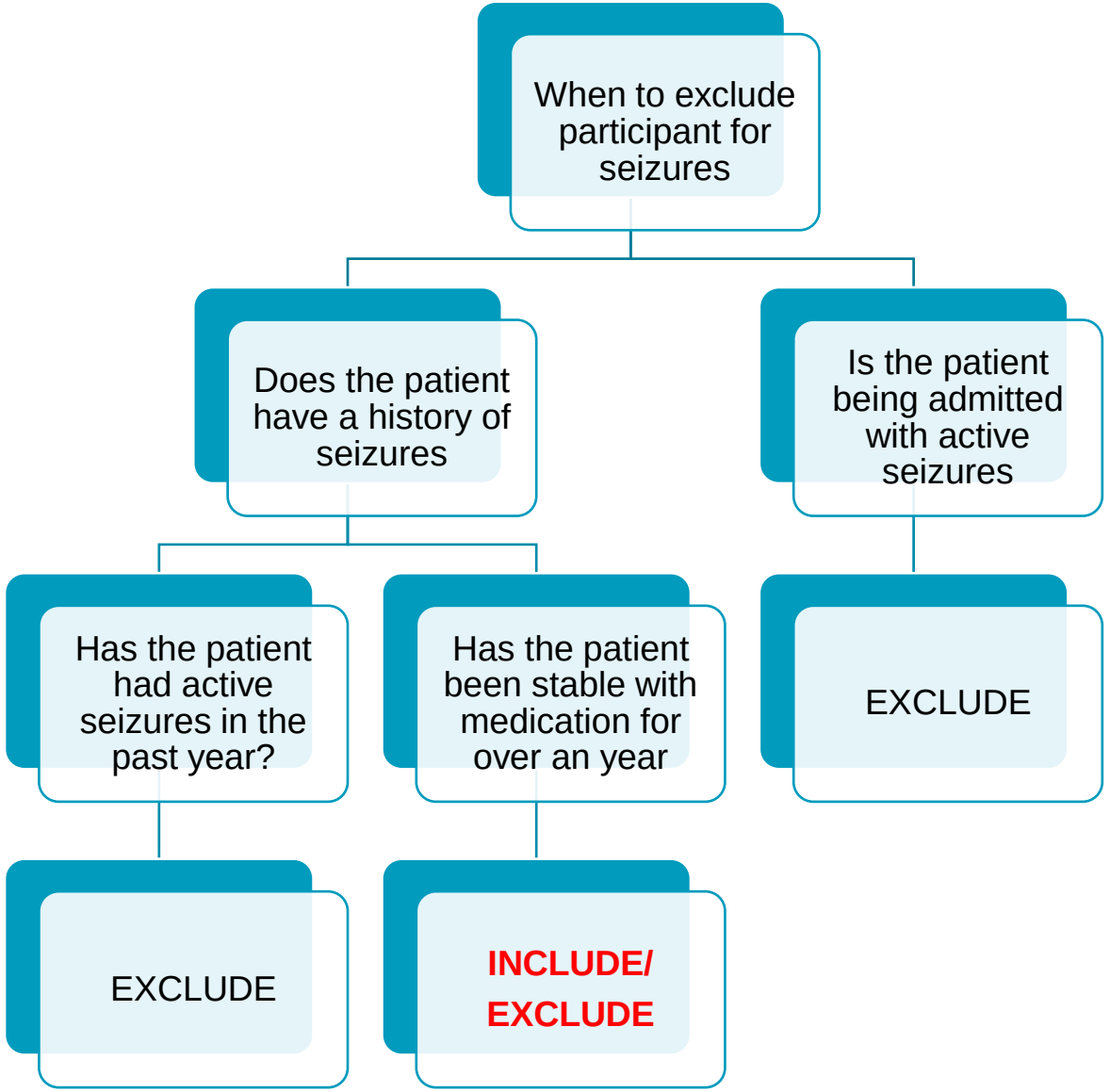
Eligibility: seizures

- 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

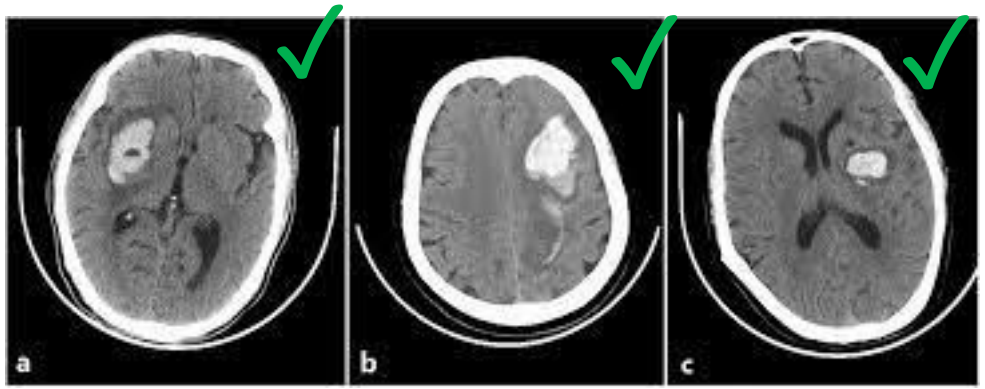


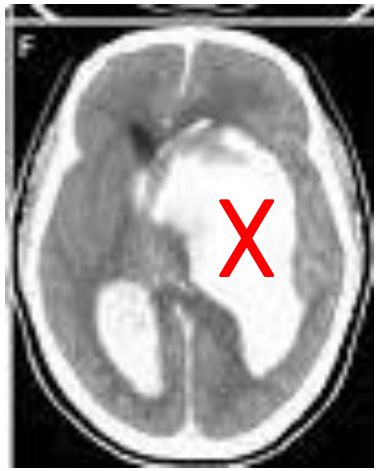
Size matters – but estimates are ok!

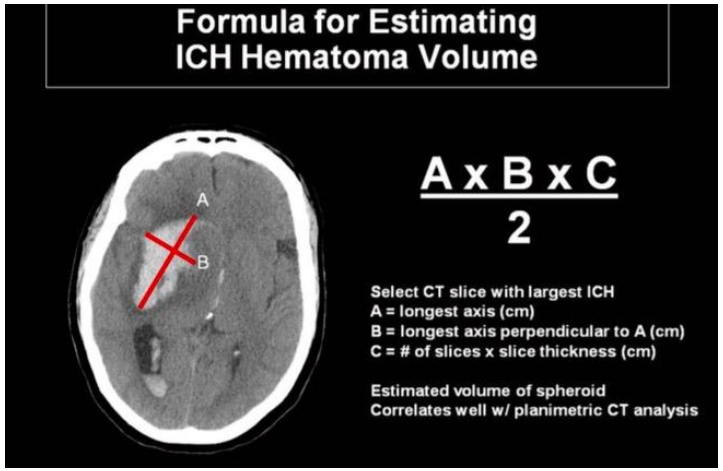
Exclude patients with massive haematoma (usually > 60ml)

