University of Nottingham
UK | CHINA | MALAYSIA

ISRCTN97695350

TRANEXAMIC ACID FOR INTRACEREBRAL HAEMORRHAGE: TICH-3 TRIAL

INVESTIGATOR TRAINING

Professor Nikola Sprigg, Brittany Hare and Chaamanti Menon

On behalf TICH-3 Trial Team

Final v3.2 18/08/2023

Funding disclosures:

- TICH-3 is funded by National Institute of Health and Care Research (Health Technology Assessment 19/59) NIHR129917
- DASH funded by National Institute of Health Research Research for Patient Benefit (RfPB)

TICH-3 Trial Registration:	ISRCTN97695350
TICH-3 CTA reference:	03057/0074/001-0001
TICH-3 IRAS Project ID:	297457
TICH-3 Trial Sponsor:	University of Nottingham

FUNDED BY NIHR | National Institute for Health and Care Research

Overview

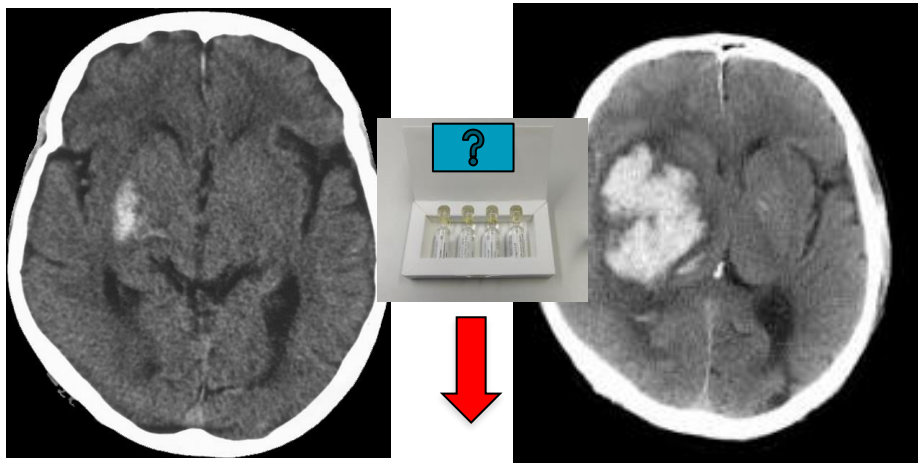
- Background – haematoma expansion
- Inclusion criteria
- Consent process
- Randomisation
- Inform trial office of enrolment - QR code randomisation alert
- Safety outcomes
- Pharmacy - Drug storage and administration
- Passwords, website access and electronic case report forms (eCRFs)
- Site file, delegation log, approvals
- Co-enrollment
- Study within a trial (SWAT)

BACKGROUND

Intracerebral Haemorrhage (ICH)

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

Key changes from TICH-2

Target participants most likely to benefit

Change	TICH-2	TICH-3
Primary outcome	Function day 90	Death by day 7 Function day 180
Recruitment target	2000	5500
Recruitment time	8 hours since onset	4.5 hours since onset
Baseline ICH volume	No maximum	Exclude massive (usually Haematoma Volume > 60ml)
Consent	Written consent	Oral consent – followed by written consent
Randomisation	On-line	Simple – lowest pack number

PROTOCOL

Version 2.0 Approved 07/10/2022

TICH-3 Synopsis

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), Contraindication to TXA e.g. Seizures

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

Intervention: Tranexamic 1g IV in 100ml sodium chloride over 10 mins, 1g in 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

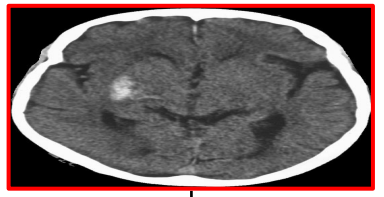
Primary Outcome: Early death (day 7)

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



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 h of onset

CT (or MRI) is conducted pre-recruitment in line with standard care, the haematoma volume measurement will help assess whether the participant is eligible.

Note - ICH secondary to ruptured aneurysm or vascular malformation or brain tumor or ischaemic stroke (haemorrhagic transformation of infarct, HTI) or thrombolysis or venous infarct is NOT spontaneous ICH

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

Exclusion criteria

- Known indication for TXA treatment (e.g. traumatic brain injury) *in view of treating physician*
- Known 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. Patients taking direct oral anticoagulants can be included and are not excluded (SA04).
- Massive ICH (usually when haematoma volume > 60ml)
- Severe coma, Glasgow Coma Scale <5
- Decision for palliative (end of life) care

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?

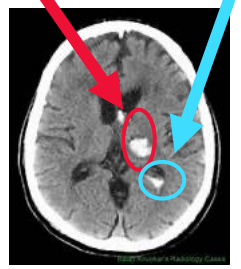
- Yes, all patients should receive standard care, and be treated as per local DOAC ICH guidelines and given anticoagulation reversal agent in accordance with local guidance i.e Idarucizumab or PCC.
  Please ensure you document which reversal agents were given in eCRF
- **Can a reversal agent/PCC be administered 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. LWHM - 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

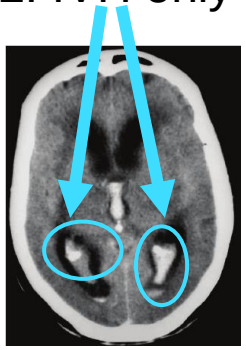
Eligibility: Frequently asked questions

- 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

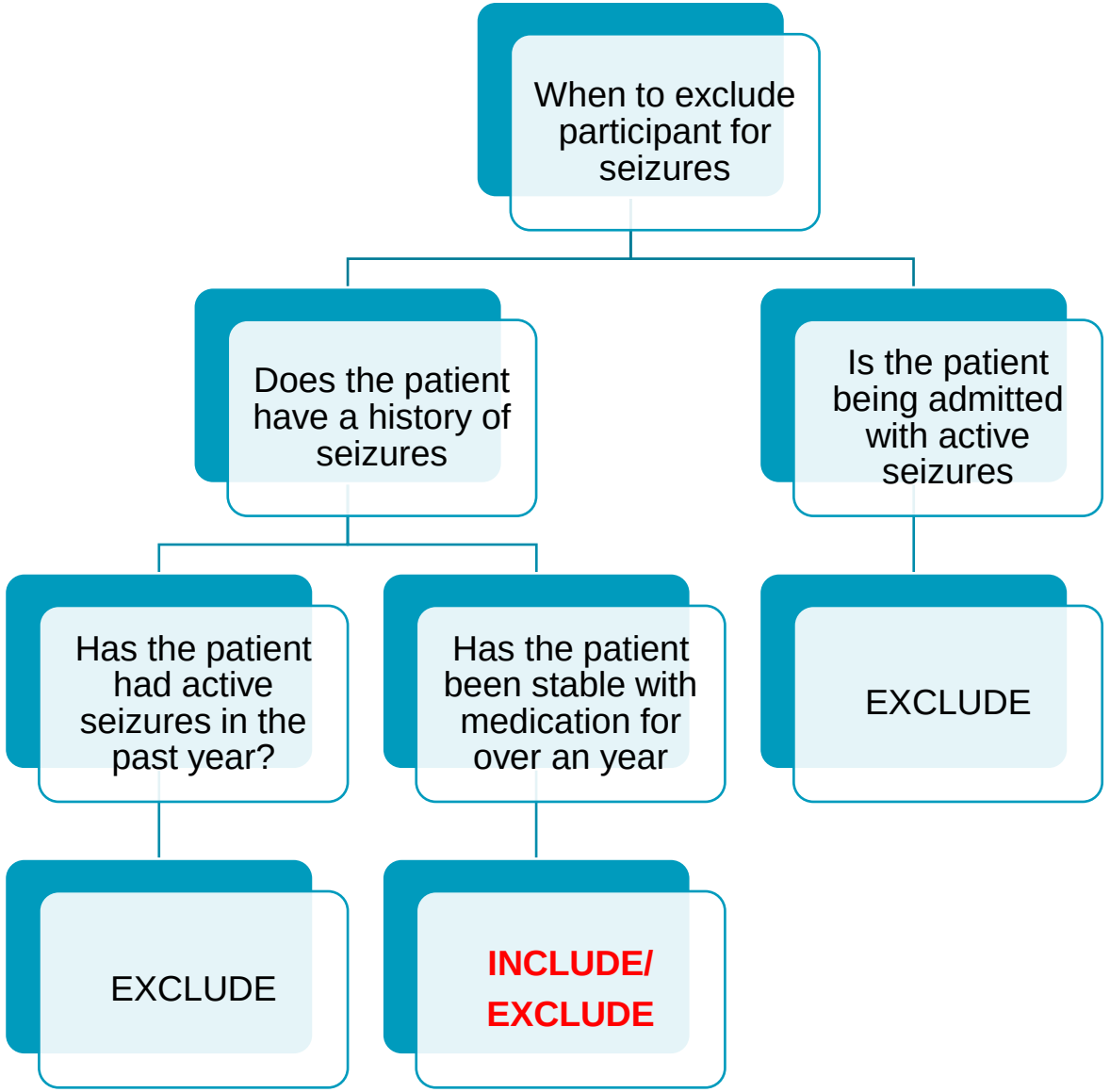
Eligibility: seizures

- 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

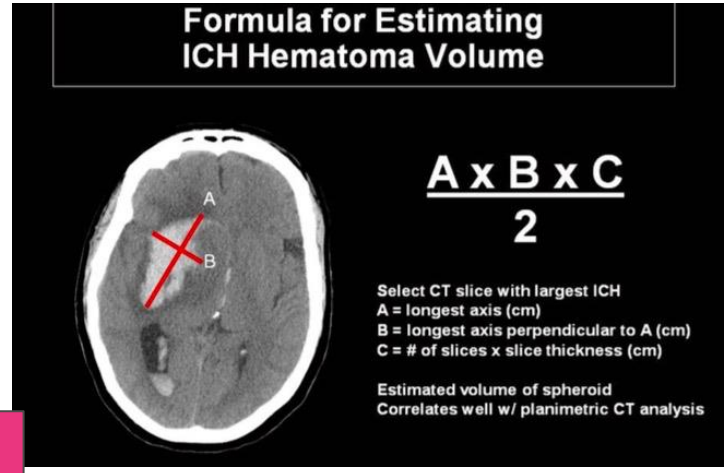


Haematoma volume measurement

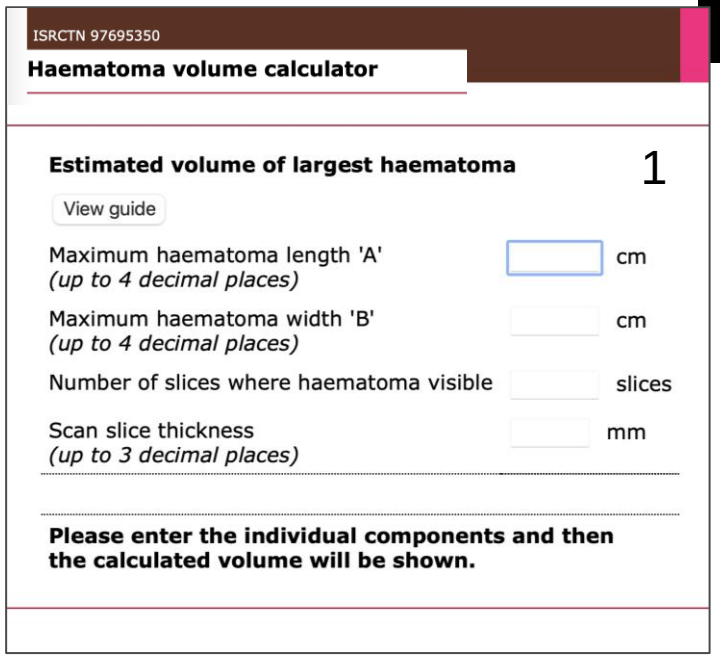
Exclude patients with massive haematoma (usually >60ml)

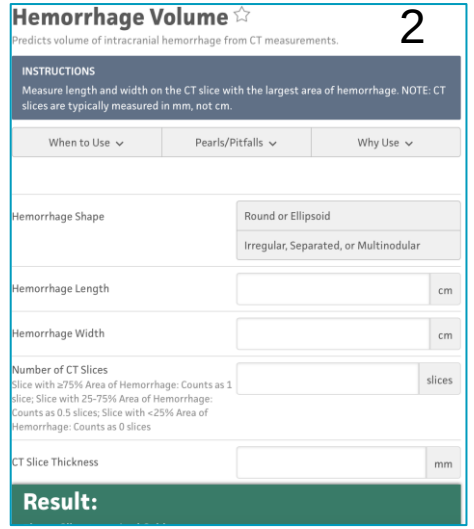
1. If CT scan uses automated haematoma volume software – patient can be enrolled if HV not greater than 60mls
2. Calculate HV manually using TICH-3 HV=ABC/2 calculator on the website[1] or alternatives e.g. mdcalc app[2] Dimensions can be obtained from neuroradiology or measured directly.
3. If ABC/2 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



The ABC/2 calculator can be used to calculate haematoma volumes during eligibility checks, without needing to be logged in.





https://www.mdcalc.com/abc2-formula-intracerebral-hemorrhage-volume

Decision to confirm eligibility rests with treating physician

CONSENT

Emergency Consent Process

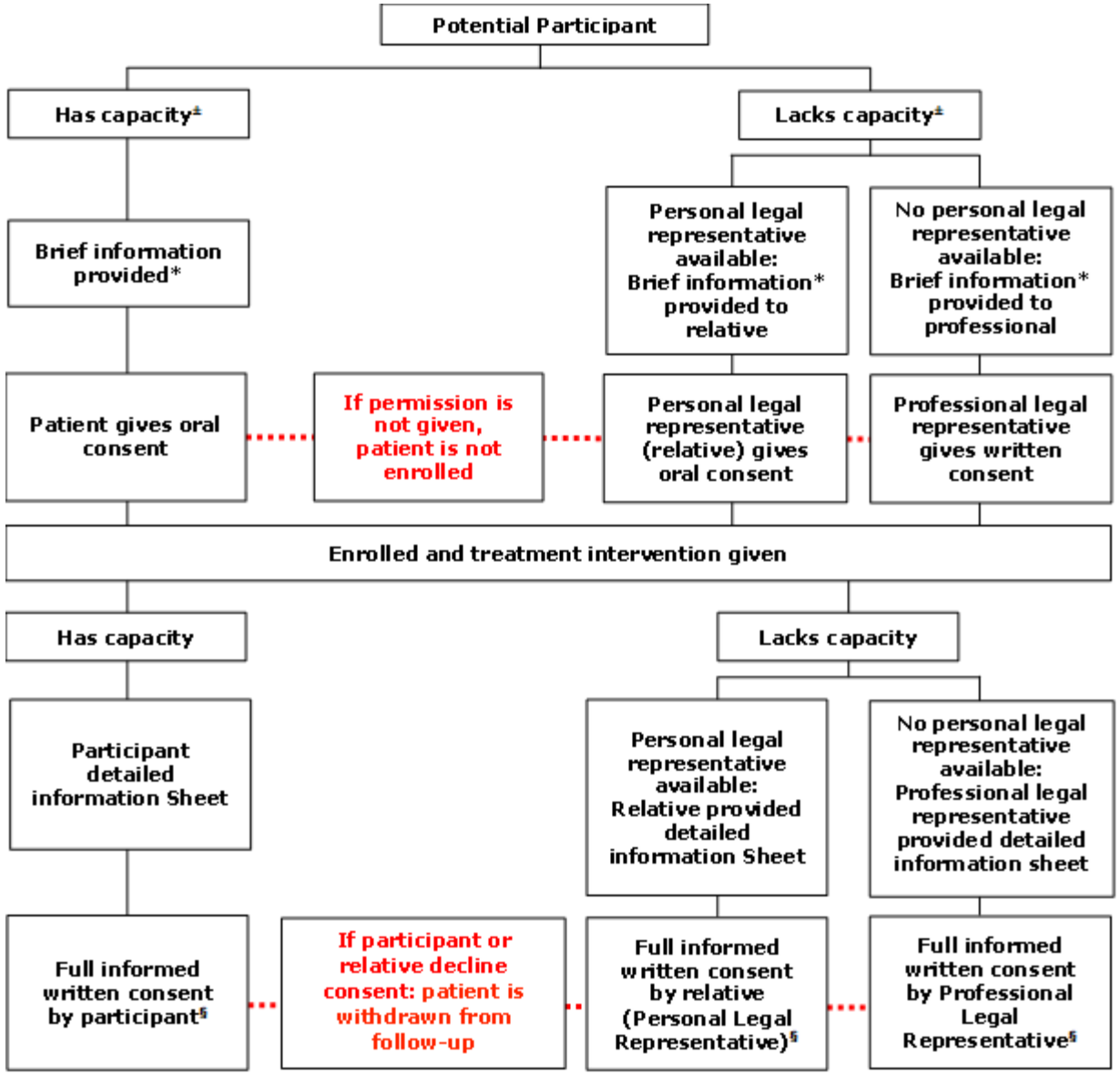
Rapid consent process, participants or relatives provide verbal consent

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

Hierarchy approach 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

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



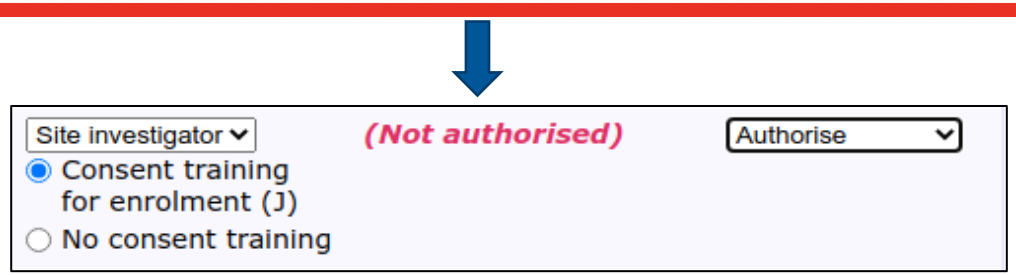
± Assessment of capacity is the responsibility of the treating clinical team
* Further written information provided if requested or required and questions answered.

