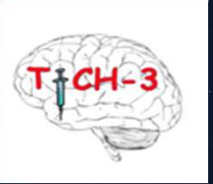




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ISRCTN97695350

A large, detailed image of the Earth as seen from space, showing the blue oceans and green/brown continents, set against a dark starry background.

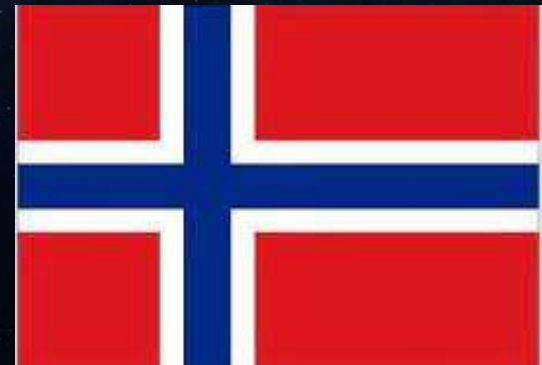
TRANEXAMIC ACID FOR INTRACEREBRAL HAEMORRHAGE: TICH-3 TRIAL

Norway Investigators

Professor Nikola Sprigg

On behalf TICH-3 Trial Team

26/10/2023



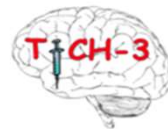


Funding:



- TICH-3 funded by National Institute of Health and Rare Research (Health Technology Assessment)

TICH-3 Trial Registration:	ISRCTN9769535
TICH-3 EU CTIS:	2022-500587-35-01
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



TICH-3 Norway

Sites

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Oslo	Oslo University Hospital (NCC)	Professor Else Charlotte Sandset (else@sandset.net)



Consent form

- What is the consent process in Norway?
- Legal representative?
- Professional legal representative?



Overview



- Welcome and introductions
- Presentation of TICH-3:
 - Inclusion criteria
 - Consent process
 - Randomisation
 - Safety outcomes
 - Pharmacy - Drug storage and administration
 - Passwords, website and electronic case report forms (eCRFs)
- Updates on ethics/research/contracts
- Q&A - PLEASE COMPLETE TRAINING LOG
- Future planning

The University of Nottingham
Record Form
RF1 TA008
Version 1.0 (TICH 3)

Title: (ATTENDANCE AT) INVESTIGATOR TRAINING
Reference SOP: TA008

Title of Protocol: TICH-3
Site: _____
Name of Trainer: Nikola Spragg
Trainer Role in the Trial: Chief Investigator

Name	Title of training type and version (Investigator, pharmacy, ED) Method of training (Live or self-directed)	Date completed training	Job Title	Role in Trial e.g. PI, doctor, pharmacist, research nurse/coordinator	Email Address	Signature

Version 1.0 | TA008 Attendance at Investigator Training (TICH 3)

Self-referral checklist

Please read through the following points carefully and indicate which are applicable, then submit at the bottom.

- I am a hospital researcher, administrator, pharmacist* or radiologist.
- I have completed the TICH-3 trial training.
- I have my signed work CV.
- I have a GCP certificate.
- I do **not** already have a TICH-3 account.
(If you do, please contact the co-ordinating office when another hospital needs to be added to your account).
- I declare my intention to participate in the TICH-3 trial.

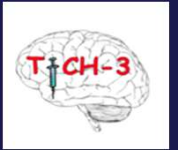
Your country: [Select...]

Submit

* - includes pharmacy technician



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](#) use the self referral form:

Name	Title of Training Unit and number of training sessions	Date of training	Job Title	Area of Training	Health Address	Signature

<http://tich-3.ac.uk/?ZSelfRef>

Self-referral checklist

Please read through the following points carefully and indicate which are applicable, then submit at the bottom.

- I am a hospital researcher, administrator, pharmacist* or radiologist.
- I have completed the TICH-3 trial training.
- I have my signed work CV.
- I have a GCP certificate.
- I do not already have a TICH-3 account.
(If you do, please contact the co-ordinating office when another hospital needs to be added to your account).
- I declare my intention to participate in the TICH-3 trial.