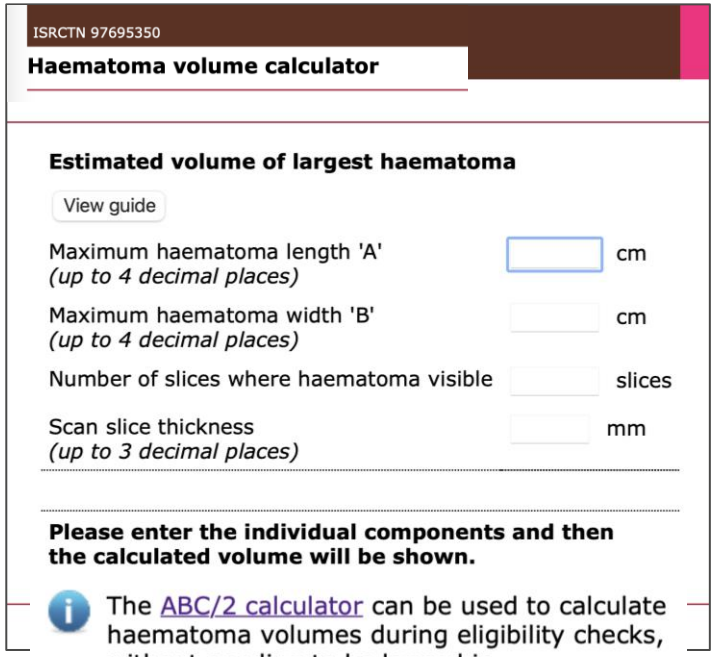
1. If CT scan uses automated haematoma volume software – patient can be enrolled if HV not greater than 60mls (+/- 10%)
2. Calculate HV manually using TICH-3 HV=ABC/2 calculator on the website[1] or alternatives e.g. mdcalc app[2] *(ignore 25 – 75% calculator and count all slices where ICH visable due 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

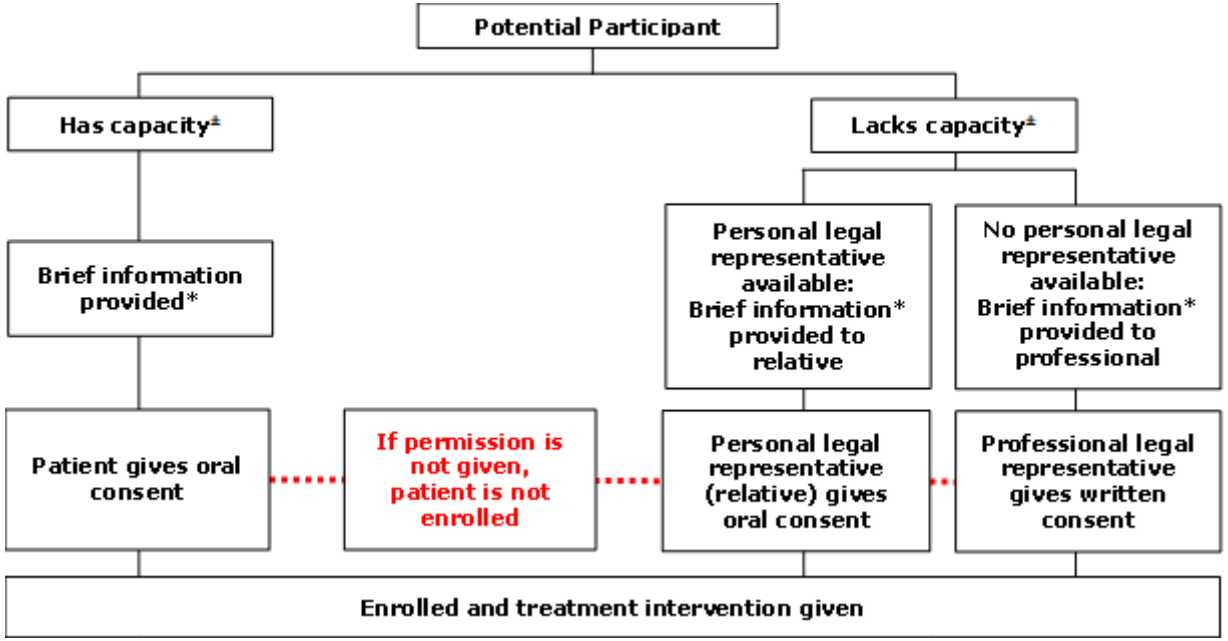
Rapid consent process, initial verbal consent

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

Hierarchy approach in UK

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

- Oral consent can be given over the telephone and then follow-on written consent obtained when relative is on site
- A delegated doctor may assess the patient via telemedicine to obtain verbal consent.
- Medical record must document that the patient meets TICH-3 eligibility criteria and oral consent was given



± Assessment of capacity is the responsibility of the treating physician

Members of research team taking consent must be appropriately trained and authorised on the TICH-3 deleagtion log

<u>If research team are not available</u> participant can be consented by a member of clinical team and documented via the eligibility checklist and enrolment form (SA_06_24)

Professional legal representative consent by an independent doctor

Enrolment consent by independent doctor

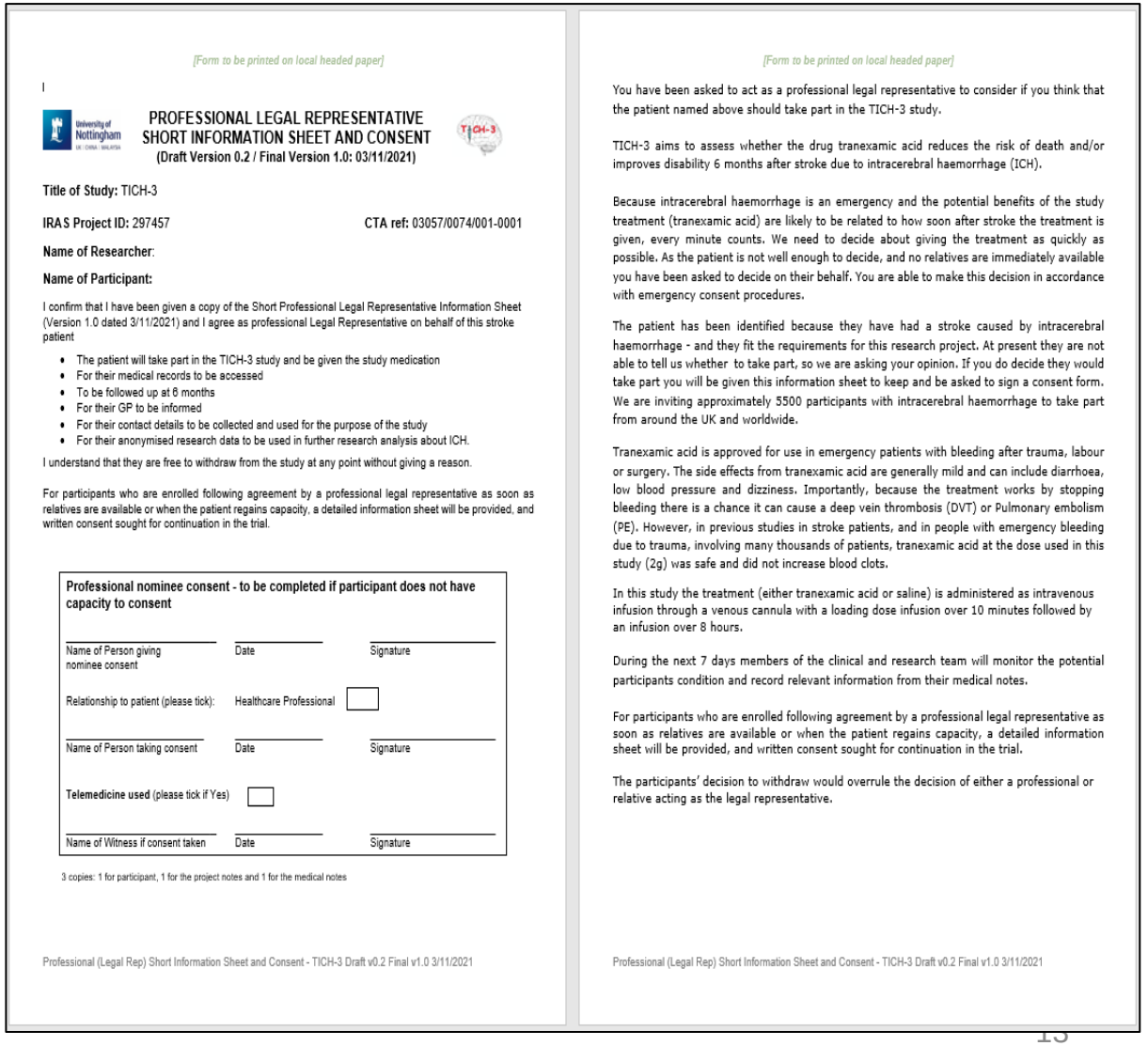
Short Information Sheet and Consent form should be used (pictured to the right). In this scenario the professional legal representative enrolment consent is handwritten and then a follow-on written consent form is not required to be completed by the independent doctor. If the participant regains capacity or a relative becomes available, they should complete the written follow-on consent.