Delegated roles for consent: J and Z

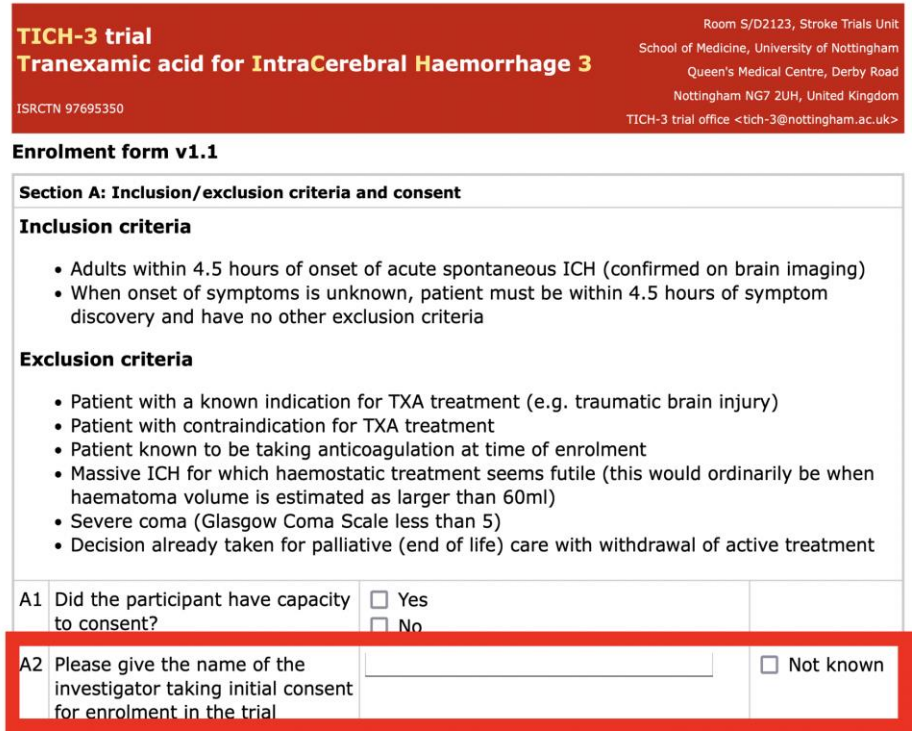
Person taking initial consent must be delegated role J

The PI must select whether code J should be applied as a delegated role.

J. Obtaining consent for enrolment (including oral consent, as appropriate to local policy and practice). **I, PI, DPI**



- Monitoring will check patient was consented by someone on delegation log


TICH-3 trial
Tranexamic acid for IntraCerebral Haemorrhage 3
ISRCTN 97695350

Room S/D2123, Stroke Trials Unit
School of Medicine, University of Nottingham
Queen's Medical Centre, Derby Road
Nottingham NG7 2UH, United Kingdom
TICH-3 trial office <tich-3@nottingham.ac.uk>

Enrolment form v1.1

Section A: Inclusion/exclusion criteria and consent

Inclusion criteria

- Adults within 4.5 hours of onset of acute spontaneous 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

Exclusion criteria

- Patient with a known indication for TXA treatment (e.g. traumatic brain injury)
- Patient with contraindication for TXA treatment
- Patient known to be taking anticoagulation at time of enrolment
- Massive ICH for which haemostatic treatment seems futile (this would ordinarily be when haematoma volume is estimated as larger than 60ml)
- Severe coma (Glasgow Coma Scale less than 5)
- Decision already taken for palliative (end of life) care with withdrawal of active treatment

A1	Did the participant have capacity to consent?	☐ Yes ☐ No	
A2	Please give the name of the investigator taking initial consent for enrolment in the trial		☐ Not known

Person taking written consent must be delegated role Z

Z assigned to those with relevant investigator roles (not pharmacists, radiology etc) and confirmed by PI.

Z. Obtaining follow-on written consent (after initial consent) to continue in the study and for follow-up. **I, PI, DPI**

Professional legal representative consent by an independent doctor

Enrolment consent by independent doctor

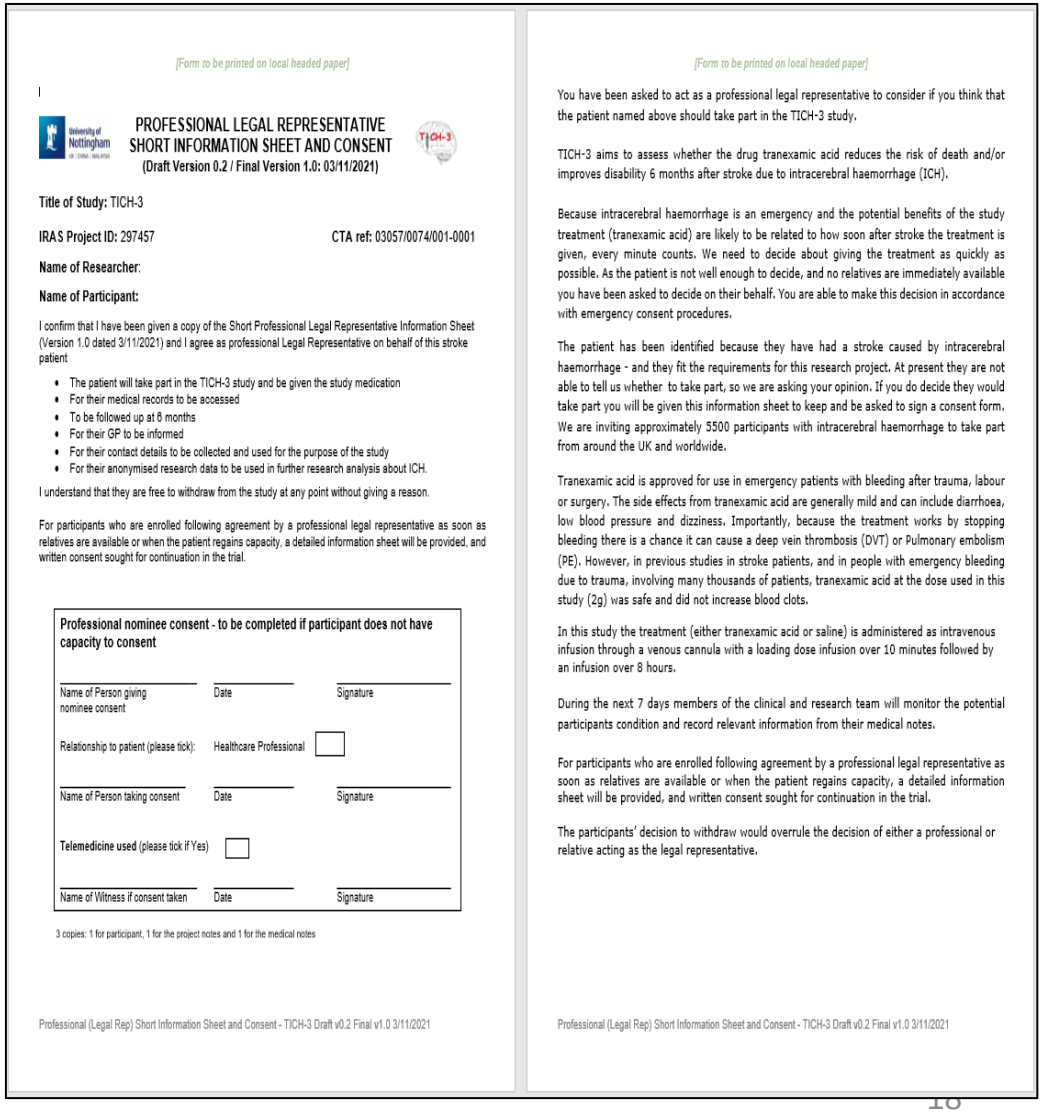
Short Information Sheet and Consent form should be used (pictured to the right). In this scenario this professional legal representative enrolment consent is handwritten and then a follow on written consent form is not required to be completed by the independent doctor. If the participant regains capacity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



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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.

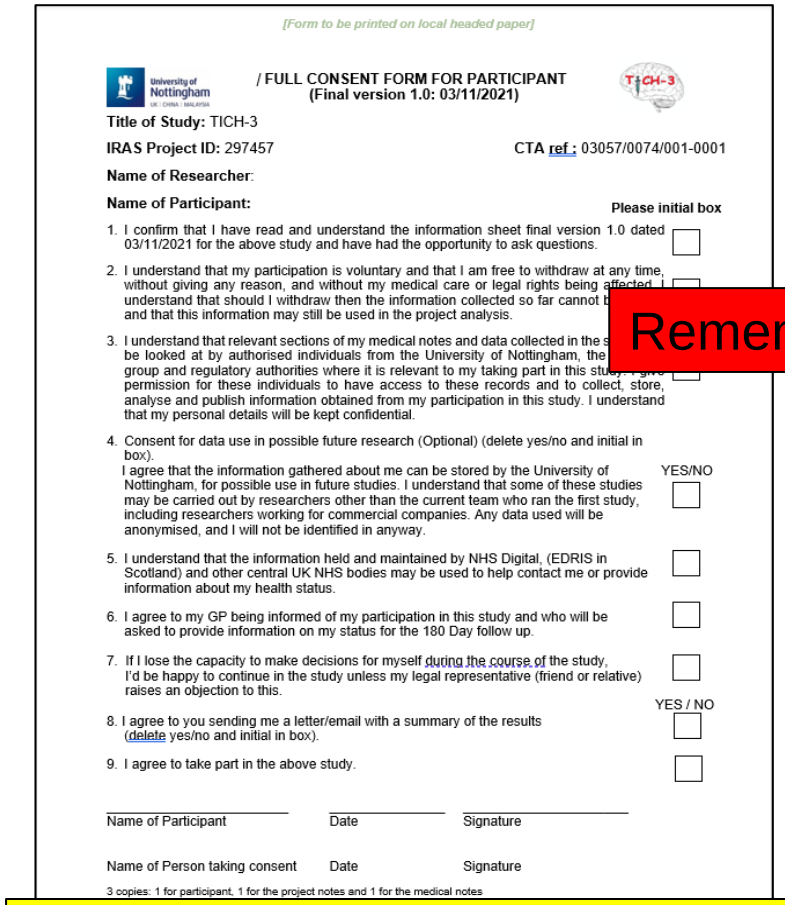
Professional (Legal Rep) Short Information Sheet and Consent - TICH-3 Draft v0.2 Final v1.0 3/11/2021

Written follow on consent

The person taking written consent must be appropriately trained and delegated code Z by the PI to take consent on the delegation log

Full, written informed consent will be sought as soon as practicable, ideally within the next 24 hours. Written informed consent will be sought for access to medical notes and for participation in the trial follow up. The participant information sheet will be provided to the participant at this time if not already provided.

Please localise the consent forms and participant information sheets prior to printing, see WPD preparing trial documentation to help you with this https://stroke.nottingham.ac.uk/sif/docs/?sid=TICH-3



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/ FULL CONSENT FORM FOR PARTICIPANT
(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:

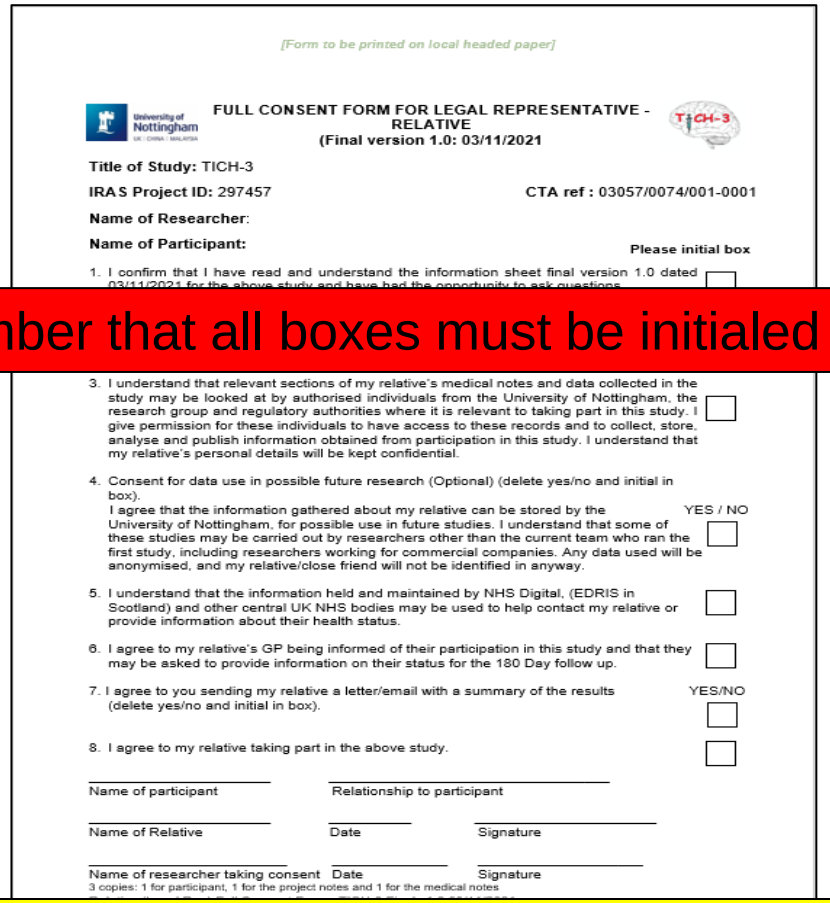
Name of Participant: **Please initial box**

1. I confirm that I have read and understand the information sheet final version 1.0 dated 03/11/2021 for the above study and have had the opportunity to ask questions.
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected. I understand that should I withdraw then the information collected so far cannot be and that this information may still be used in the project analysis.
3. I understand that relevant sections of my medical notes and data collected in the s be looked at by authorised individuals from the University of Nottingham, the group and regulatory authorities where it is relevant to my taking part in this stu permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from my participation in this study. I understand that my personal details will be kept confidential.
4. Consent for data use in possible future research (Optional) (delete yes/no and initial in box).
   I agree that the information gathered about me can be stored by the University of Nottingham, for possible use in future studies. I understand that some of these studies may be carried out by researchers other than the current team who ran the first study, including researchers working for commercial companies. Any data used will be anonymised, and I will not be identified in anyway. YES/NO
5. I understand that the information held and maintained by NHS Digital, (EDRIS in Scotland) and other central UK NHS bodies may be used to help contact me or provide information about my health status.
6. I agree to my GP being informed of my participation in this study and who will be asked to provide information on my status for the 180 Day follow up.
7. If I lose the capacity to make decisions for myself during the course of the study, I'd be happy to continue in the study unless my legal representative (friend or relative) raises an objection to this.
8. I agree to you sending me a letter/email with a summary of the results (delete yes/no and initial in box). YES / NO
9. I agree to take part in the above study.