Your country:

* - includes pharmacy technician

- 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.
 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>

BACKGROUND

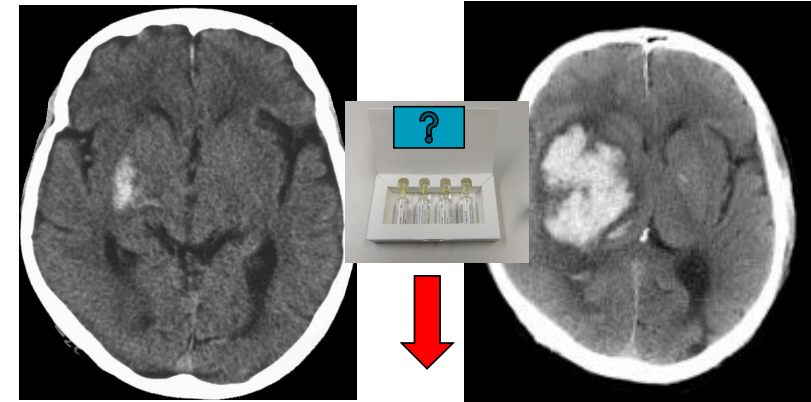


Intracerebral Haemorrhage (ICH)



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.



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



Other TXA in ICH trials

Completed trials	TXA timing after symptom onset (hours)	TXA Bolus	Total recruitment
Arumugam 2015	8	1g bolus 1g infusion	30
Liu TRAIGE 2021	8	1g bolus 1g infusion	171
Meretoja STOP – AUS 2020	4.5	1g bolus 1g infusion	100
Ni 2020	8	1g bolus 1g infusion	152
Seiffge TICH NOAC 2022	12	1g bolus 1g infusion	63 (stopped early)
Sprigg TICH 1 2014	24	1g bolus 1g infusion	24
Sprigg TICH 2 2018	8	1g bolus 1g infusion	2325

Ongoing trials	Registration	TXA timing after symptom onset (hrs)	TXA dose	Target recruitment
Ezati 2019	IRCT20191014045103N1	Not reported	1g bolus 1g infusion	Not reported
Jiang 2020 THE-ICH trial	ChiCTR1900027065	4.5	1g bolus 1g infusion	2400
Li Qi 2021 TARGET trial	ChiCTR2100045022	3	1g bolus 1g infusion	200
Pandian 2022 INTRINSIC trial	Not registered	4.5	2g bolus	Not reported
Pokhrel 2021	NCT04742205	24	1g bolus 1g infusion	142
Woo 2017 TRANSACT trial	NCT03044184	3	1g bolus 1g infusion	220
Zhao 2017 STOP-MSU	NCT03385928	2	1g bolus 1g infusion	326

PROTOCOL

EU Protocol v4.2 30.03.23 approved on 19.04.2023



TICH-3 Synopsis



ICH emergency condition - facilitate rapid enrolment

Design: Double blind randomised clinical trial, pragmatic streamlined design

Participants: Inclusion: < 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 guidelines¹

Randomisation: Simple - use the lowest available treatment pack number

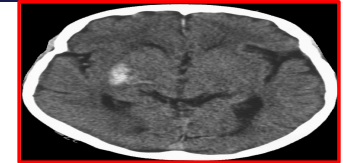
Primary Outcome: Early death (day 7)

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 start UK recruitment early 2022



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

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.**
- Massive ICH (usually when haematoma volume > 60ml)
- Severe coma, Glasgow Coma Scale <5
- Decision for palliative (end of life) care

EU Protocol v4.2 approved on 19.04.2023



TICH-3: Patients taking DOACs



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

- **Direct thrombin inhibitor** – Dabigatran or **Factor 10a inhibitor** – Apixaban, rivaroxaban, edoxaban
- If they have only recently started taking a DOAC, for as long as they have regularly taken it for the last 48 hours, we would enrol them as patients taking regular DOAC

Types of anticoagulation (blood thinners) that cannot be included:

- warfarin or therapeutic low molecular weight heparin. Note if LMWH is being used prophylactically at low dose to prevent DVT and PE these patients can be included in TICH-3

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 PCC or anticoagulation reversal agent (i.e Idarucizumab) in accordance with the treating physician. Please ensure you document which reversal agents were given in eCRF

Can TICH-3 participants be co-enrolled to the Annexa-4 trial?