Follow on written consent by independent doctor

The follow-on written consent form for professional legal representative should only be used if participant has capacity and consents for enrolment orally, then loses capacity and no relatives are contactable to provide the handwritten follow-on consent. If the participant regains capacity or a relative becomes available, they should complete the written follow-on consent.

Informing relatives

The clinician at site has full responsibility for informing relatives of participant when professional legal representative consent has taken place. In event of a patient dying after being enrolled by a professional legal representative but before relatives can be contacted the clinical team should inform the relatives of the patient's involvement in the study and provide information about the study.



[Form to be printed on local headed paper]

I

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PROFESSIONAL LEGAL REPRESENTATIVE SHORT INFORMATION SHEET AND CONSENT
(Draft Version 0.2 / Final Version 1.0: 03/11/2021)

Title of Study: TICH-3

IRAS Project ID: 297457 **CTA ref:** 03057/0074/001-0001

Name of Researcher:

Name of Participant:

I confirm that I have been given a copy of the Short Professional Legal Representative Information Sheet (Version 1.0 dated 3/11/2021) and I agree as professional Legal Representative on behalf of this stroke patient

- The patient will take part in the TICH-3 study and be given the study medication
- For their medical records to be accessed
- To be followed up at 6 months
- For their GP to be informed
- For their contact details to be collected and used for the purpose of the study
- For their anonymised research data to be used in further research analysis about ICH.

I understand that they are free to withdraw from the study at any point without giving a reason.

For participants who are enrolled following agreement by a professional legal representative as soon as relatives are available or when the patient regains capacity, a detailed information sheet will be provided, and written consent sought for continuation in the trial.

Professional nominee consent - to be completed if participant does not have capacity to consent

Name of Person giving nominee consent | Date | Signature

Relationship to patient (please tick): Healthcare Professional ☐

Name of Person taking consent | Date | Signature

Telemedicine used (please tick if Yes) ☐

Name of Witness if consent taken | Date | Signature

3 copies: 1 for participant, 1 for the project notes and 1 for the medical notes

Professional (Legal Rep) Short Information Sheet and Consent - TICH-3 Draft v0.2 Final v1.0 3/11/2021

[Form to be printed on local headed paper]

You have been asked to act as a professional legal representative to consider if you think that the patient named above should take part in the TICH-3 study.

TICH-3 aims to assess whether the drug tranexamic acid reduces the risk of death and/or improves disability 6 months after stroke due to intracerebral haemorrhage (ICH).

Because intracerebral haemorrhage is an emergency and the potential benefits of the study treatment (tranexamic acid) are likely to be related to how soon after stroke the treatment is given, every minute counts. We need to decide about giving the treatment as quickly as possible. As the patient is not well enough to decide, and no relatives are immediately available you have been asked to decide on their behalf. You are able to make this decision in accordance with emergency consent procedures.

The patient has been identified because they have had a stroke caused by intracerebral haemorrhage - and they fit the requirements for this research project. At present they are not able to tell us whether to take part, so we are asking your opinion. If you do decide they would take part you will be given this information sheet to keep and be asked to sign a consent form. We are inviting approximately 5500 participants with intracerebral haemorrhage to take part from around the UK and worldwide.

Tranexamic acid is approved for use in emergency patients with bleeding after trauma, labour or surgery. The side effects from tranexamic acid are generally mild and can include diarrhoea, low blood pressure and dizziness. Importantly, because the treatment works by stopping bleeding there is a chance it can cause a deep vein thrombosis (DVT) or Pulmonary embolism (PE). However, in previous studies in stroke patients, and in people with emergency bleeding due to trauma, involving many thousands of patients, tranexamic acid at the dose used in this study (2g) was safe and did not increase blood clots.

In this study the treatment (either tranexamic acid or saline) is administered as intravenous infusion through a venous cannula with a loading dose infusion over 10 minutes followed by an infusion over 8 hours.

During the next 7 days members of the clinical and research team will monitor the potential participants condition and record relevant information from their medical notes.

For participants who are enrolled following agreement by a professional legal representative as soon as relatives are available or when the patient regains capacity, a detailed information sheet will be provided, and written consent sought for continuation in the trial.

The participants' decision to withdraw would overrule the decision of either a professional or relative acting as the legal representative.

Professional (Legal Rep) Short Information Sheet and Consent - TICH-3 Draft v0.2 Final v1.0 3/11/2021

Eligibility checklist and enrolment form FAQs (SA_06_24 and MA_24_24)

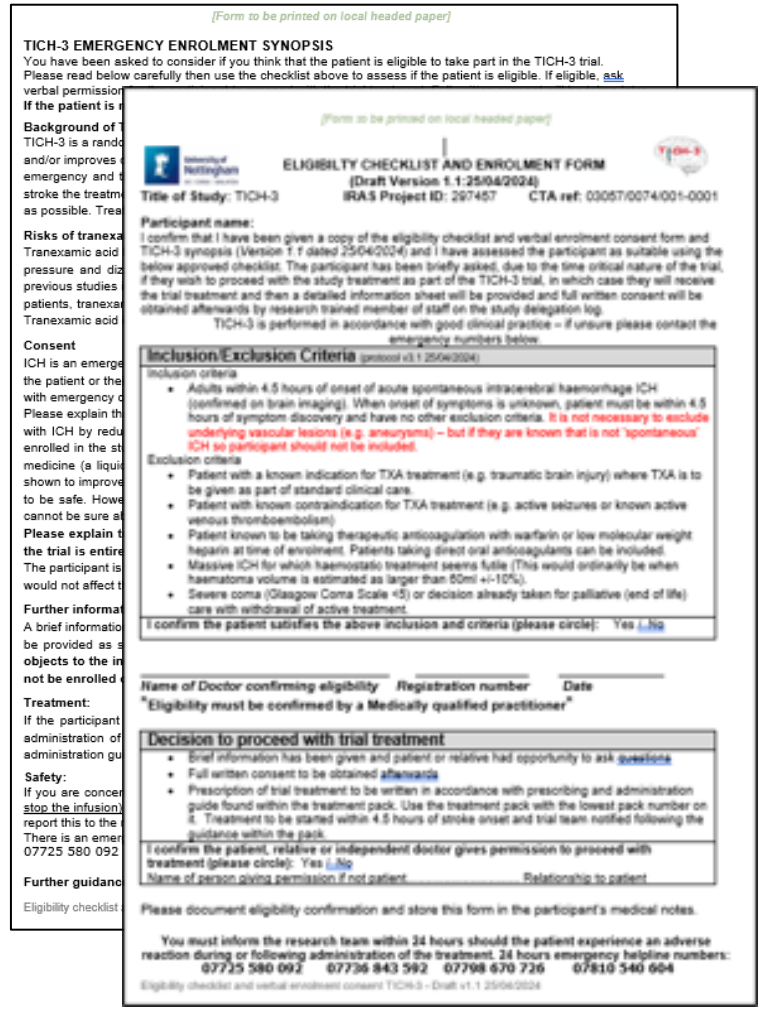
When can this method of consent be used? This is ONLY to be used when the delegated research team are not available to consent participants into TICH-3.