Name of Participant Date Signature

Name of Person taking consent Date Signature

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



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FULL CONSENT FORM FOR LEGAL REPRESENTATIVE - RELATIVE
(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: **Please initial box**

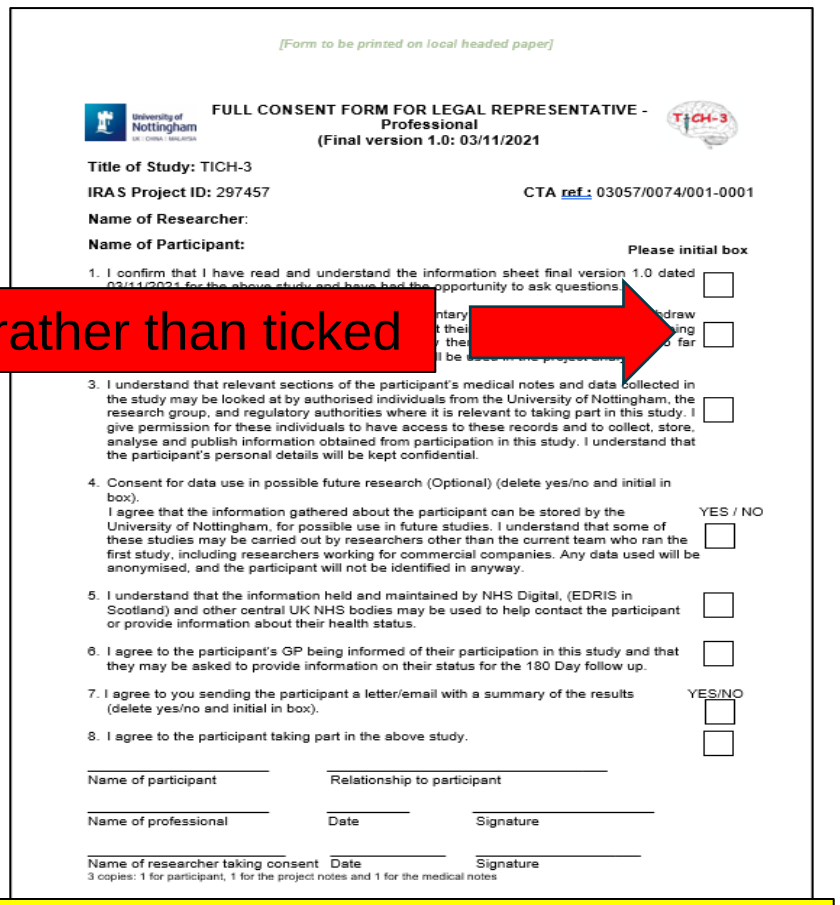
1. I confirm that I have read and understand the information sheet final version 1.0 dated 03/11/2021 for the above study and have had the opportunity to ask questions.
3. I understand that relevant sections of my relative's medical notes and data collected in the study may be looked at by authorised individuals from the University of Nottingham, the research group and regulatory authorities where it is relevant to taking part in this study. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from participation in this study. I understand that my relative's personal details will be kept confidential.
4. Consent for data use in possible future research (Optional) (delete yes/no and initial in box).
   I agree that the information gathered about my relative can be stored by the University of Nottingham, for possible use in future studies. I understand that some of these studies may be carried out by researchers other than the current team who ran the first study, including researchers working for commercial companies. Any data used will be anonymised, and my relative/close friend will not be identified in anyway. YES / NO
5. I understand that the information held and maintained by NHS Digital, (EDRIS in Scotland) and other central UK NHS bodies may be used to help contact my relative or provide information about their health status.
6. I agree to my relative's GP being informed of their participation in this study and that they may be asked to provide information on their status for the 180 Day follow up.
7. I agree to you sending my relative a letter/email with a summary of the results (delete yes/no and initial in box). YES/NO
8. I agree to my relative taking part in the above study.

Name of participant Relationship to participant

Name of Relative Date Signature

Name of researcher taking consent Date Signature

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



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FULL CONSENT FORM FOR LEGAL REPRESENTATIVE - Professional
(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: **Please initial box**

1. I confirm that I have read and understand the information sheet final version 1.0 dated 03/11/2021 for the above study and have had the opportunity to ask questions.
3. I understand that relevant sections of the participant's medical notes and data collected in the study may be looked at by authorised individuals from the University of Nottingham, the research group, and regulatory authorities where it is relevant to taking part in this study. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from participation in this study. I understand that the participant's personal details will be kept confidential.
4. Consent for data use in possible future research (Optional) (delete yes/no and initial in box).
   I agree that the information gathered about the participant can be stored by the University of Nottingham, for possible use in future studies. I understand that some of these studies may be carried out by researchers other than the current team who ran the first study, including researchers working for commercial companies. Any data used will be anonymised, and the participant will not be identified in anyway. YES / NO
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6. I agree to the participant's GP being informed of their participation in this study and that they may be asked to provide information on their status for the 180 Day follow up.
7. I agree to you sending the participant a letter/email with a summary of the results (delete yes/no and initial in box). YES/NO
8. I agree to the participant taking part in the above study.

Name of participant Relationship to participant

Name of professional Date Signature

Name of researcher taking consent Date Signature

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

Remember that all boxes must be initialed rather than ticked

If your site is randomised to enhanced consent in swat - please use video before taking written consent

3 copies of consent form – 1 patient, 1 medical notes, 1 research

Consent: Frequently asked questions

Who can act as the professional legal representative?

Independent doctor must not be an investigator in the TICH-3 trial (i.e. not on delegation log), no specific grade of doctor is required (but usually registrar or above).The independent doctor can give permission via telemedicine if not on site.

How is consent witnessed?

When a witness is used for consent the independent observer can be anyone, they do not need to be on the delegation log, it could be one of the ward staff, for example. The witness should note what they are witnessing (i.e. participant gave consent but unable to sign due to dominant hand weakness), print their name, sign and date. This should be documented on the consent form in the blank space near the signature section.

Where should we document the consent process?

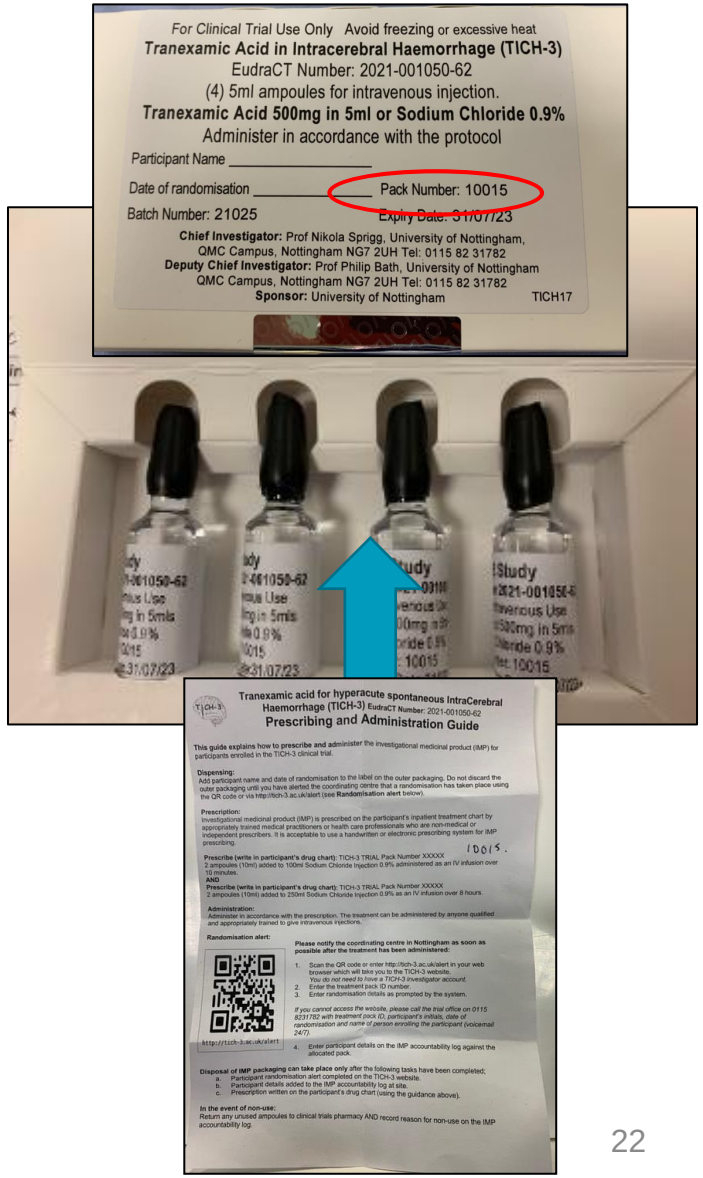
The consent process should be clearly detailed in the medical notes

SEE ADDITIONAL SLIDES OBTAINING ORAL CONSENT AND DOCUMENTING CONSENT AT THE END OF THIS PRESENTATION

RANDOMISATION

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 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

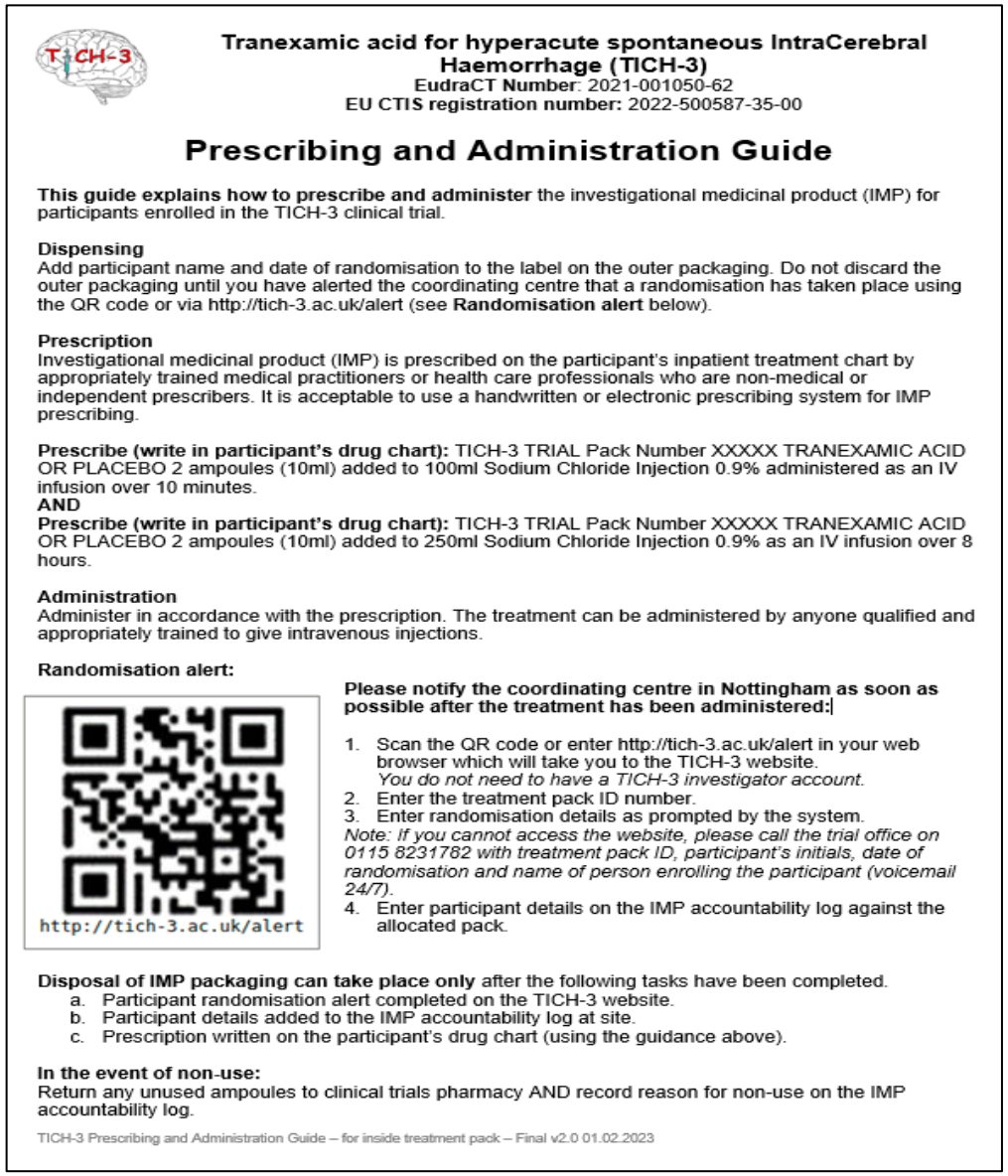
TICH-3 TRIAL Pack Number XXXXX

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 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).

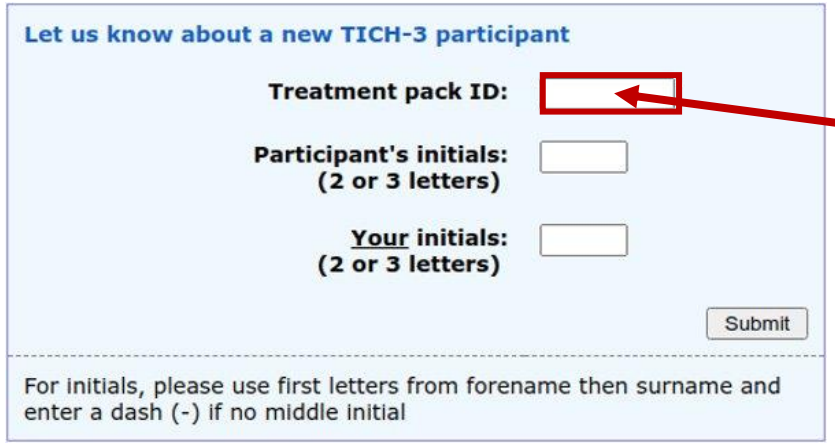
In the event of non-use:
Return any unused ampoules to clinical trials pharmacy AND record reason for non-use on the IMP accountability log.

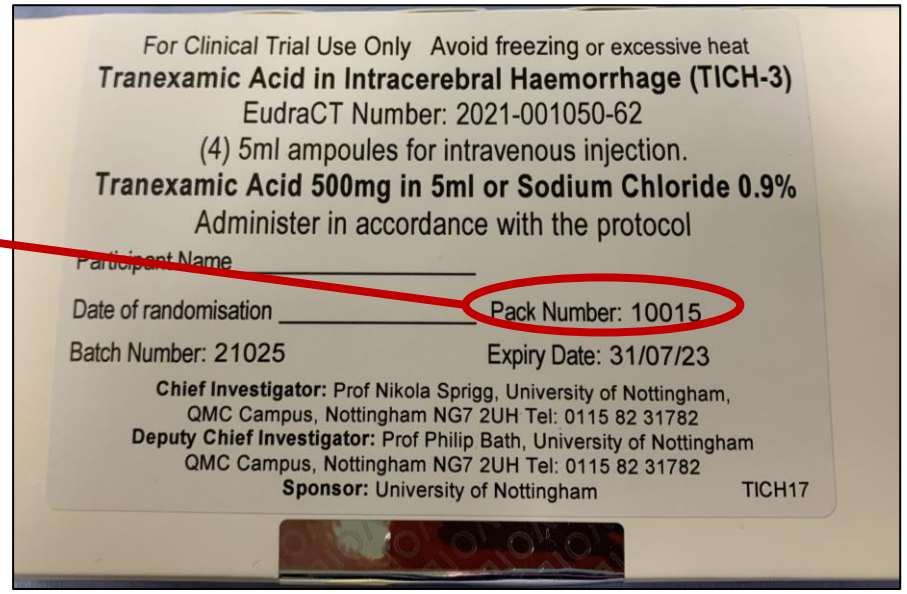
Randomisation Alert

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

✓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 WPD (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

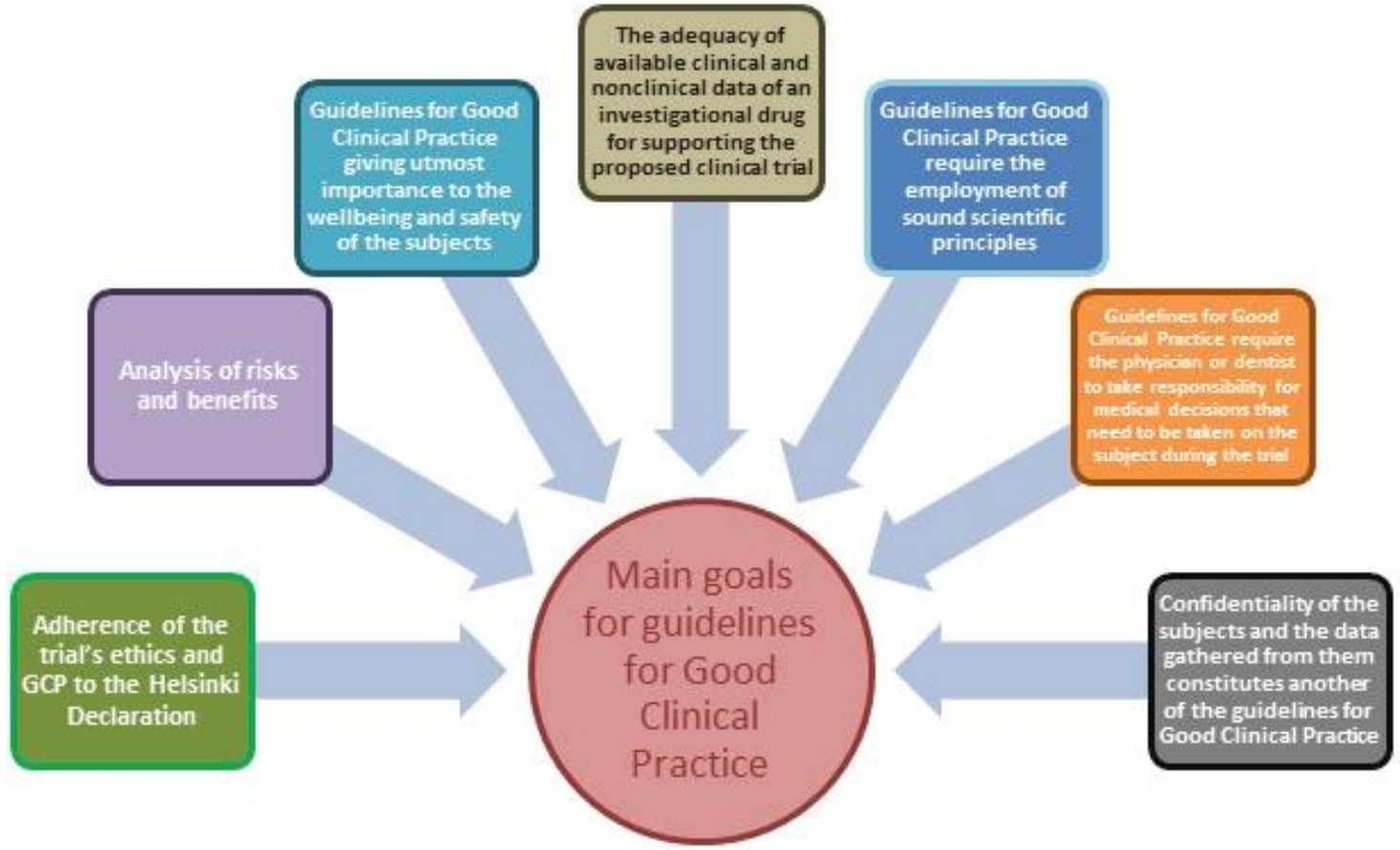
SAFETY MONITORING

Safety outcomes
Serious adverse reaction (SAR)
Suspected Unexpected Serious Adverse Reaction (SUSAR)
Serious adverse event (SAE)