Who can take consent via this method? Site PI may delegate enrolment and administration of the IMP to appropriately trained members of the treating clinical team (not on TICH-3 delegation log, does not need to be GCP trained or have CV on file). There is no minimum grade doctor. Eligibility must be assessed by a medically qualified practitioner under the clinical trial regulations.

How is this consent process documented? This would be facilitated and documented by the use of an approved study synopsis, eligibility checklist and enrolment form which then would be stored in the participant's medical record.

What happens after this consent? Participant will be enrolled, and treatment administered by appropriate trained team members at the site. Full written consent would then be obtained as soon as practicable by a member of the local research team who is GCP trained and delegated the responsibility on the study delegation log.

Alternative text: screenshot of the eligibility checklist and enrolment form



[Form to be printed on local headed paper]

TICH-3 EMERGENCY ENROLMENT SYNOPSIS

You have been asked to consider if you think that the patient is eligible to take part in the TICH-3 trial. Please read below carefully then use the checklist above to assess if the patient is eligible. If eligible, ask verbal permission

If the patient is

Background of

TICH-3 is a rando and/or improves emergency and stroke the treatm as possible. Trea

Risks of tranexa

Tranexamic acid pressure and diz previous studies patients, tranexa Tranexamic acid

Consent

ICH is an emerge the patient or the with emergency Please explain th with ICH by redu enrolled in the st medicine (a liqui shown to improve to be safe. Howe cannot be sure al

Please explain t

the trial is entire

The participant is would not affect t

Further informat

A brief informatio be provided as s

objects to the in

not be enrolled

Treatment:

If the participant administration of administration gu

Safety:

If you are concer stop the infusion) report this to the There is an emer 07725 580 092

Further guidanc

Eligibility checklist

[Form to be printed on local headed paper]

ELIGIBILTY CHECKLIST AND ENROLMENT FORM

(Draft Version 1.1 25/04/2024)

Title of Study: TICH-3 IRAS Project ID: 297457 CTA ref: 03057/0074/001-0001

Participant name:

I confirm that I have been given a copy of the eligibility checklist and verbal enrolment consent form and TICH-3 synopsis (Version 1.1 dated 25/04/2024) and I have assessed the participant as suitable using the below approved checklist. The participant has been briefly asked, due to the time critical nature of the trial, if they wish to proceed with the study treatment as part of the TICH-3 trial, in which case they will receive the trial treatment and then a detailed information sheet will be provided and full written consent will be obtained afterwards by research trained member of staff on the study delegation log.

TICH-3 is performed in accordance with good clinical practice – if unsure please contact the emergency numbers below

Inclusion/Exclusion Criteria (protocol v3.1 25/04/2024)

Inclusion criteria

- Adults within 4.5 hours of onset of acute spontaneous intracerebral haemorrhage ICH (confirmed on brain imaging). When onset of symptoms is unknown, patient must be within 4.5 hours of symptom discovery and have no other exclusion criteria. It is not necessary to exclude underlying vascular lesions (e.g. aneurysms) – but if they are known that is not 'spontaneous' ICH so participant should not be included.

Exclusion criteria

- Patient with a known indication for TXA treatment (e.g. traumatic brain injury) where TXA is to be given as part of standard clinical care.
- Patient with known contraindication for TXA treatment (e.g. active seizures or known active venous thromboembolism)
- Patient known to be taking therapeutic anticoagulation with warfarin or low molecular weight heparin at time of enrolment. Patients taking direct oral anticoagulants can be included.
- Massive ICH for which haemostatic treatment seems futile (This would ordinarily be when haematoma volume is estimated as larger than 60ml +/-10%).
- Severe coma (Glasgow Coma Scale <5) or decision already taken for palliative (end of life) care with withdrawal of active treatment.

I confirm the patient satisfies the above inclusion and criteria (please circle): Yes / No

Name of Doctor confirming eligibility Registration number Date

"Eligibility must be confirmed by a Medically qualified practitioner"

Decision to proceed with trial treatment

- Brief information has been given and patient or relative had opportunity to ask questions
- Full written consent to be obtained afterwards
- Prescription of trial treatment to be written in accordance with prescribing and administration guide found within the treatment pack. Use the treatment pack with the lowest pack number on it. Treatment to be started within 4.5 hours of stroke onset and trial team notified following the guidance within the pack.

I confirm the patient, relative or independent doctor gives permission to proceed with treatment (please circle): Yes / No

Name of person giving permission if not patient Relationship to patient

Please document eligibility confirmation and store this form in the participant's medical notes.

You must inform the research team within 24 hours should the patient experience an adverse reaction during or following administration of the treatment. 24 hours emergency helpline numbers: 07725 580 092 07736 843 592 07798 670 726 07810 540 604

Eligibility checklist and verbal enrolment consent TICH-3 - Draft v1.1 25/04/2024

Streamlined recruitment process

CT/MRI scan shows bleeding and is within 4.5 hours of symptom discovery

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 the** process of eligibility and consent 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.
   - *Members of research team taking consent must be appropriately trained and authorised on the TICH-3 deleagtion log with code J applied (enrolment consent for CTIMPs)*
   - ***<u>If research team are not available</u>** participant can be consented by a member of clinical team and documented via the eligibility checklist and enrolment form (SA_06_24 & MA_24_24)*
3. **Lowest numbered TICH-3 treatment pack** is prescribed and administered by appropriately trained staff (they do not need to be on the delegation log or GCP trained)
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

PRAGMATIC METHODS ALLOWS FOR STREAMLINED RECRUITMENT OUT OF HOURS

Consent process flowchart

Trained staff on TICH-3 delegation log available

Verbal consent obtained by trained staff on TICH-3 delegation log (code J)

No trained staff on delegation log, that can take enrolment consent, available

Clinical team use eligibility checklist and enrolment form

Open next lowest numbered treatment pack to randomise.

Prescribe and administer trial treatment.

QR code recruitment alert.

Document in medical notes eligibility and consent process.

When research team next on site

Follow on written consent obtained by trained staff on TICH-3 delegation log (code Z)

Add participant to TICH-3

Add a new participant

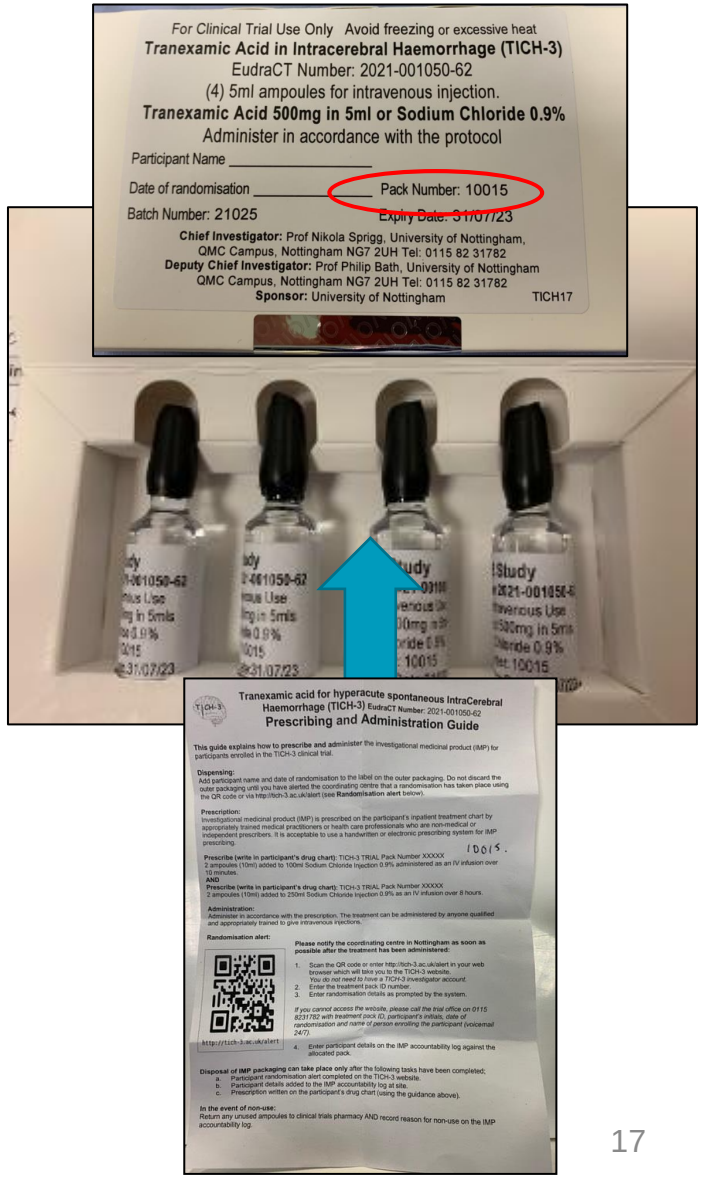
Upload consent form to secure vault.

Collect contact details and add to secure vault.

Begin eCRF data collection.

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

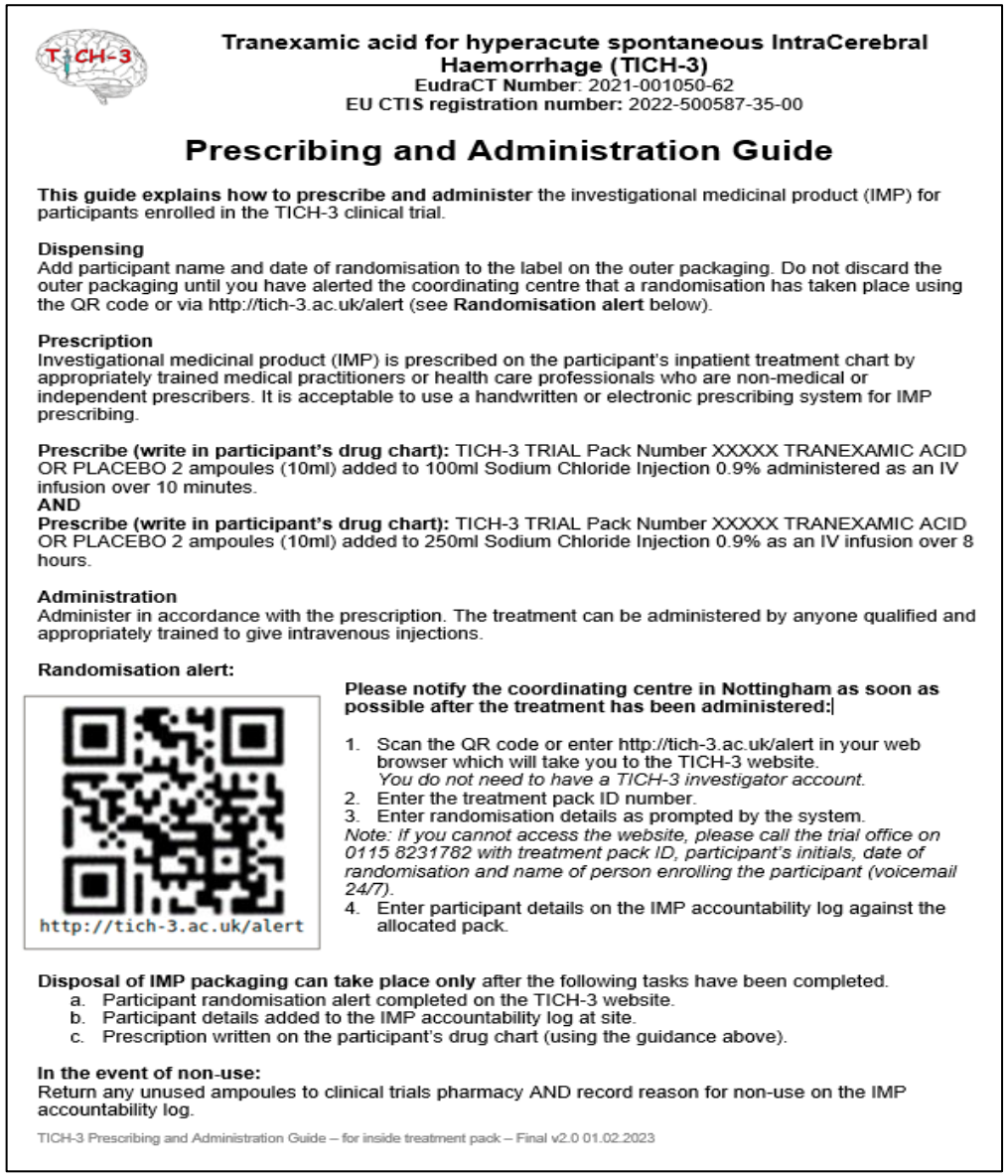
TICH-3 TRIAL Pack Number XXXXX

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).

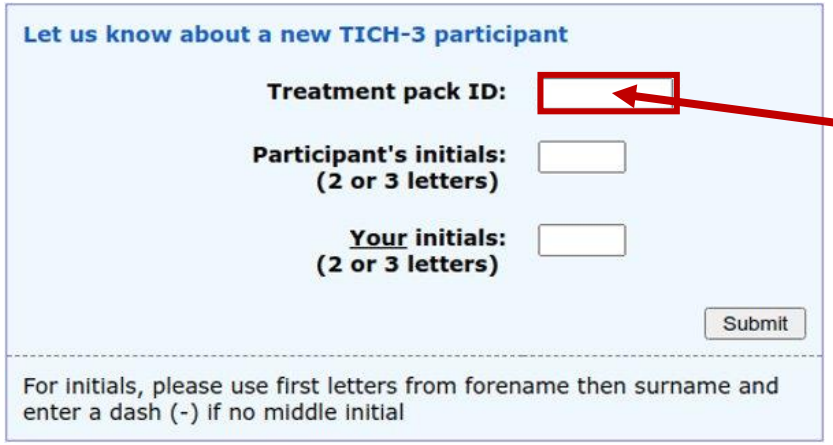
In the event of non-use:
Return any unused ampoules to clinical trials pharmacy AND record reason for non-use on the IMP accountability log.

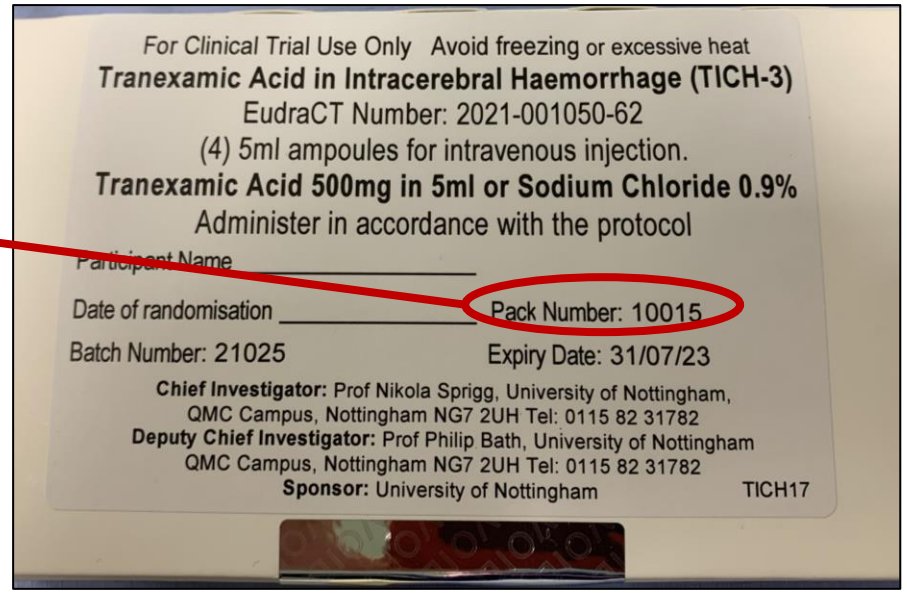
Randomisation Alert

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.