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

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

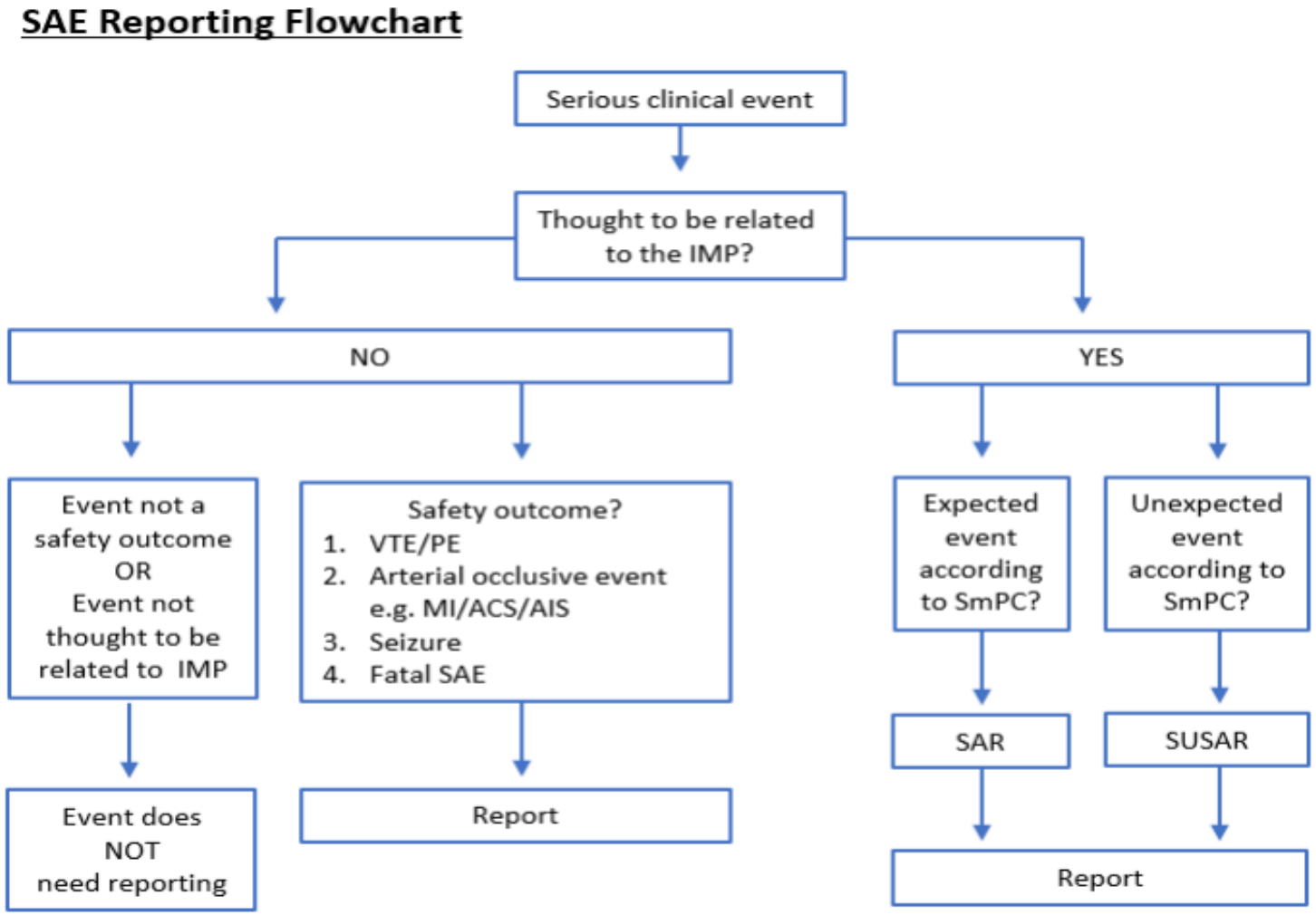
Serious adverse reactions (SAR) or Suspected Unexpected Serious Adverse Reactions (SUSAR):

- 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



REPORTING SAEs (1)

Assessing relation to the study drug

When submitted SAEs or safety events please select possible only if you suspect the IMP may be related to the event. If you think it is unlikely but cannot absolutely exclude a relationship, please select improbable. All events that are reported as probable need to have causality assessed as could be a SAR or SUSAR. If in doubt, please speak to your PI, site medic or contact the coordinating centre.

A10a Relationship to study drug	☐ Not related ☐ Improbable ☐ Possible ☐ Probable ☐ Definite

Event classification

MHRA guidelines are that if you suspect an event to be possibly/probably/defiantly related that the event categorisation must be a SAR or a SUSAR, if you think it is unlikely to be related to the study drug (not related/improbable) then this is an SAE.

A10b Please classify the event	☐ SAR ☐ SAE ☐ SUSAR **Please assess if expected according to SmPC.** Expectedness should only be assessed in events that are thought to be possibly/probably/definitely related to the IMP.

REPORTING SAEs (2)

Please remember to update on-going SAEs when resolved if patient dies

A12a	Clinical outcome of this event	☐ Resolved ☐ Event ongoing ☐ Recovered with sequelae ☐ Died
A12b	If event ongoing or recovered with sequelae, please provide details	

Ongoing SAEs

If an ongoing SAE submitted e.g. seizure/PE and then patient dies, unless you think the death was related to this event please complete a data correction that this event was resolved and then submit a new SAE for the fatal event.

Cause of death

Please make sure you always provide details in question A4 of what was the cause of death – only use death unattended when patient is found in the community with no known cause

A4	Please describe the event, e.g. new limb weakness, crushing chest pain, bleeding gums, rash **Note: Death is an end result, not an independent event**	

Suspected SUSARs

If you are suspecting a SUSAR please call the emergency helpline phone numbers.

For urgent medical enquiries (including unblinding), and for randomisation problems, you can contact the following emergency mobile numbers.

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

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

What to do in Case of Emergency

Safety events during the infusion

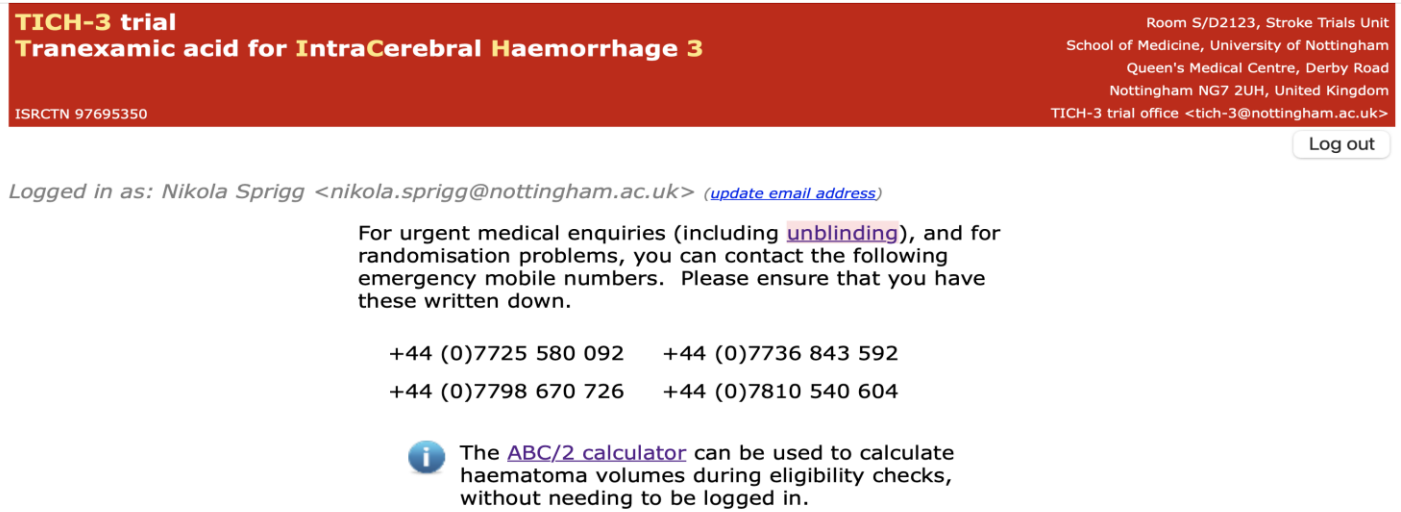
If seizure, thrombosis or arterial occlusion occurs during infusion, the infusion must be stopped immediately. This will be recorded as part of the trial documentation and safety monitoring.

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.



What to do in the event of a Protocol Violation

A protocol violation is a major variation in practice from the trial protocol, for example where a participant is enrolled in spite of not fulfilling all the inclusion and exclusion criteria (e.g. lack of consent, randomisation after 4.5 hours after ICH), or where deviations from the protocol could affect participant safety, the trial delivery or interpretation significantly.

Important to report any protocol violations to coordinating centre straight away

All protocol violations must be reported to the Chief Investigator, via the online electronic case report form and/or telephone call. The CI will notify the Sponsor if a violation has an impact on participant safety or integrity of the trial data. The Sponsor will advise on appropriate measures to address the occurrence, which may include reporting of a serious GCP breach, internal audit of the trial and seeking counsel of the trial committees.

Sponsors SOPS on the document page; see TA016 Serious GCP Breach Reporting

IMP AND PHARMACY

Storage of IMP

Temperature monitoring is not required. The packs will be stored at room temperature and protected from excessive heat and freezing.

The IMP is stored in a secure, limited access storage area, this could be in the A&E, stroke ward or thrombolysis bag.

Each site will maintain an accountability log and be responsible for the storage and issue of trial treatment.

Ensure all members of the local team are aware of where the IMP and related documents (consent forms/PIS) are stored.

The local site is responsible for the accountability and monitoring of the IMP.

Drug dispatch

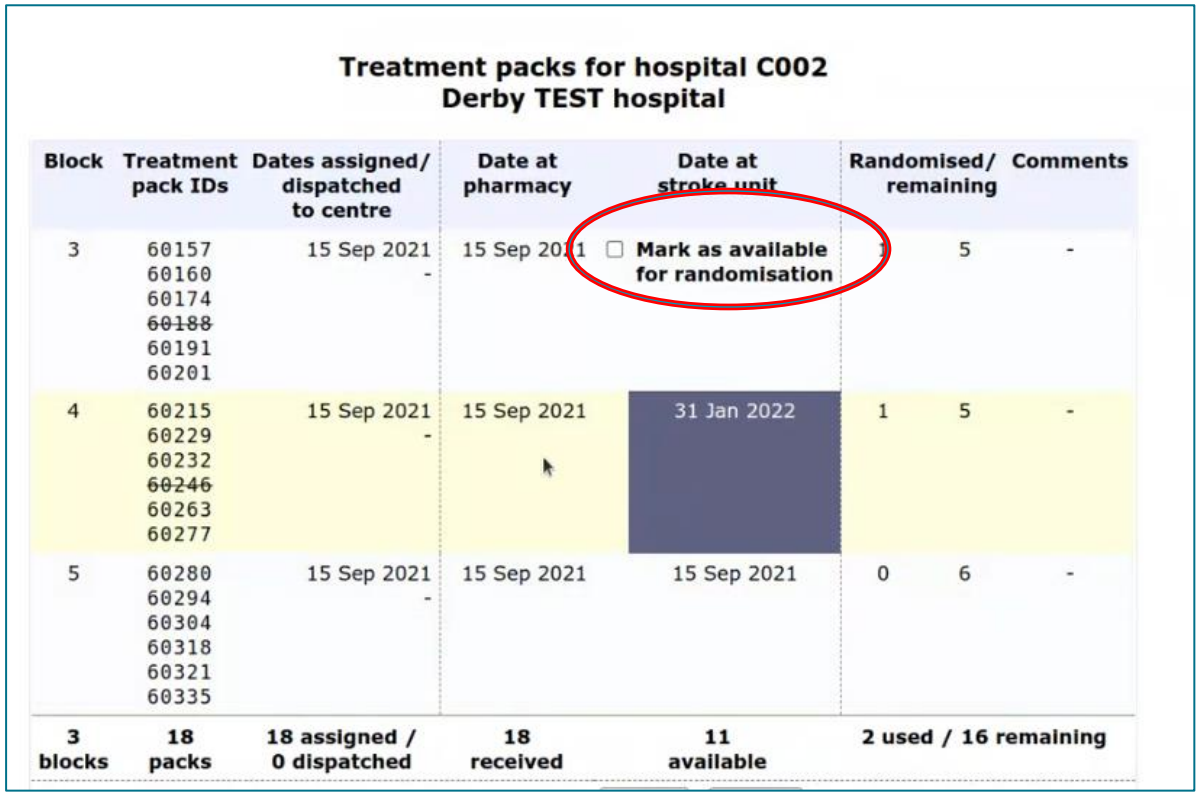
- Coordinating centre will order drug for dispatch once site is nearly ready to commence recruitment
- Blinded treatment packs will be randomly assigned to sites in blocks of 6 treatment packs

- Pharmacy informed of dispatch by email
- Delivery after noon next day of ordering

  > No deliveries out of hours/weekends

- Pharmacy complete inventory log and part of accountability log and pass accountability log and treatment packs to research team for storage

- Investigator (this can be research team or pharmacy team) needs to ‘mark available for randomisation’ on TICH-3 website
- Coordinating centre will re-order/issue when stock running low or when drug due to expire



Treatment packs for hospital C002
Derby TEST hospital

Block	Treatment pack IDs	Dates assigned/ dispatched to centre	Date at pharmacy	Date at stroke unit	Randomised/ remaining		Comments
3	60157 60160 60174 ~~60188~~ 60191 60201	15 Sep 2021 -	15 Sep 2021	☐ Mark as available for randomisation	1	5	-
4	60215 60229 60232 ~~60246~~ 60263 60277	15 Sep 2021 -	15 Sep 2021	31 Jan 2022	1	5	-
5	60280 60294 60304 60318 60321 60335	15 Sep 2021 -	15 Sep 2021	15 Sep 2021	0	6	-
3 blocks	18 packs	18 assigned / 0 dispatched	18 received	11 available	2 used / 16 remaining		

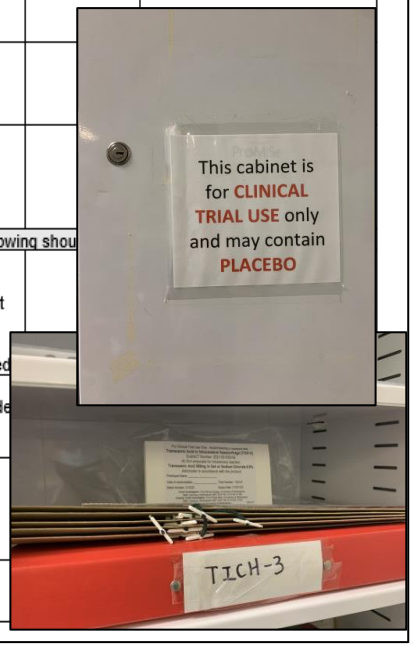
IMP Paperwork (1): Set up, IMP receipt

1

Assessment and monitoring of remote IMP storage

Study Title:	Tranexamic acid for hyperacute spontaneous IntraCerebral Haemorrhage (TICH-3)
EudraCT No:	2021-001050-62
Chief Investigator:	Professor Nikola Sprigg
Site:	
Principal Investigator:	

Description of proposed area for IMP		Suitable for use (Yes/No)	Comments
Security measures in place (location, access controls etc)			
Size and description of proposed storage area (shelves, cupboards etc)			
If not for exclusive use, what controls are in place to segregate IMP from other medicines			
Description of IMP management. The following shou			
Dispensing procedure with documented training for research team	Select the next lowest numbered available treatment pack. Prescribing and administration guide to be followed		
Accountability procedure with documented training for research team	Prescribing and administration guide to be followed.		
A procedure for transfer of IMP between pharmacy and proposed storage facility			
Proposed methods of maintaining pharmacy oversight			



1. Assessment & monitoring of remote IMP storage – Pre-set up:

Pharmacy and trial team to complete form as part of site set up, Pharmacy and local trial team to complete, sign and then return to coordinating centre as part of site set up, before green light can be issued.