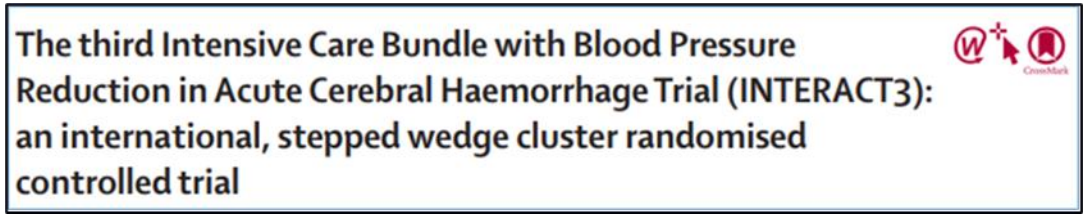
Standard of care for ICH

- 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

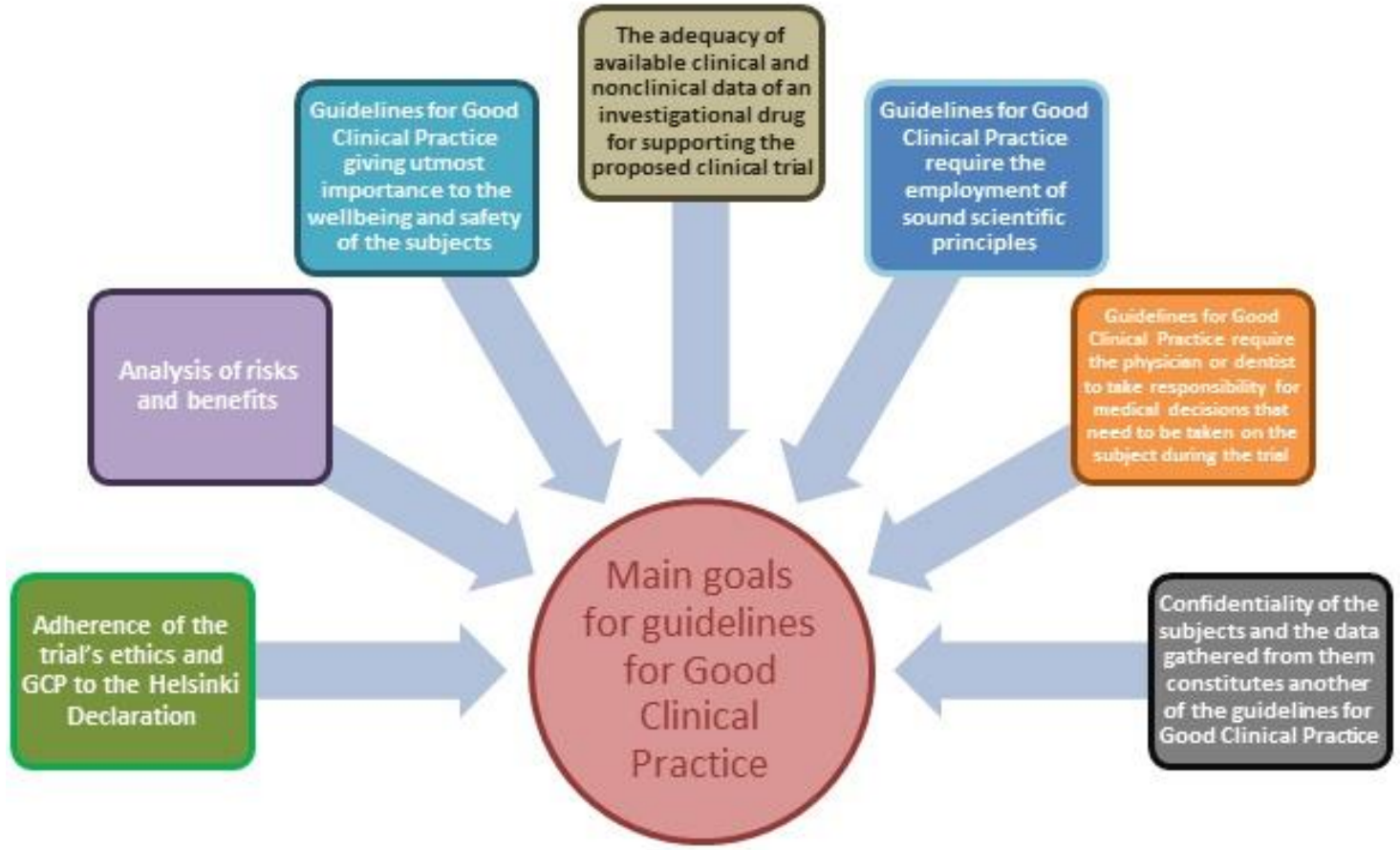
x Do not open another treatment pack

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**

Safety Events, SARS and SUSARS

Please remember that investigators have a legal responsibility to report applicable SAEs to the chief investigator within 24 hours of being made aware of the event.

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

PI oversight of SAEs

The local PI to assess the event for causality and relatedness to the IMP, this review is now electronic.

When an SAE report is submitted or has a data correction, the PI is emailed to review the online SAE report.

Dear Principal Investigator,

New SAR details for participant [redacted]0052 - FPP have been recorded.

- Please review the new SAE report (SAE 15).

You will be automatically redirected immediately after logging into TICH-3, or taken directly to the page if already authenticated.

As Principal Investigator at your site, please demonstrate that you have fulfilled your legal obligation in assessing this event for causality and relatedness to the IMP. Review the online SAE case report form (using the link above). If the record is printed and signed, please ensure that the signed copy is filed in the trial site file.

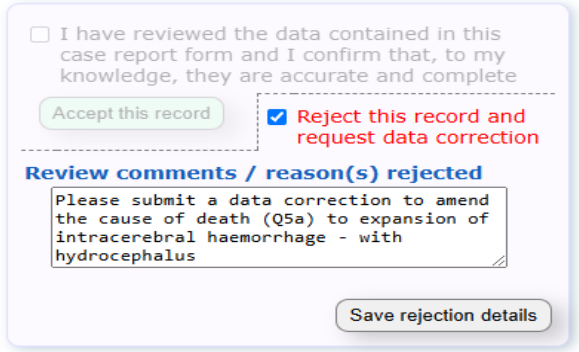
Your cooperation is appreciated, and compliance with this request will be checked at site monitoring.

Please remember that investigators have a legal responsibility to report applicable SAEs to the chief investigator within 24 hours.

At the bottom of the eCRF you will now see a review dialogue box. You can either accept the SAE report (figure A) or reject the report (figure B) as more information is required e.g. cause of death

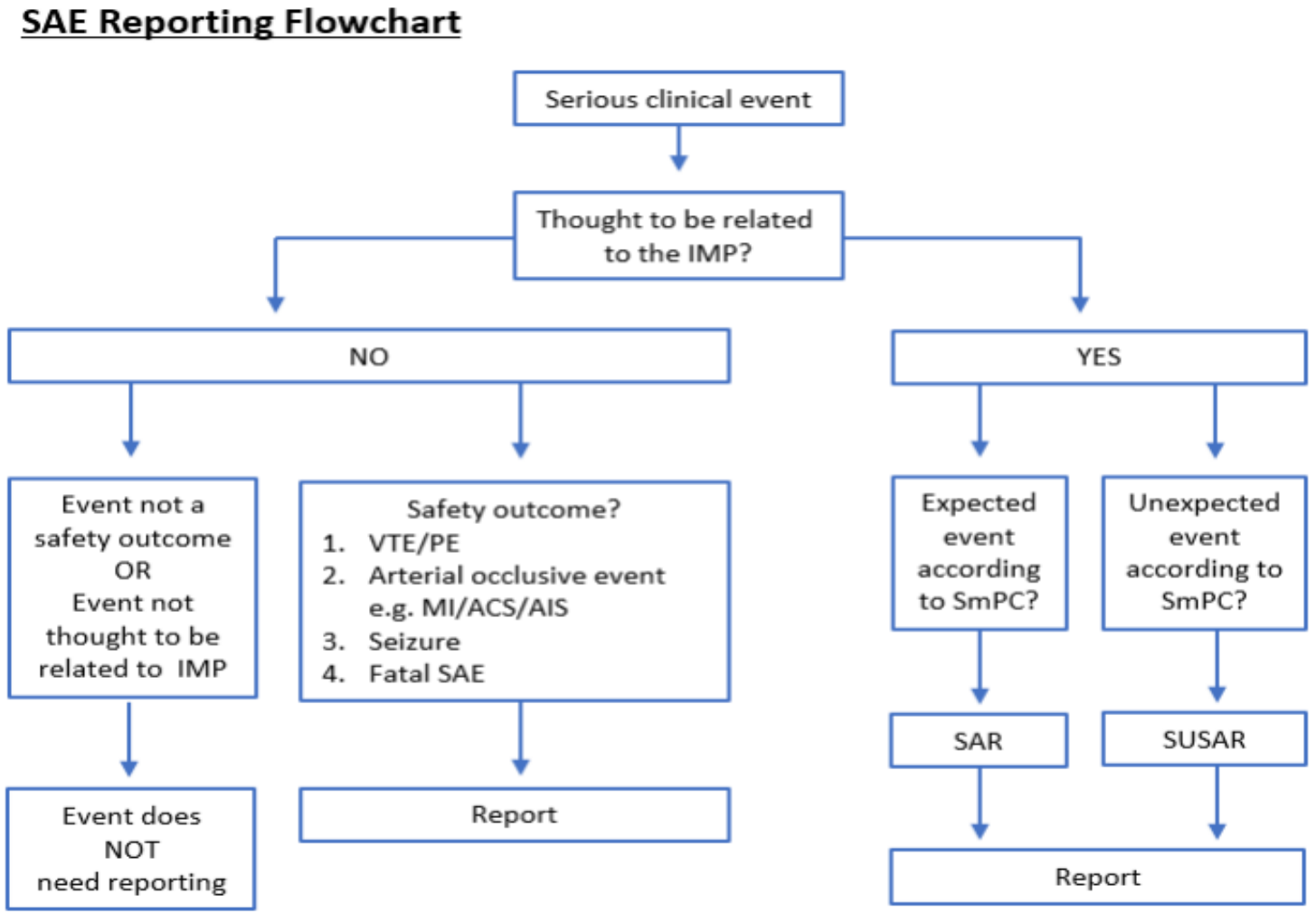
Figure A

Figure B



If more information is needed another email will be sent to the local team to complete a data correction, once completed the local PI will then re-review the SAE report and can accept or reject.

SAE Reporting Flowchart



What to do in Case of Emergency

Safety events during the infusion

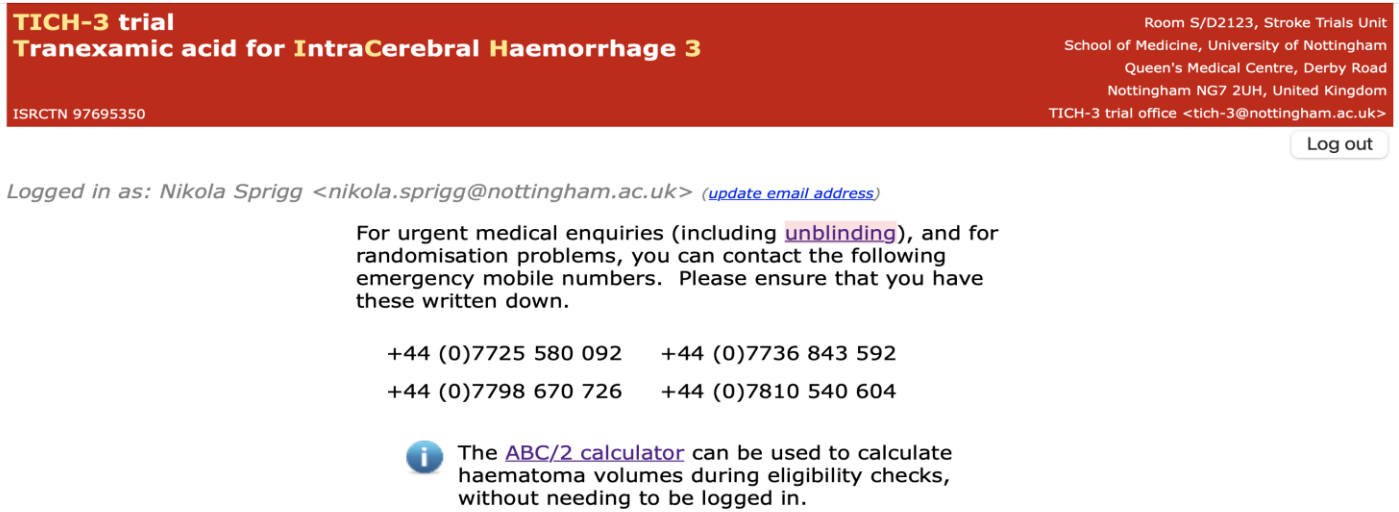
If seizure, thrombosis or arterial occlusion occurs during infusion, the infusion must be stopped immediately. This will be recorded as part of the trial documentation and safety monitoring.

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.



Co-enrolment with TICH-3

We are open to co-enrolment however we need to have a co-enrolment agreement in place with other interventional studies before co-enrolment is permitted.

There is a co-enrolment log on the TICH-3 documents page, please check this to review if co-enrolment with the respective trial is permitted
https://stroke.nottingham.ac.uk/sif/docs/?sid=TICH-3

If the trial is not listed on listed please contact us so we can start the process to get a co-enrolment agreement in place.

CO-ENROLMENT MUST NOT TAKE PLACE UNLESS THERE IS AN AGREEMENT IN PLACE

ACTION - DELEGATION 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

SCAN TO COMPLETE SELF-REFERRAL

https://stroke.nottingham.ac.uk/tich-3/?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

If you are a medical trainee – we are the trial for you!