2. IMP Inventory Log

Pharmacy to complete inventory upon receipt of the IMP treatment packs (will be sent to sites in blocks of 6 treatment packs). Inventory log to be retained in the pharmacy site file.

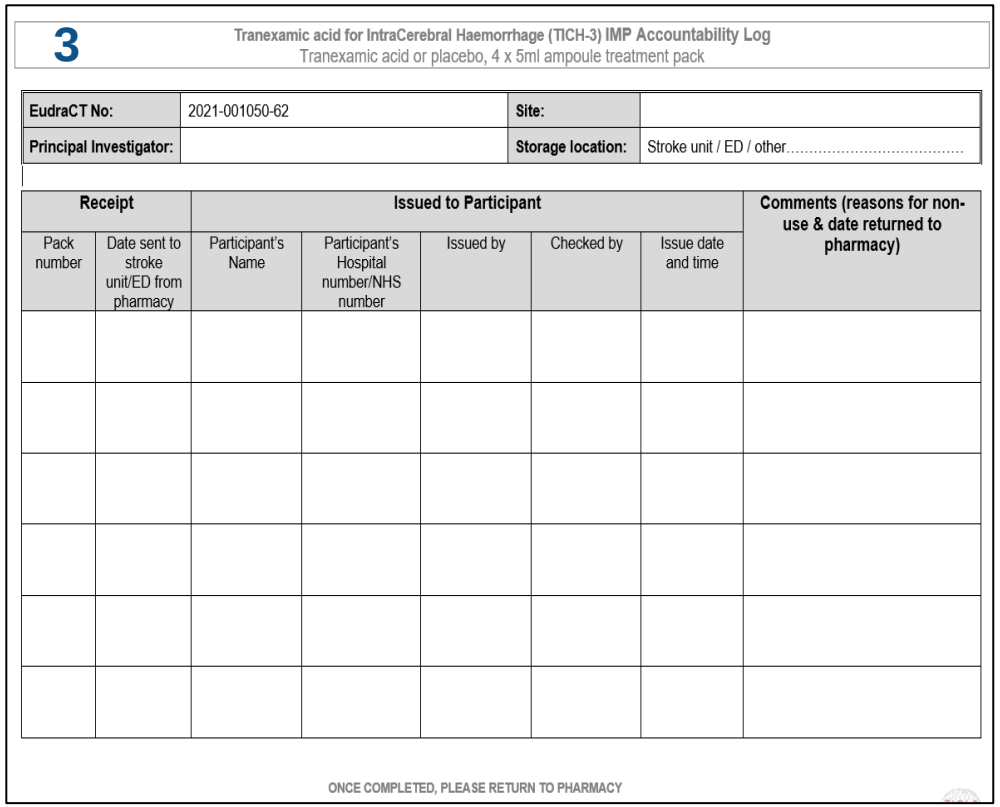
2

Tranexamic acid for IntraCerebral Haemorrhage (TICH-3) IMP Inventory Log
Tranexamic acid or placebo, 4 x 5ml ampoule treatment pack

EudraCT No:	2021-001050-62	**Site:**	
Principal Investigator:		**Storage location:**	Stroke unit / ED / other……

Date	Block number	Pack number	Do not use after	Received by	Date sent to stroke unit/ED from pharmacy	Initials	Comments

IMP Paperwork (2): Ongoing



3

Tranexamic acid for IntraCerebral Haemorrhage (TICH-3) IMP Accountability Log
Tranexamic acid or placebo, 4 x 5ml ampoule treatment pack

EudraCT No:	2021-001050-62	**Site:**	
Principal Investigator:		**Storage location:**	Stroke unit / ED / other.....

Receipt		**Issued to Participant**					**Comments (reasons for non-use & date returned to pharmacy)**
Pack number	Date sent to stroke unit/ED from pharmacy	Participant's Name	Participant's Hospital number/NHS number	Issued by	Checked by	Issue date and time	

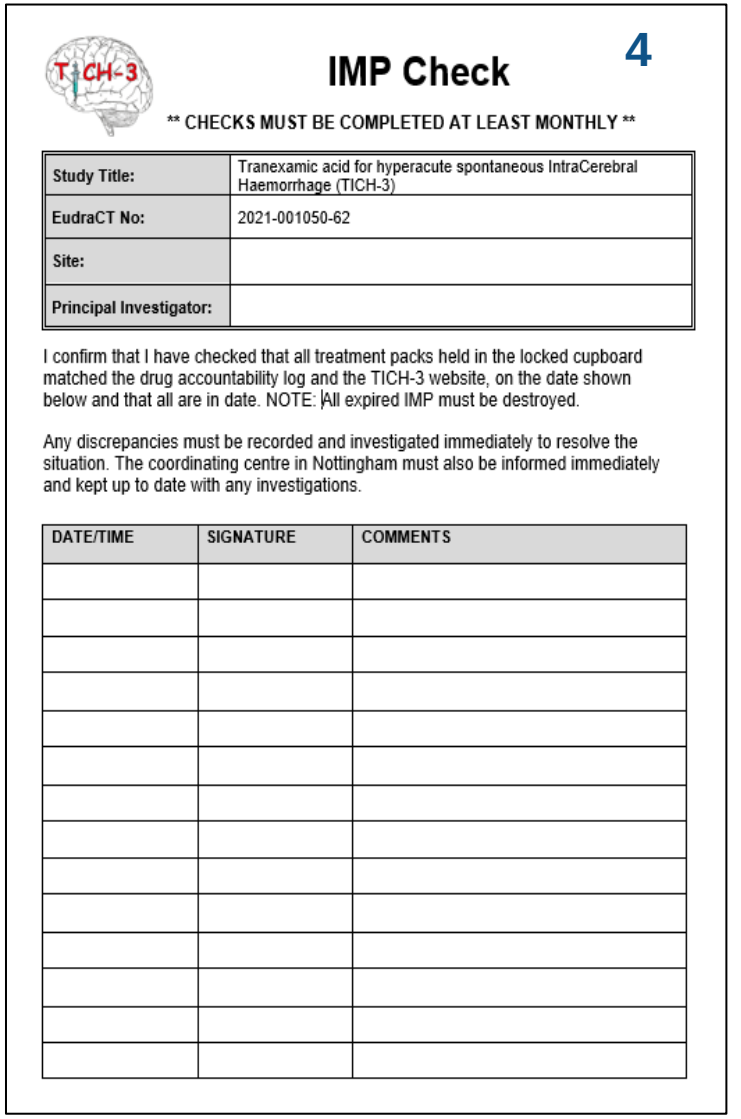
ONCE COMPLETED, PLEASE RETURN TO PHARMACY

3. IMP Accountability Log

Pharmacy to complete the first two left columns (pack number and date sent to stroke unit/ED). The accountability log will then be passed to the research team for them to complete when a treatment pack is randomised to a participant. Once the IMP is in the storage place please mark on the TICH-3 website that the treatment pack is ready for randomisation. Once this form is complete please return to local site pharmacy.

Note: person completing 'issued by' and 'checked by' do not need to be on delegation log or GCP trained.

4. IMP Check



4

IMP Check

** CHECKS MUST BE COMPLETED AT LEAST MONTHLY **

Study Title:	Tranexamic acid for hyperacute spontaneous IntraCerebral Haemorrhage (TICH-3)
EudraCT No:	2021-001050-62
Site:	
Principal Investigator:	

I confirm that I have checked that all treatment packs held in the locked cupboard matched the drug accountability log and the TICH-3 website, on the date shown below and that all are in date. NOTE: All expired IMP must be destroyed.

Any discrepancies must be recorded and investigated immediately to resolve the situation. The coordinating centre in Nottingham must also be informed immediately and kept up to date with any investigations.

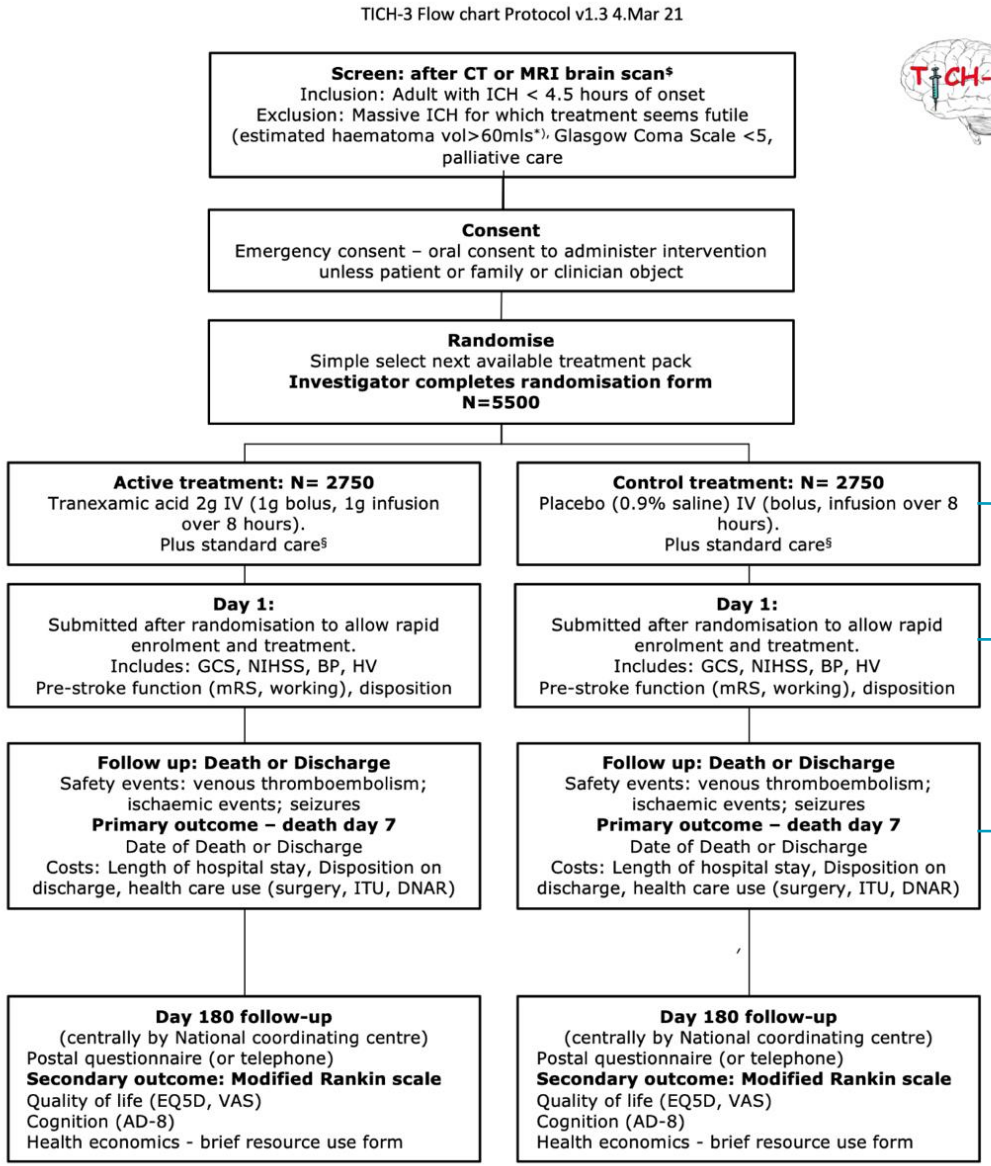
DATE/TIME	SIGNATURE	COMMENTS

The research team should complete checks of the IMP at least monthly. Any discrepancies are required to be investigated immediately and reported to the coordinating centre.

The inventory logs, completed accountability logs and IMP check should be stored in your site file. We do not require these to be uploaded to the TICH-3 website or sent to us unless requested.

DATA COLLECTION

Trial Flow Chart:



Electronic Case Report Forms (eCRFs) to be completed by local site

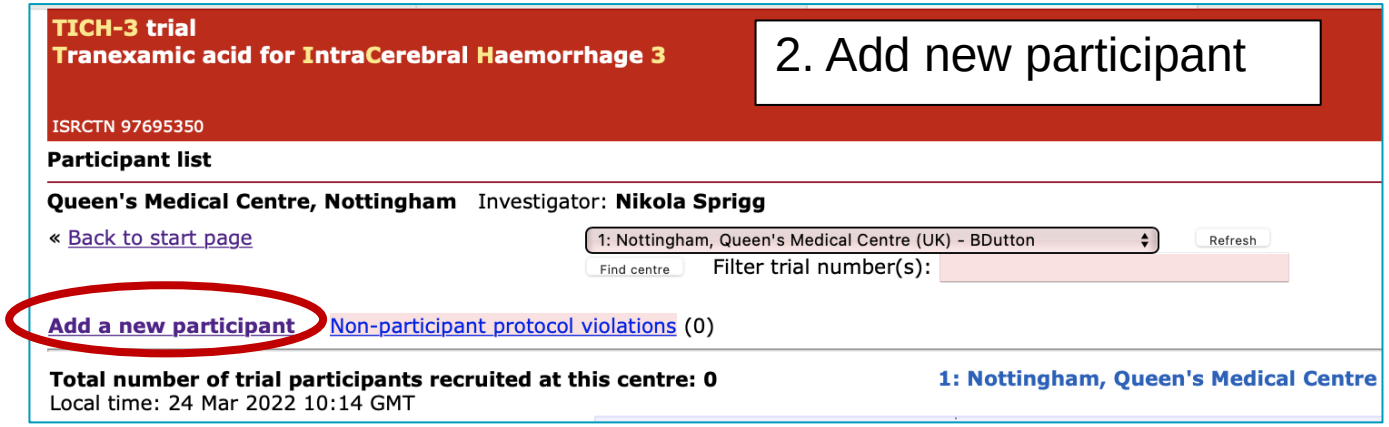
- QR code Randomisation alert (as soon as possible after treatment started)
- Enrolment form
- Contact details form
- Day 7 follow-up AND Discharge/death

(See separate guidance for completion of these eCRFs)

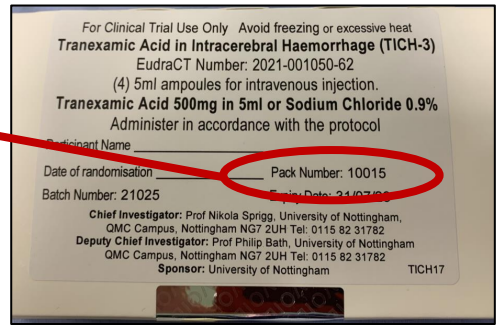
Adding a new participant to the database

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

1. Complete randomisation alert

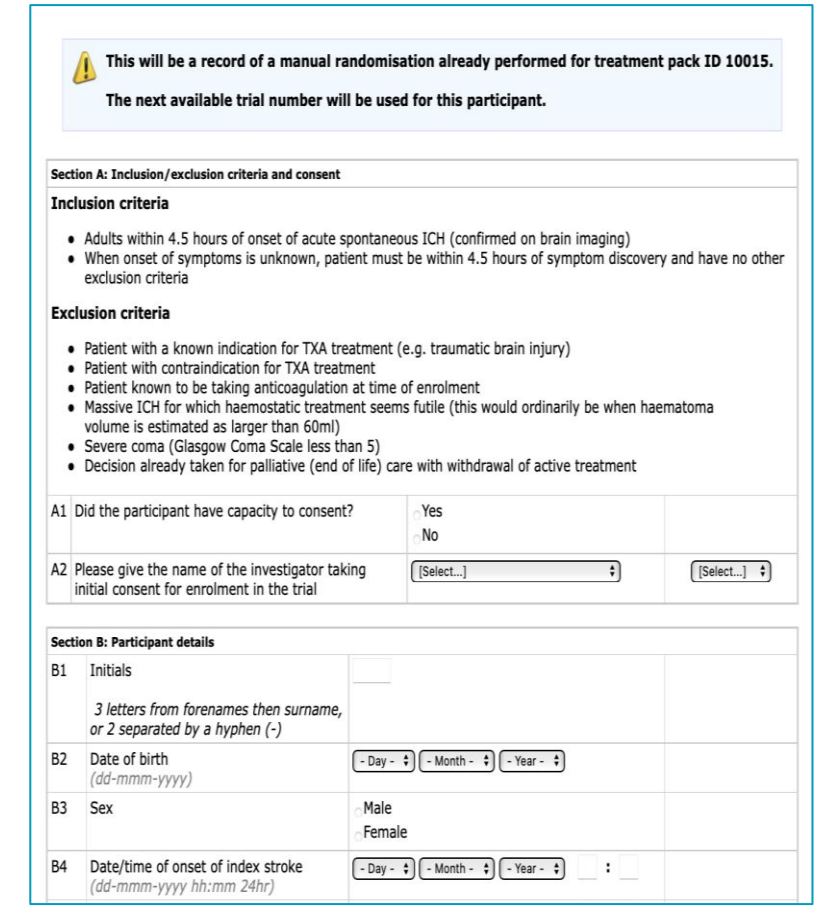


3. Need treatment pack ID number

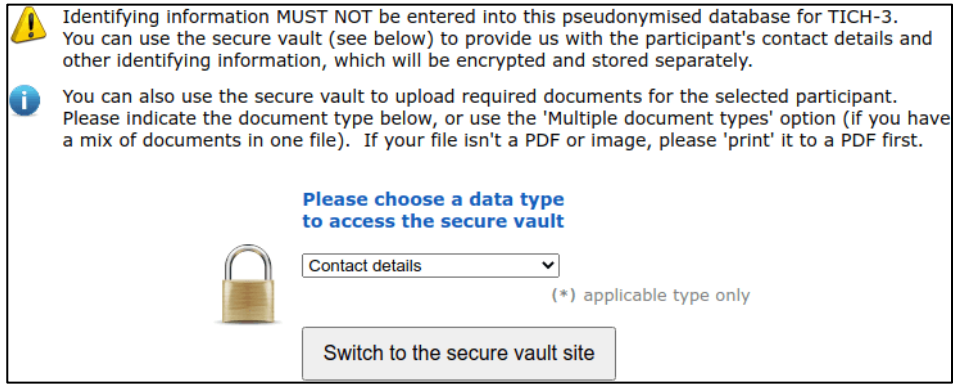


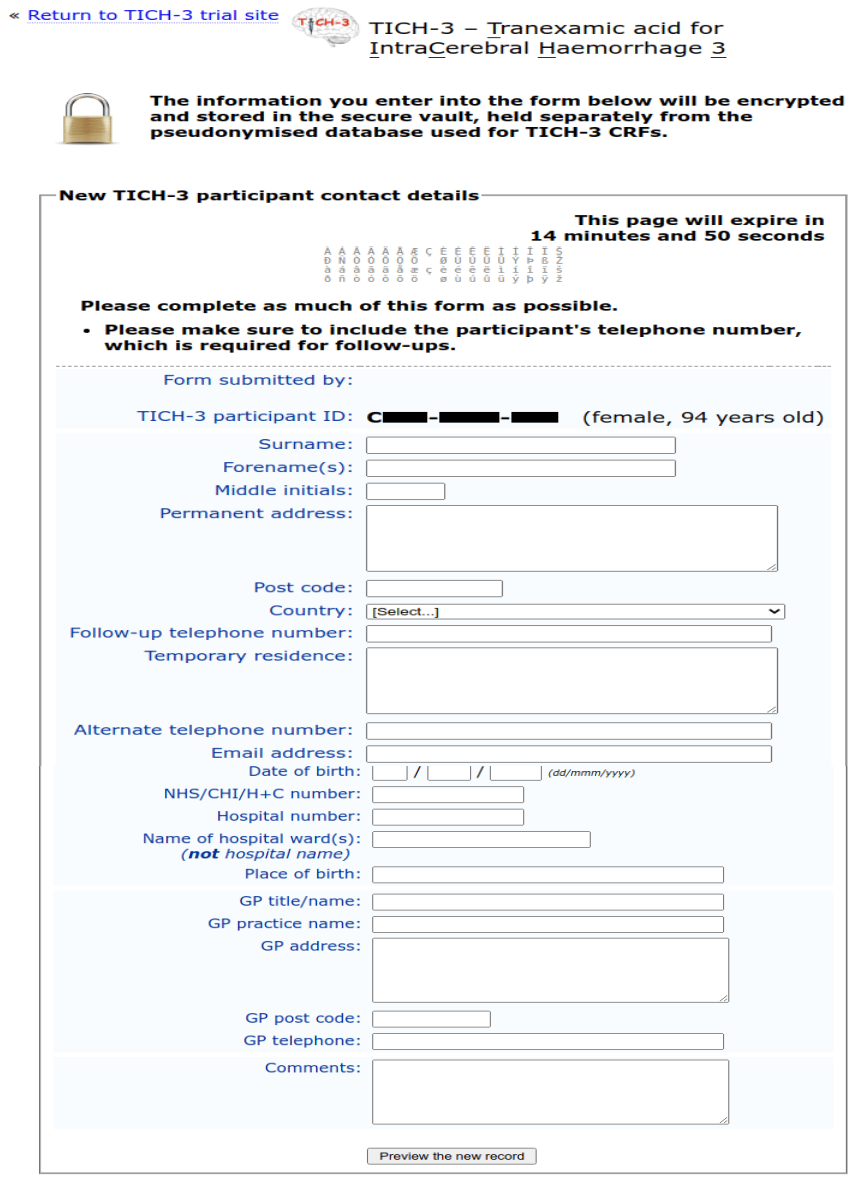
4. Confirm randomisation site

5. Complete enrollment form



Contact Details Form





It is really important to collect the participants identifiable data (as agreed on the consent form) so that the coordinating centre can contact the participant and the participant's GP for the Day 180 follow-up.

Identifiable data will be collected in the ‘secure vault’ which is accessed via the TICH-3 website. The secure vault site will encrypt the identifiable data so that it can only be accessed by the co-ordinating team, stored separately from the other data collected.

Enrolment, Day 7 follow-up and Discharge/death eCRF

- The following eCRFs need to be completed in order on the TICH-3 website http://tich-3.ac.uk/live/

1. Enrolment form
2. Day 7 follow-up
3. Discharge or death in hospital

Total number of trial participants recruited at this centre: 2
Local time: 6 Apr 2022 13:13 BST

✔ There are no active data queries

1: Nottingham, Queen's Medical Centre (UK) - BD

Participant ID/age at randomisation	Event date	Treatment pack ID	Randomised	Contacts/ documents	Day 7 follow-up	Discharge/ death	SAEs
C001-0001-F-G 93	23 Mar 2022	10015	23 Mar 2022	Y NNN	29 Mar 2022	27 Mar 2022	‡ Select 1
C001-0002-F-0 65	29 Mar 2022	10029	29 Mar 2022	Y NNN	4 Apr 2022	–	Select

- Trial team members on the delegation log will have received an investigator ID and password to securely log in to the TICH-3 website
- You will need to enter the participants date of birth when entering data to confirm correct participant
- The forms can be completed early if the participant dies or is discharged before day 7
  Only trial team members signed off on the delegation log can enter data

Participant repatriated prior to day 7

Site to site transfer

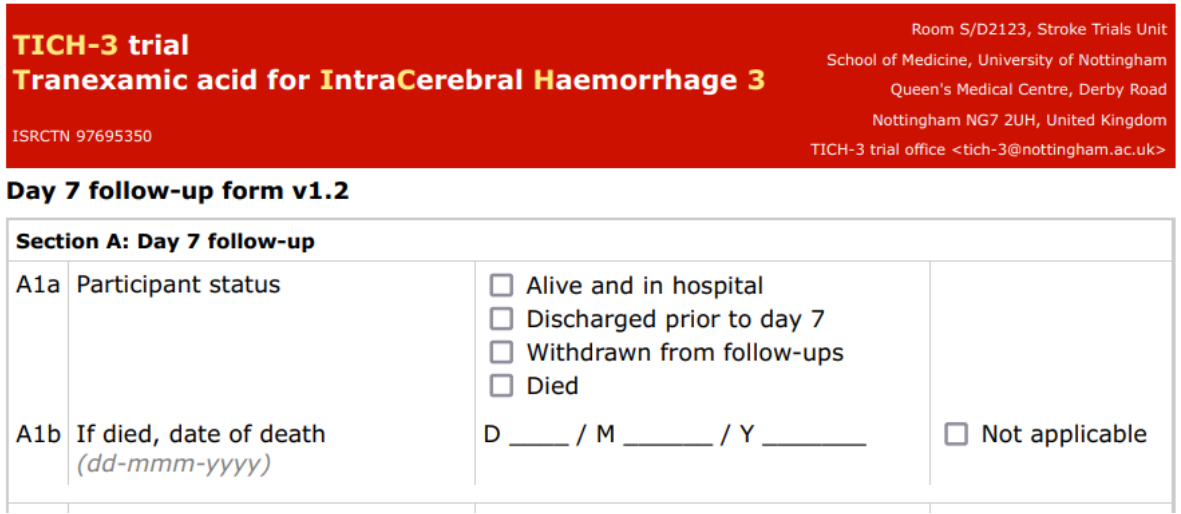
If participant is transferred to another TICH-3 centre prior to day 7 please complete site to site transfer, this appears as a button on the death/discharge eCRF. Both sites can then complete the day 7 eCRF and discharge/death or submit a data correction to the eCRFs, there will only ever be one death/discharge form per participant.

Repatriated to another site within the same trust but not a TICH-3 site

If the rehab centre is not an active TICH-3 site but is within the same trust do not complete discharge form until the participant is discharged from the trust and do not complete day 7 early. Not technically classed as discharge as within same trust. C&C approvals would be in place for the trust. We ask that the staff at the recruiting site could contact the sister site in the same trust to ask for the data and record it themselves on the eCRFs.

Repatriated to non TICH-3 site and outside trust

If the rehab centre is not an active TICH-3 site and is outsides of the trust, then death/discharge would be completed on the day of repatriation and complete day 7 eCRF early. We just ask that if possible if you could try and find out dead/alive status on day 7 by contacting the hospital and if they have died enter this data on the day 7 eCRF by completing a data correction.



TICH-3 trial
Tranexamic acid for IntraCerebral Haemorrhage 3
ISRCTN 97695350

Room S/D2123, Stroke Trials Unit
School of Medicine, University of Nottingham
Queen's Medical Centre, Derby Road
Nottingham NG7 2UH, United Kingdom
TICH-3 trial office <tich-3@nottingham.ac.uk>

Day 7 follow-up form v1.2

Section A: Day 7 follow-up

A1a	Participant status	☐ Alive and in hospital ☐ Discharged prior to day 7 ☐ Withdrawn from follow-ups ☐ Died	
A1b	If died, date of death *(dd-mmm-yyyy)*	D ____ / M _____ / Y _____	☐ Not applicable

SAE reporting cause of death

IF PARTICIPANT DIES PRIOR TO DISCHARGE FROM HOSPITAL PLEASE REMEMBER TO COMPLETE SAE FORM

- Please complete SAE as soon as possible and also complete the discharge/death eCRF.
- Please provide details in question A4 and cause of death in question A5 e.g. Pneumonia, cerebral oedema
- Please only use death unattended in the rare situation when a patient has completely unexplained death e.g. in community

A4	Please describe the event, e.g. new limb weakness, crushing chest pain, bleeding gums, rash **Note: Death is an end result, not an independent event**	
A5a	Event sub-categorisation *Please only enter a code/description from the SAE sub-category list*	

Inclusion of DOAC patient

Enrolment form

Section D: Medical history			
D1	History of antiplatelet therapy on admission (aspirin, dipyridamole and/or clopidogrel)?	☐ Yes ☐ No	☐ Not known
D2	History of direct oral anticoagulant(s) on admission (edoxaban, rivaroxaban, apixaban, dabigatran)?	☐ Yes ☐ No	☐ Not known
D3	History of hypertension?	☐ Yes ☐ No	☐ Not known
D4	History of ischaemic stroke or transient ischaemic attack (TIA)?	☐ Yes ☐ No	☐ Not known
D5	History of ischaemic heart disease?	☐ Yes ☐ No	☐ Not known
D6	History of venous thromboembolism?	☐ Yes ☐ No	☐ Not known

On the enrolment forms there is an added question regarding patients taking DOACs (please note patients taking treatment dose LMWH and/or Warfarin are still excluded)

Day 7 follow up form

Section B: Treatment during first 6 hours after stroke onset			
B2	If the participant was taking direct oral anticoagulant(s) on admission, which reversal agents were given?	☐ Prothrombin complex concentrate (PCC) ☐ Idarucizumab ☐ None	☐ Not applicable

On the day seven follow up form we have asked if patients on DOAC received any reversal as a part of standard care

Uploading Participant Data - Monitoring

The coordinating centre will complete ongoing monitoring of the eCRF data and consent forms.

Consent forms

Please upload consent forms to the secure vault site via the TICH-3 website as soon as possible after enrolment. Please do not anonymise consent forms as we need to see who gave and received consent.

Drug charts and baseline CT scan reports

To reduce burden at sites, the coordinating centre no longer require sites to routinely upload the participant's drug charts and baseline CT scan. We will continue to monitor the eCRF data for CT scan results and haematoma volume estimations and treatment pack numbers are recorded on accountability logs and on the eCRF.

- As per good clinical practice please do continue to ensure treatments pack IDs are added to the participants prescription.

Baseline CT scan images

To be uploaded to the TICH-3 website, not the secure vault (MUST be anonymised).

- The scans must include the date/time present at a minimum
- It's also preferable to retain some pseudonymised data - such as date of birth and sex - to allow the system to ensure that the correct scans are being uploaded.
- See CT scan upload guidance and WPD on the TICH-3 documents page https://stroke.nottingham.ac.uk/sif/docs/?sid=TICH-3

GP Letter

University of Nottingham
UK | CHINA | MALAYSIA

To be printed on Trust Headed paper

Tranexamic acid for hyperacute spontaneous Intracerebral Haemorrhage (TICH-3)

Date

GP Address

Dear [name of GP]

Name of patient:	
Date of Birth:	

This is to inform you that the above patient registered under your care is participating in the Tranexamic acid for hyperacute spontaneous Intracerebral Haemorrhage (TICH-3) trial. Add REC and CTA reference numbers when available.

CTA: 03057/0074/001-0001

REC: 21/EM/0243

Consent has been obtained from the patient, or proxy consent has been obtained from their legal representative professional/relative, both for their participation in the trial and to provide you with this information.

This trial will assess the clinical effectiveness of Tranexamic acid after spontaneous Intracerebral Haemorrhage and determine whether Tranexamic acid should be used in clinical practice.

It is aimed that around 5500 patients with spontaneous Intracerebral Haemorrhage worldwide will be randomised into this study.

I enclose a copy of the participant information sheet for your information.

We may contact you to check on the patient's vital status prior to contacting them at 6 months.

If you need any more information or have any questions then please do not hesitate to contact your patient's research team using the contact details below.

Yours sincerely,

Name: *insert name* Job Title: *insert job title*

RESEARCH TEAM CONTACT DETAILS

Add local research team contact details here

TICH-3 - GP letter Final v1.0 03/11/2021

- Please send a letter to the participants general practitioner to inform them of the patients participation in the trial.
- A template for this is available on the TICH-3 documents page https://stroke.nottingham.ac.uk/sif/docs/?sid=TICH-3
- File a copy in the local site file with the consent form (both documents are unanonymised) and in the participants medical notes.
- The GP letter and other trial documents (participant information sheets and consent forms) are to be localised by the local site, see WPD W004 Preparing Trial Documentation on the TICH-3 documents page.

LOCAL SITE FILE

Sponsors SOPS can be found on the document page; see TA010 TSF Set up

Local Site File Contents

- Please see the TICH-3 website http://tich-3.ac.uk/docs/ where you can download a contents page for the local investigator site file.
- The coordinating centre will not be sending local (investigator) hardcopy sites files in the post for reasons due to sustainability and version control.
- All documents will be available on the TICH-3 website http://tich-3.ac.uk/docs/ – if the local site want to print their own local site file that is their choice and their responsibility to keep the hardcopy site file up to date (this applies to electronic as well).
- The coordinating centre will send any amendment notifications electronically with guidance of if any documents need superseding, we will then put the updated documentation on the TICH-3 website.
- Sites need to ensure that there is an AUDIT trail for monitoring purposes – and all up to date documents are available.
- Safety – file SAE forms in site file after sign off by PI

TICH-3 trial – Tranexamic acid for IntraCerebral Haemorrhage 3

Trial documents

Emergency contacts

This page does not provide the emergency mobile numbers.

Please log in to view them, or bookmark the main documents page instead of this one.

Approved protocol

- Protocol Final v1.0 03.11.2021 fully signed.pdf

Expression of interest

- Online expression of interest form

Trial documents

- Contact List 08.03.22.pdf
- File Note v1.0 01.05.21.docx
- Poster for ED v1.0 05.01.22.pdf
- Site File Index v1.0 20.10.21.pdf

UK site training

- Enrolling Investigator Training Final v1.0 17.03.2022.pdf (updated 3 days ago)
- Investigator Training Final v1.7 17.03.2022.pdf (updated 3 days ago)
- Pharmacy Training Final v1.0 02.02.2022.pdf

Information sheets and consent forms

- Participant Full Consent Form -TICH-3 - Final v1.0 - 03.11.2021.docx
- Participant Information Sheet - TICH-3 - Final v1.0 - 03.11.2021.docx
- Participant Short Information Sheet - TICH-3 - Final v1.0 - 03.11.2021.docx
- Professional (Legal Rep) Full Consent Form - TICH-3 - Final v1.0 - 03.11.2021.docx
- Professional (Legal Rep) Information Sheet - TICH-3 - Final v1.0 - 03.11.2021.docx
- Professional (Legal Rep) Short Information Sheet and Consent TICH-3 - Final v1.0 - 03.11.2021.docx
- Relative (Legal Rep) Full Consent Form - TICH-3 - Final v1.0 - 03.11.2021.docx
- Relative (Legal Rep) Information Sheet TICH-3 Final v1.0 - 03.11.2021.docx
- Relative (Legal Rep) Short Information TICH-3 Final v1.0 - 03.11.2021.docx
- GP letter final v1.0 03.11.2021.docx

Pharmacy documents

- Assessment and monitoring of remote IMP storage Final v1.0 20.12.2021.docx
- IMPD Final v2.0 09.03.2022.pdf
- IMP Accountability log Final v1.0 07.12.2021.docx
- IMP Check Final v1.0 20.12.2021.docx
- IMP Inventory Log Final v1.0 20.12.2021.docx
- Information for Pharmacy Final v1.0 20.12.2021.pdf
- Prescribing and administration guide Final v1.0 17.11.2021.pdf
- Treatment packs specification.pdf

Electronic Delegation Log

Only people appropriately trained and delegated responsibility on the delegation log can take consent.