NIHR PI associate scheme and join the TICH 3 team

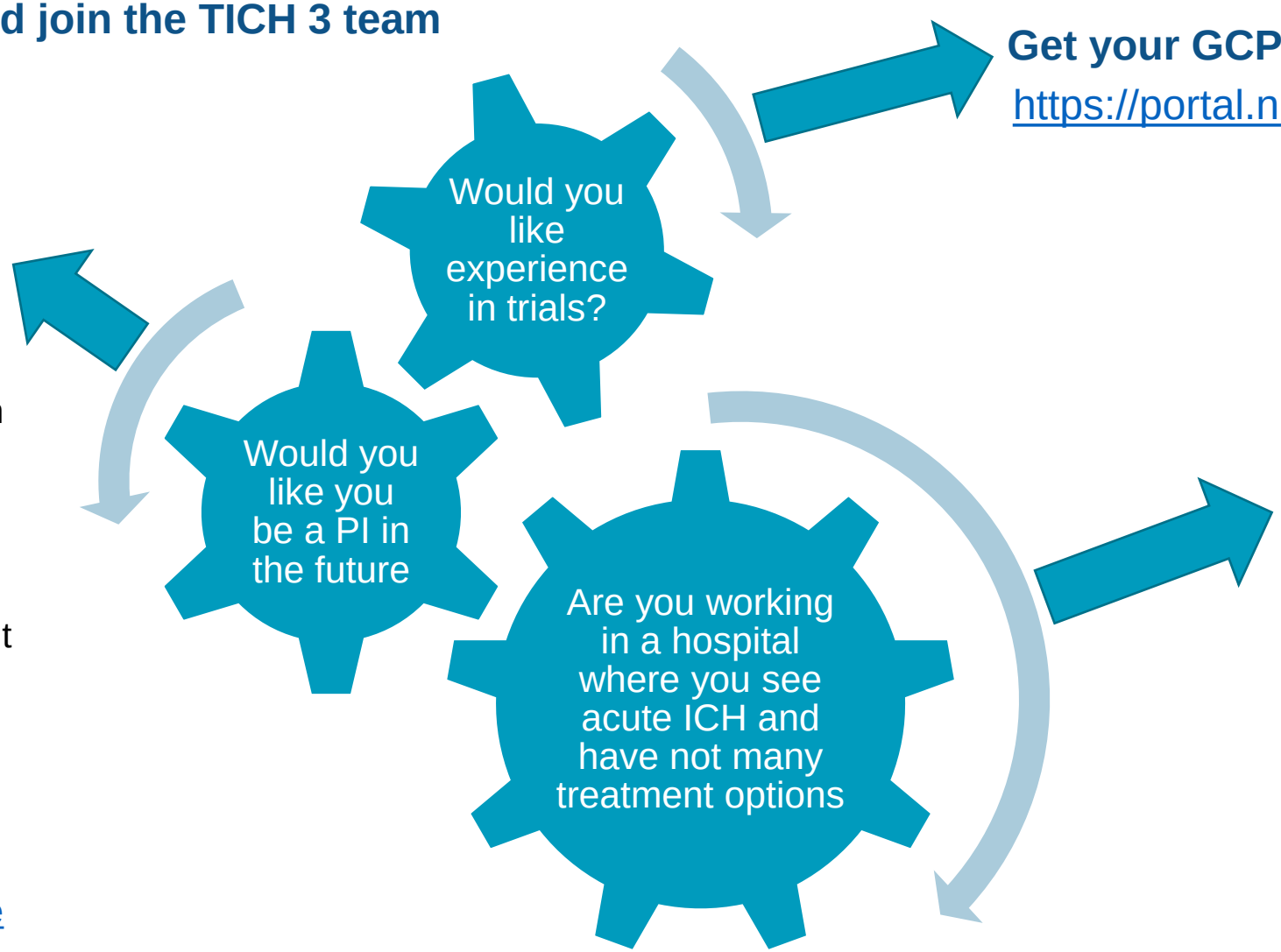
TICH-3 is registered for the Associate PI scheme, this is a great opportunity for doctors, nurses and other healthcare professionals to gain knowledge of what it means to deliver an NIHR portfolio trial.

Key points

- A 6 month in-work training opportunity providing practical experience for healthcare professionals starting their research career.
- Receive a certificate endorsed by NIHR and Royal Colleges
- Ideally you will apply to form the scheme 1 month before the site is ready to open and begin recruitment
- Engage with the TICH-3 coordinating centre during the 6 month scheme (we will sign off part of your checklist

You can find more information here: NIHR Associate PI Scheme Website.

You can register here: NIHR Associate PI Scheme Applicant Registration Form.



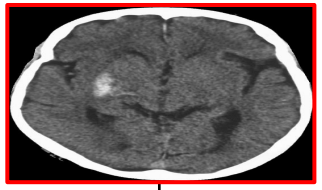
Get your GCP

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

Join the TICH-3 team!

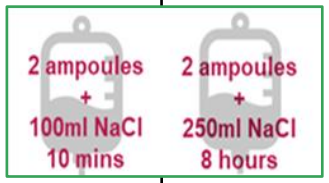
Complete the TICH-3 training to be added to your sites local TICH-3 online delegation log

TICH-3 Key Points



Verbal permission

Randomise - open lowest numbered treatment pack



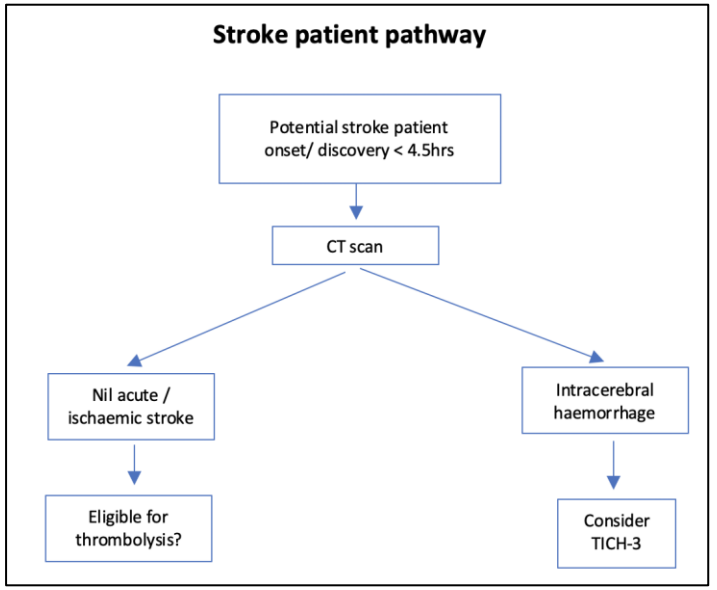
Recruitment Alert

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



University of Nottingham Trial Team

Name	Role	Contact Information
Brittany Hare	Clinical Trials Manager (UK Site Recruitment)	E: brittany.hare@nottingham.ac.uk
Jodie Newham	Clinical Trials Manager (International Site Recruitment)	E: jodie.newham2@nottingham.ac.uk
Solomon Adegbola	Follow Up Coordinator	E: solomon.adegbola@nottingham.ac.uk
Oliver Matias	Follow Up Coordinator	E: oliver.matias@nottingham.ac.uk
Christopher Cheung	Research Coordinator	E: christopher.cheung@nottingham.ac.uk
Kennedy Cadman	Research Coordinator	E: kennedy.cadman@nottingham.ac.uk
Chaamanti Menon	Trial Medic	E: chaamanti.menon@nottingham.ac.uk
Tiffany Hamilton	Senior Trial Manager	E: tiffany.hamilton@nottingham.ac.uk
Nikola Sprigg	Chief Investigator	E: nikola.sprigg@nottingham.ac.uk

Trial Coordinating Centre contact information:

+44(0)115 823 1782

TICH-3@nottingham.ac.uk

University of Nottingham
UK | CHINA | MALAYSIA

THANK YOU!

Any questions?

TICH-3@nottingham.ac.uk

Audit list of updates to training presentations

Previous version 3.0 23/04/2024 Added protocol slide with updated protocol version v3.1 25/04/2024, removed protocol version from eligibility slide

- Added to Safety Events, SARS and SUSARS – legal responsibility to inform CI within 24 hours of being aware event
- Edited Emergency Consent Process slide that person taking consent code J if research team or if not available medic can use eligibility checklist and enrolment form
- Removed consent FAQ slide as this is repeated elsewhere in presentation
- Slide Out of hours recruitment clarified members of research team must be delegated code J on delegation log, if research team not available a member of clinical team can take consent and document using the eligibility checklist and enrolment form. Combined streamlined process slide/out of hours slide/remote recruitment process slide.
- Added consent process flowchart
- Added slide eligibility checklist and enrolment form FAQs (SA_06_24 and MA_24_24)

This version 3.1 17/12/2024

- Updated SAE review for local PI that now is electronic
- Updated co-enrolment slide, removing specific trial details and to refer to the log so that the training slides don't have to be updated every time a co-enrolment agreement is fully executed
- Updated contact details