Anyone who is involved in the trial needs to be on the delegation log; nurses, admin entering data onto online platform, doctors, pharmacist handling the IMP. Can have as many people on the delegation log as required.

The training and roles delegated should be appropriate to the respective job role.

Completing training log will generate an email to the PI asking them to sign you on to the log

Requirements for the local team member to be able to go on the TICH-3 delegation log;

- Up to date investigator CV
- Evidence of GCP training
- Completion of TICH-3 training relevant to role in trial

It is the local PI's responsibility to check local teams investigator CV and GCP before they can be signed off on the delegation log

New members to the team need adding to the delegation log (meeting the requirements above) before they can start working on the TICH-3 trial.

If staff leave the team the PI is required to sign and date 'role finished' against their name.

For site initiation we require a <u>minimum</u> of the following team members signed off on the delegation log

- Principal Investigator
- Research Nurse/coordinator
- Pharmacist

➢ Please return the training log to us as soon as possible after training completed

Electronic Delegation Log

TICH-3 delegation log for C001
Nottingham, Queen's Medical Centre

Chief investigator: Nikola Sprigg

Principal investigator: Kailash Krishnan

Log ID	Investigator name/ID	Certificate/ date trained	Roles and responsibilities*	Delegation log status
1	**Kailash Krishnan** *Consultant Physician* (KKrishnan)	G9L3P7 2 Feb 2022	**Principal investigator** ABCDEFGHIJKLMNOPQRSTUVWXY	7 Mar 2022 08:23 **Authorised** *Kailash Krishnan*
2	**Nikola Sprigg** *Professor of stroke medicine* (NSprigg)	L9N9E7 2 Feb 2022	**Site investigator** BFHIJKLNOPQRSYZ	7 Mar 2022 08:25 **Authorised** *Kailash Krishnan*
3	**Rachel Facilitator** *Researcher* (RFacilitator)	L3N3F7 2 Feb 2022	**Site investigator** BFHIJKLNOPQRSTY	7 Mar 2022 08:25 **Authorised** *Kailash Krishnan*
4	**Clara Researcher** *Clinical Trials Researcher* (CResearcher)	K7H7C6 4 Feb 2022	**Site investigator** BFHIJKLNOPQRSTY	7 Mar 2022 08:25 **Authorised** *Kailash Krishnan*
5	**Any Doctor** *Researcher* (ADoctor)	F3C9T7 2 Feb 2022	**Site investigator** BFHIJKLNOPQRSYZ	7 Mar 2022 08:25 **Authorised** *Kailash Krishnan*
6	**Zee Pharmacist** *Pharmacy DTO* (ZPharmacist)	Y7X6Y7 2 Mar 2022	**Pharmacist ‡** FHLNPQSY	12 Mar 2022 08:49 **Authorised** *Kailash Krishnan*

Delegated roles:

Investigators should only be delegated roles for which they are appropriately skilled and trained.

Staff who work across multiple sites can be on multiple delegation logs as investigators at multiple sites but must be approved by the PI at each site. Example – doctors providing telemedicine acute stroke cover across sites

PI is responsible for signing investigators on and off the log

A. Overall responsibility for study at site and responsible for local financial management where appropriate. **PI**

B. Medical care and supervision of trial patients. **I, PI, DPI**

C. Obtain local ethics committee and R&D approvals and communication of subsequent amendments. **PI, DPI**

D. Ensuring all staff delegated to work on the trial are adequately informed as to the protocol requirements and trained in study procedures. **PI, DPI**

E. Delegation and authorisation of study related duties. **PI, DPI**

F. Act as document controller for trial related documents. **I, P, PI, DPI**

G. Set up and maintenance of Site File. **PI, DPI**

H. Implementation of subject recruitment strategy and obtaining informed consent. **I, P, PI, DPI**

I. Screening of potential subjects. **I, PI, DPI**

J. Obtaining consent for enrolment (including oral consent, as appropriate to local policy and practice). **I, PI, DPI**

K. Randomisation (allocation of trial intervention). **I, PI, DPI**

L. Completion and return of CRFs, including electronic entries. **I, P, R, PI, DPI**

M. Authorisation of CRF. **PI, DPI**

N. Respond to data queries. **I, P, R, PI, DPI**

O. Prescription of and administration of IMP. **I, PI, DPI**

P. Be familiar with IMP safety data and disseminate to staff. **I, P, PI, DPI**

Q. Ensure IMP accountability. **I, P, PI, DPI**

R. Documentation of adverse events and timely SAE reporting. **I, PI, DPI**

S. Adhere to CI recommendations in response to SAEs. **I, P, PI, DPI**

T. Collection of trial related biological samples. (n/a)

U. Initiation (training) of new trial personnel. **PI, DPI**

V. Prepare and be available for audit and inspections. **PI, DPI**

W. Archiving of trial data. **PI, DPI**

X. Responsibility for data monitoring. **PI, DPI**

Others as locally applicable or trial specific (list)

Y. Destruction of IMP. **I, P, PI, DPI**

Z. Obtaining follow-on written consent (after initial consent) to continue in the study and for follow-up. **I, PI, DPI**

Associate PI Scheme

Are you a new researcher looking for training in research studies?

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.

We recommend sites consider appointing an associate PI – please discuss if any questions.

FUNDED BY NIHR National Institute for Health and Care Research

Co-enrolment with TICH-3

Co-enrolment is permitted, and sponsor approved for the following University of Nottingham sponsored trials (contract with site not required)

- MAPS-2 (IC now up-to 24 hours to enrol)
- PhEAST

Co-enrolment has been agreed with the following non-University of Nottingham sponsored CTIMPs (contract with site REQUIRED before co-enrolment is permitted)

- TRIDENT
- ENRICH-AF (MASTER CONTRACT NOW AGREED)

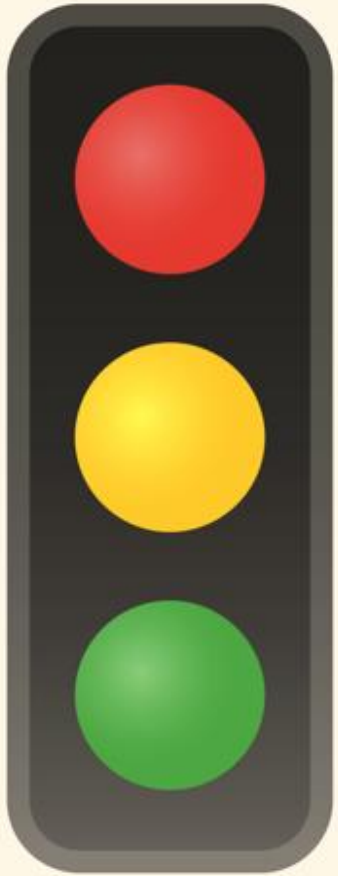
Triple therapy prevention of Recurrent Intracerebral Disease EveNts Trial

If you are taking part in either trial, please let us know so your site (PI and R&I) can document they agree to co-enrolment at your site.

Please let us know if there are any other trials you may wish to co-enrol with so that we can begin the contracts process.

There is a co-enrolment log on the TICH-3 documents page
https://stroke.nottingham.ac.uk/sif/docs/?sid=TICH-3

Site requirements before start up



Attendance at training for minimum PI, one research nurse/coordinator and one pharmacist

Paperwork - send documents to coordinating centre via email.

- Signed and dated recent investigator CV and GCP certificate of the local Principal Investigator
- Attendance investigator training log
- Assessment and monitoring of remote IMP storage form
- Fully executed non-commercial agreement and confirmation of local capacity and capability

Electronic delegation log

Local PI to authorise all local team members onto the online delegation log via the TICH-3 website.

Drug dispatch

Drug will be dispatched when the delegation log has been countersigned by the PI, drug needs to be marked as received and then marked as available for randomisation on the TICH-3 website.

Green light

We will advise once everything has been checked and confirm that the site can open to TICH-3 by sending the regulatory green light email from the University of Nottingham sponsor.

- All documents are required to be stored in your local investigator site file (electronic or hardcopy)

****Investigators may only work on the trial once signed off on the delegation log and the site may only begin enrolling participants in the trial after green light has been received from the sponsor****

STUDY WITHIN A TRIAL (SWAT)

SWAT Sub-study

Aim: To reduce inequalities in enrolling participants from minority communities.

Population: All individuals recruited to the TICH-3 trial in the UK.

Intervention: Animated participant video

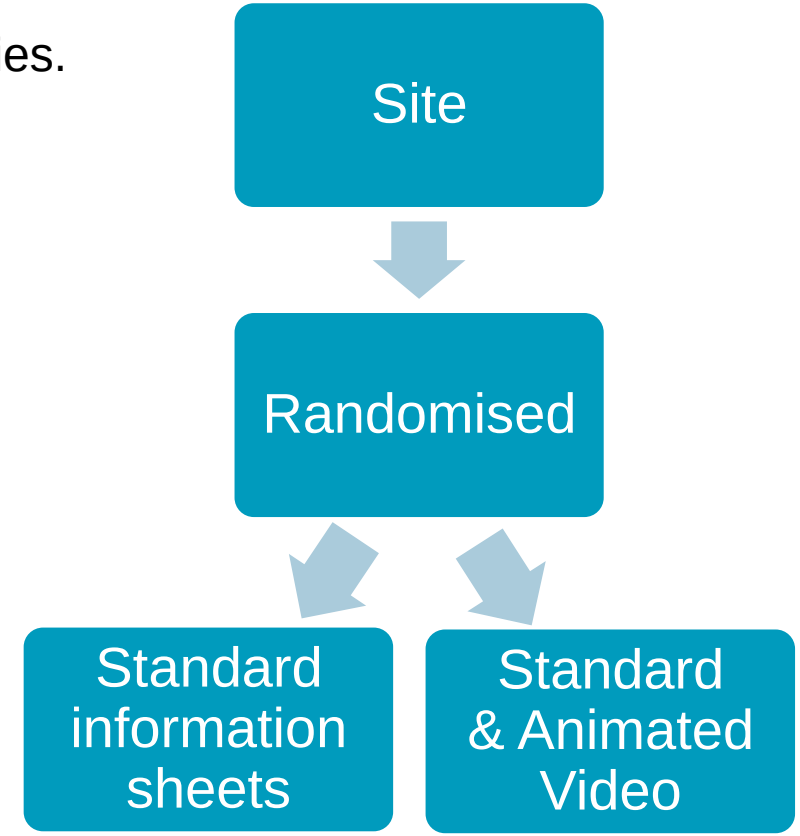
Control: Standard information sheets

Outcome measures:

1. Proportion providing consent for follow up:
   i. In the TICH-3 UK study population as a whole
   ii. By ethnic minority groups versus non-ethnic minority groups
2. Follow up completion rates in the control and intervention groups.

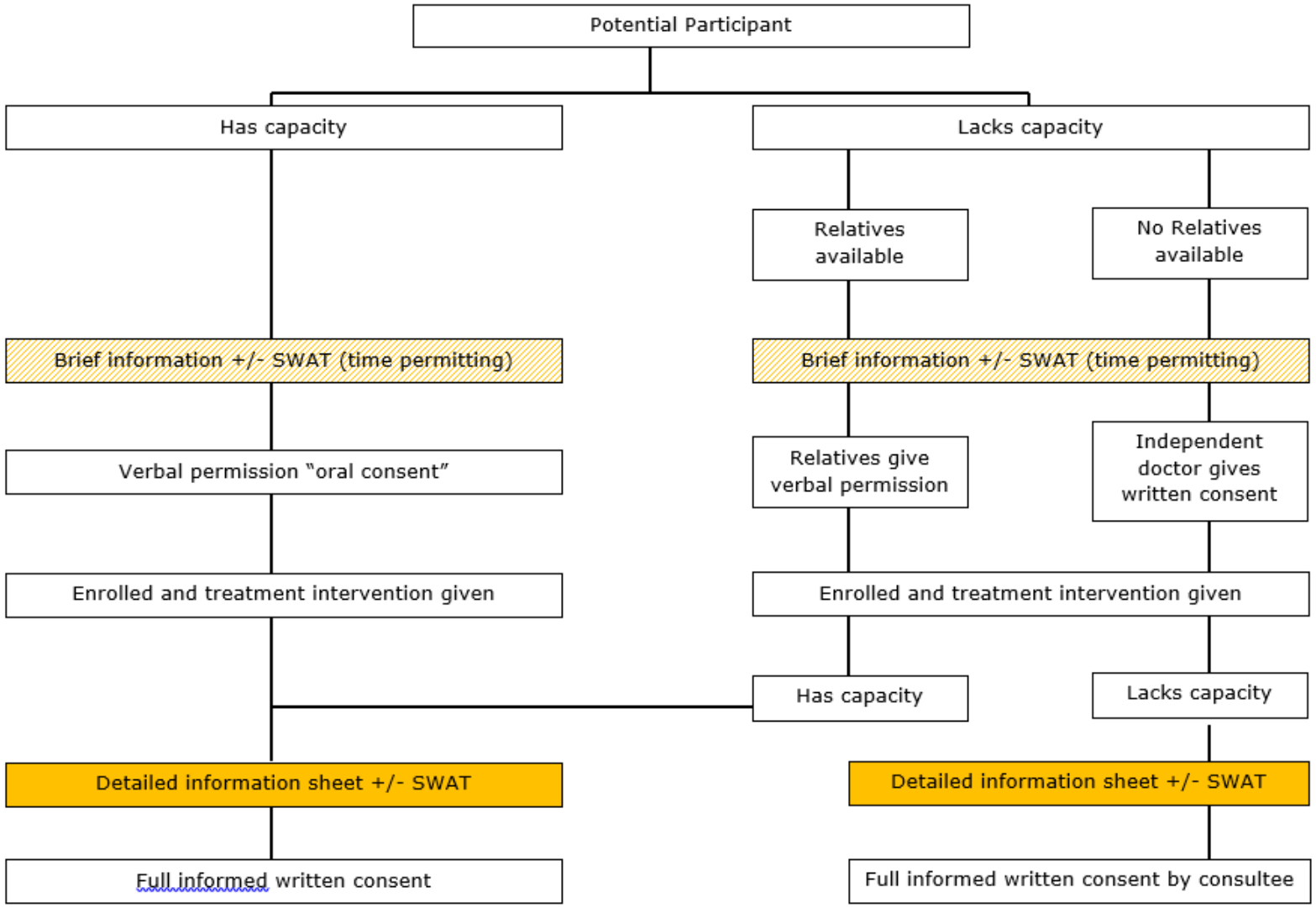
Design: Cluster randomisation at site level

Sites will be informed of their randomisation prior to initiation and Sites will be given training on how to use the video if randomised to animated video



Note: Animated video will be used **in addition** to the standard consent process and information sheets. Given the age and recent stroke, the intervention **may improve understanding of all participants** not just those in ethnic minority groups, we will therefore **include all UK participants** rather than the sub-set from ethnic minority groups in the SWAT.

SWAT Consent Process



- All participants give follow on written consent.
- Sites randomised to the enhanced process will have access to the website with the video in 5 languages.
- On day 7 the eCRF will capture if the video was used.
- The database will also record when the video is accessed.

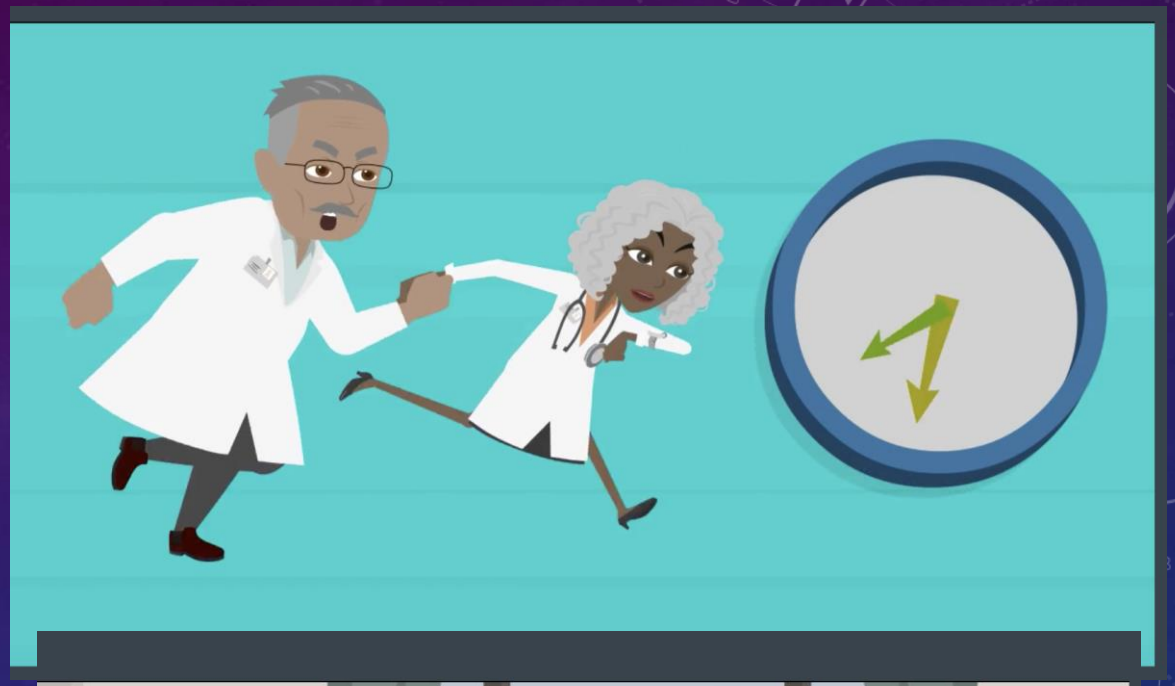
Only sites randomised to enhance consent will be given access links to the videos

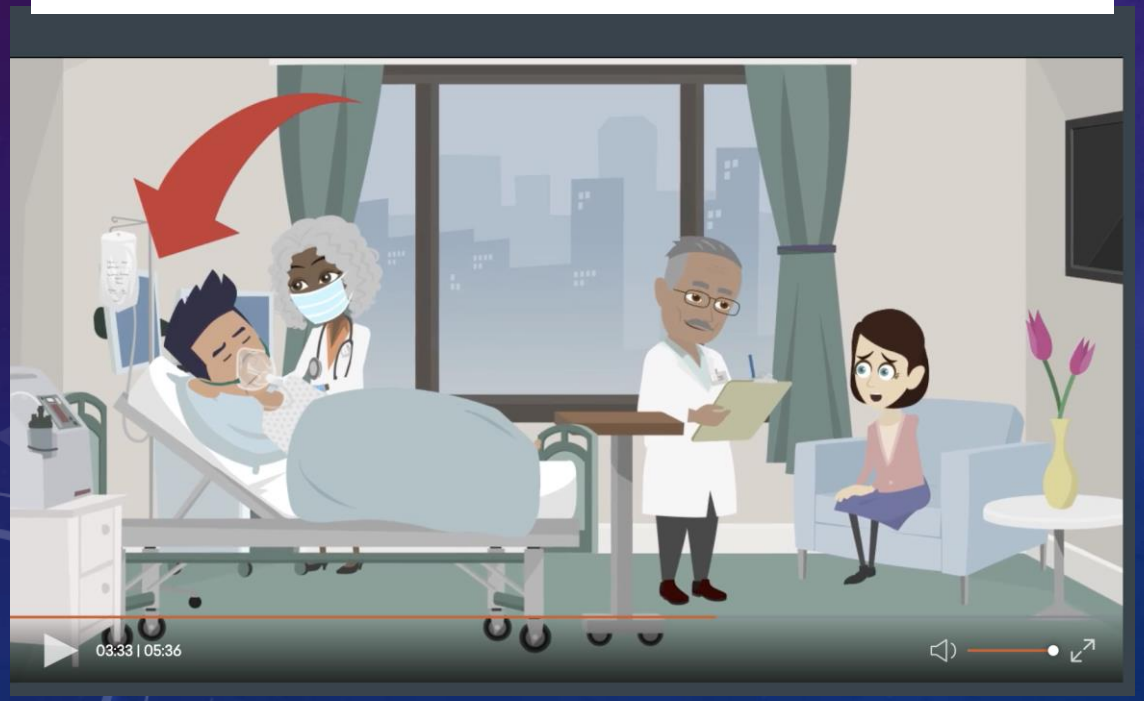
TICH-3 consent

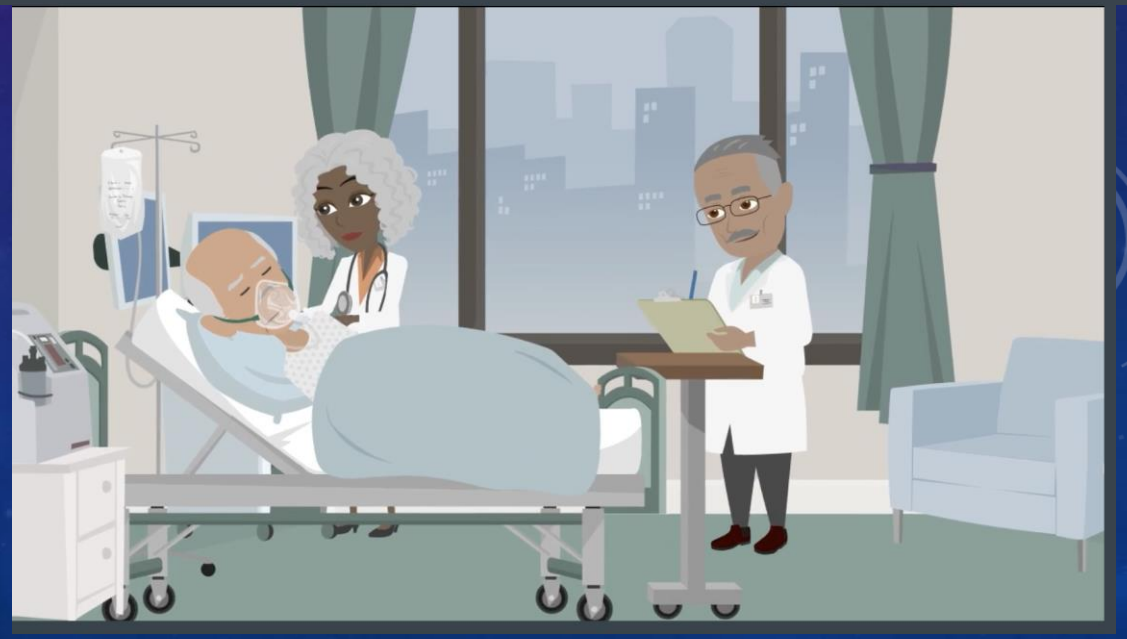
Welcome to TICH-3, which is a clinical trial to assess whether tranexamic acid reduces death and dependency after hyperacute (within 4.5 hours of onset) spontaneous intracerebral haemorrhage.

Please select the most suitable language for the patient

- English
- Polish polski polszczyzna
- Bengali Bangla বাংলা
- Punjabi Panjabi پنجابی ਪੰਜਾਬੀ
- Urdu اُردُو

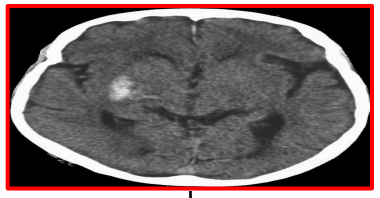






SUMMARY

TICH-3 Key Points



Verbal permission

Randomise - open lowest numbered treatment pack

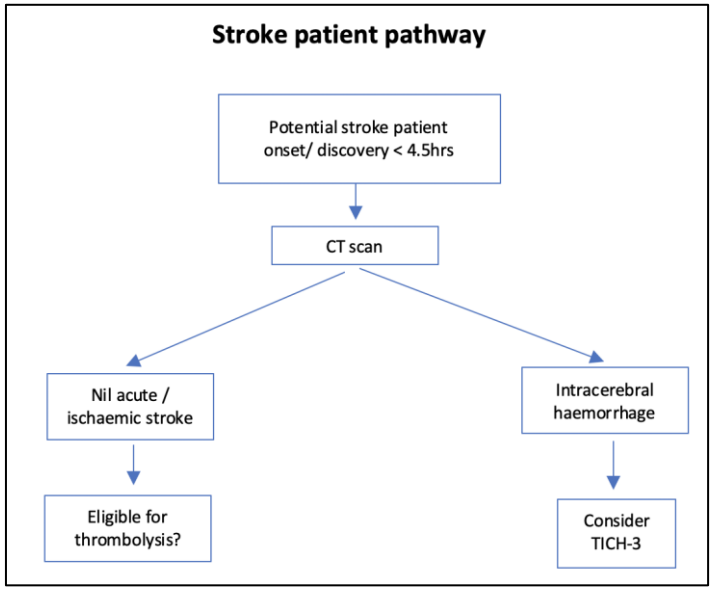
Recruitment Alert

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



ACTION – Return Training Log

- Please complete the investigator training log and return via email to the coordinating centre
  Click here for direct download of training log
- Or use the self referral form: 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

CONTACT INFORMATION

University of Nottingham Trial Team

Name	Role	Contact Information
Brittany Hare	Clinical Trials Manager (UK Site Recruitment)	E: brittany.hare@nottingham.ac.uk
Joseph Dib	Clinical Trials Manager (International Site Recruitment)	E: joseph.dib4@nottingham.ac.uk
Solomon Adegbola	Follow Up Coordinator	E: solomon.adegbola@nottingham.ac.uk
Kerry Larkin	Follow Up Coordinator	E: kerry.larkin@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
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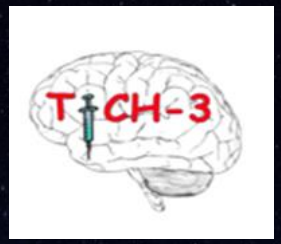
Nikola Sprigg	Chief Investigator	E: nikola.sprigg@nottingham.ac.uk

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?

Audit list of updates to training presentations

Previous versions

Final version 3.1 13/04/2023

- Added box for 'Randomise - open lowest numbered treatment pack' to flow diagram which is present on synopsis and key points slides
- 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
- Added DOAC FAQs
- Highlighted ICH and IVH on eligibility FAQ slide
- Merged TICH-2 slide with TXA in other conditions and renamed to 'Tranexamic acid in other trials'
- Moved amendment information to add end under additional information
- Deleted Simplicity of trial procedures slide
- Merged Professional legal representative consent by an independent doctor into 1 slide instead of 2 and simplified the FAQs
- Moved What to do in the event of a Protocol Violation to safety monitoring section
- Deleted Logging onto TICH-3 website slide
- Deleted slide of eCRF screenshots
- Updated co-enrolment slide
- Updated associate PI scheme slide
- Updated trial team
- Updated HV estimation slide
- Deleted consent form flow chart

This version 3.2 18/08/2023

- SAE reporting updated following sponsor audit that if report event such as seizure and ppt dies unless the seizure is attributed to ppt death then the SAE should be updated to resolved (if was classed ongoing) and then separate SAE submitted to report death
- Page 10 added 'IMP treatment should be started within the 4.5 hours inclusion window'
- Added e.g. Seizures to synopsis page
- Deleted one of the DOAC FAQ pages after merging them on to one page
- Consent – added reminder initials not ticks
- Updated TICH-3 trial team

ADDITIONAL INFORMATION

Obtaining Oral Consent

The person taking verbal consent must be appropriately trained and delegated by the PI to take consent on the delegation log

- "The responsible doctor or delegate will explain that the patient has had stroke caused by bleeding in the brain known as intracerebral haemorrhage (ICH) and will receive the usual emergency treatments for ICH. That, in addition to the usual care, the patient may be enrolled in a research study that aims to improve the treatment of patients with ICH once confirmed by a brain scan. Whilst we hope that TXA will improve recovery after ICH, at present we cannot be sure about this."
- A brief information sheet will be provided but detailed written information will only be provided if the patient requests at this point.
- We recommend that a maximum of approximately 10 minutes should be taken obtaining initial oral permission (consent) due to emergency nature of treatment administration. If the potential participant does not want to decide in such a short time frame they will not be enrolled.
- The case report form and medical records will record that the patient meets the TICH-3 eligibility criteria and initial oral consent was given.
- If patient lacks capacity - relatives (or close friends) can provide oral consent if they can be contacted rapidly in time frame required. Oral consent can be given over the telephone, bearing in mind emergency nature of the clinical situation.
- Where the doctor assesses the patient via telemedicine, verbal consent will be obtained and witnessed by someone present in the hospital and this will be recorded in the medical notes.

Documenting Consent

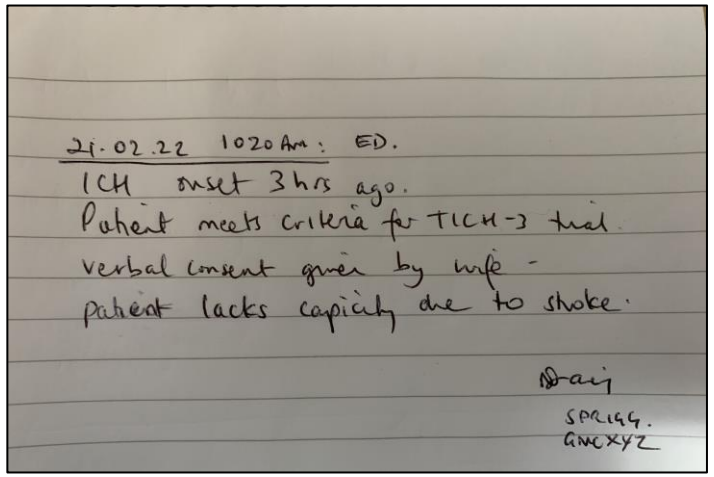
Yes

ALL CONSENT PROCESSES NEED TO BE RECORDED IN THE PARTICIPANT'S MEDICAL NOTES

For example:

- Patient meets criteria for TICH-3 and gives oral consent
- Patient meets criteria for TICH-3, but lacks capacity, wife provided oral consent over the telephone, witnessed by staff nurse Mr ED Nurse (Figure 1)
- Patient meets criteria for TICH-3, but lacks capacity, attempt to contact relative with no response so independent doctor provided written consent
- Patient meets criteria for TICH-3 study, oral consent was obtained after discussion over telemedicine with Dr O Call
- Patient meets criteria for TICH-3, but lacks capacity, no relatives available, independent doctor provided written consent via telemedicine – witnessed and recorded on written form (figure 2)

1



2

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

Dr Indi Pendent	01.01.01	electronic
Name of Person giving nominee consent	Date	Signature

Relationship to patient (please tick): Healthcare Professional Yes

Name of Person taking consent	Date	Signature

Telemedicine used (please tick if Yes) Yes

Ms. Staff Nurse	01.01.01	S. Nurse
Name of Witness if consent taken	Date	Signature

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

Inform trial office: Randomisation Alert

Please notify the coordinating centre that a randomisation has taken place as soon as possible after administration.

EXAMPLE QR CODE

A QR code has been created to go inside the treatment packs, on the prescribing and administration guide, which will take the person scanning the code directly to the TICH-3 website.

- Ease of use - generate alerts without needing to log in (do not need a username and password)
- Alternatively, investigators can type in link under QR code without scanning or log in as normal
- The coordinating centre will monitor the alert log and to follow-up sites/participants

QR code not working or unable to access TICH-3 website

If you cannot access the website, please call the trial office on +44 (0)115 823 1782 with treatment pack ID, participant's initials, date of randomisation and name of person enrolling the participant (voicemail 24/7).

Amendments approval

- SA_01_22

Professor Nikola Sprigg formally reinstated as CI. IMP be defined by active substance only rather than by a specific product.

Submitted – 22/11/2021

Approved - REC 17/12/2021, HRA 19/01/2022, MHRA Approved as part of first clinical trial authorisation received on 03/11/2021 CTA document

- SA_02_22

SWAT video completed and transcript uploaded for ethical approval.

Submitted – 21/02/2022

Approved – REC and HRA 31/03/2022, MHRA not required

- SA_03_22

Health economics resource questionnaire and cover letter.

Approved - REC and HRA 21/07/2022, MHRA not required

Amendments approval

- SA_04_22 approved 30/01/2023

Protocol amendment, the protocol that sites should adhere by is now TICH-3 Protocol Final v2.0 30.01.2023

Summary of changes

1. Patients that are on DOACs at the time of ICH are now eligible to be enrolled into TICH-3
2. Trial background information literature review updated
3. Inclusion of adults clarified to (≥ 18 years)
4. Safety reporting – pregnancies occurring in trial participants or partners of trial participants will not be followed up as TXA has a short half life and TXA is very commonly used during pregnancy.
5. Appendix 1
    i. Table one wording has been amended to EXPECTED EVENTS NOT SUBJECT TO EXPEDITED SUSAR REPORTING. Note: Table one isn't whether the event is to be reported or not but states the events that are expected after tranexamic acid but not subject to expedited reported as they are expected so are not a SUSAR.
    ii. Table two been removed as they are common side effects after haemorrhagic stroke and are unnecessary to be reported. Table 1's text has been updated so that it is clear the events that should be reported isn't whether the event is to be reported or not but states the events that are expected after tranexamic acid but not subject to expedited reported as they are expected so are not a SUSAR.
6. Health economics outcomes have been moved from the Health economics chapter to secondary outcomes.
7. Layout corrections