No, if they have been recruited for the ANNEXA-4 trial they cannot be recruited for 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 undertaken 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



Investigator questions



Q: If the patient has neurosurgery and is then given tranexamic acid is this a protocol violation?

- Only if it was known at the time of enrollment that the patient was to be given tranexamic acid (Indication for tranexamic acid is an exclusion criteria). However it should be noted that there is currently no evidence that TXA is effective in ICH and it is not routinely used.

Q: **If MRI is used for the diagnosis of ICH, which sequence should be used to measure the haematoma volume.**

- **T2* or GRE or SWI could be used to measure $abc/2$ to calculate the haematoma volume or automated software if it is available.**

Q: If the relatives want longer to make a decision (more than 10 minutes as suggested in the protocol) is that ok?

- Yes – they should take as long as they need, but need to explain to them that in other bleeding conditions TXA is more effective if given as soon as possible after stroke onset, when the risk of bleeding (haematoma expansion) is greatest. If they cannot decide within the 4.5hours since stroke onset the patient should not be included.



Haematoma volume measurement

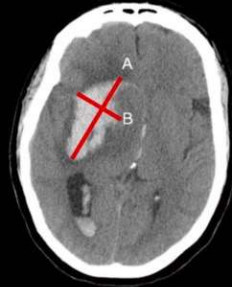


Exclude patients with massive haematoma (usually >60ml)

1. If CT scan uses automated software – e.g. RAPID, BRAINOMIX patient can be enrolled if HV not greater than 60mls
2. Calculate HV manually using TICH-3 HV=ABC/2 calculator on the website¹ or alternatives e.g. mdcalc app² 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 in measurements
 - HV can be estimated by anyone trained to do so

i The [ABC/2 calculator](#) can be used to calculate haematoma volumes during eligibility checks, without needing to be logged in.

Formula for Estimating ICH Hematoma Volume



$$\frac{A \times B \times C}{2}$$

Select CT slice with largest ICH
 A = longest axis (cm)
 B = longest axis perpendicular to A (cm)
 C = # of slices x slice thickness (cm)

Estimated volume of spheroid
 Correlates well w/ planimetric CT analysis

ISRCTN 97695350

Haematoma volume calculator

Estimated volume of largest haematoma 1

[View guide](#)

Maximum haematoma length 'A'
(up to 4 decimal places) cm

Maximum haematoma width 'B'
(up to 4 decimal places) cm

Number of slices where haematoma visible slices

Scan slice thickness
(up to 3 decimal places) mm

Please enter the individual components and then the calculated volume will be shown.

Hemorrhage Volume

Predicts volume of intracranial hemorrhage from CT measurements. 2

INSTRUCTIONS
 Measure length and width on the CT slice with the largest area of hemorrhage. NOTE: CT slices are typically measured in mm, not cm.

When to Use: Pearls/Pitfalls: Why Use:

Hemorrhage Shape: Round or Ellipsoid
 Irregular, Separated, or Multinodular

Hemorrhage Length: cm

Hemorrhage Width: cm

Number of CT Slices: slices
 Slice with ≥75% Area of Hemorrhage: Counts as 1
 Slice with 25-75% Area of Hemorrhage: Counts as 0.5 slices; Slice with <25% Area of Hemorrhage: Counts as 0 slices

CT Slice Thickness: mm

Result:

<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

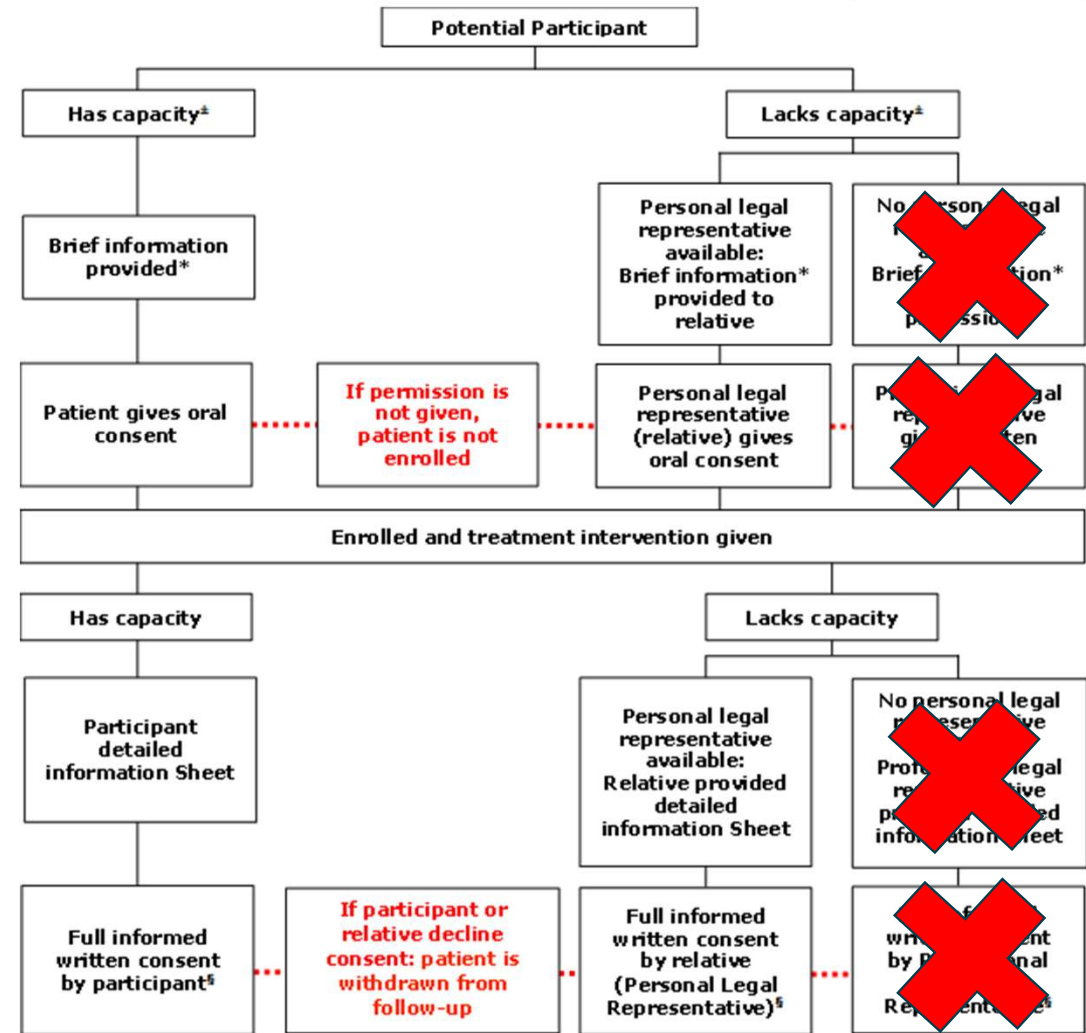
Full informed written consent to be obtained later after administration of IMP

Hierarchy approach

Patient has capacity – gives oral consent

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

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





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**

(Not authorised)

Site investigator ▾	Authorise ▾
<input checked="" type="radio"/> Consent training for enrolment (J)	
<input type="radio"/> No consent training	

- 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?	<input type="checkbox"/> Yes <input type="checkbox"/> No	
A2 Please give the name of the investigator taking initial consent for enrolment in the trial	<input type="text"/>	<input type="checkbox"/> 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**



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](https://stroke.nottingham.ac.uk/sif/docs/?sid=TICH-3)

[Traneksamsyre ved akutt intracerebral blødning, Versjon 0.1 221020]

JEG SAMTYKKER TIL Å DELTA I STUDIEN OG TIL AT MINE PERSONOPPLYSNINGER OG MITT BIOLOGISKE MATERIALE BRUKES SLIK DET ER BESKREVET

Navn: Dato:

Signert av prosjektdeltaker

Stedfortredende samtykke når berettiget, enten i tillegg til personen selv eller istedenfor

Navn: Dato:

Signert av nærstående

BEKREFTELSE PÅ AT INFORMASJON ER GITT DELTAKEREN I STUDIEN

Jeg bekrefter å ha gitt informasjon om studien

Navn: Dato:

Signert av prosjektmedarbeider

.....

Rolle i studien

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

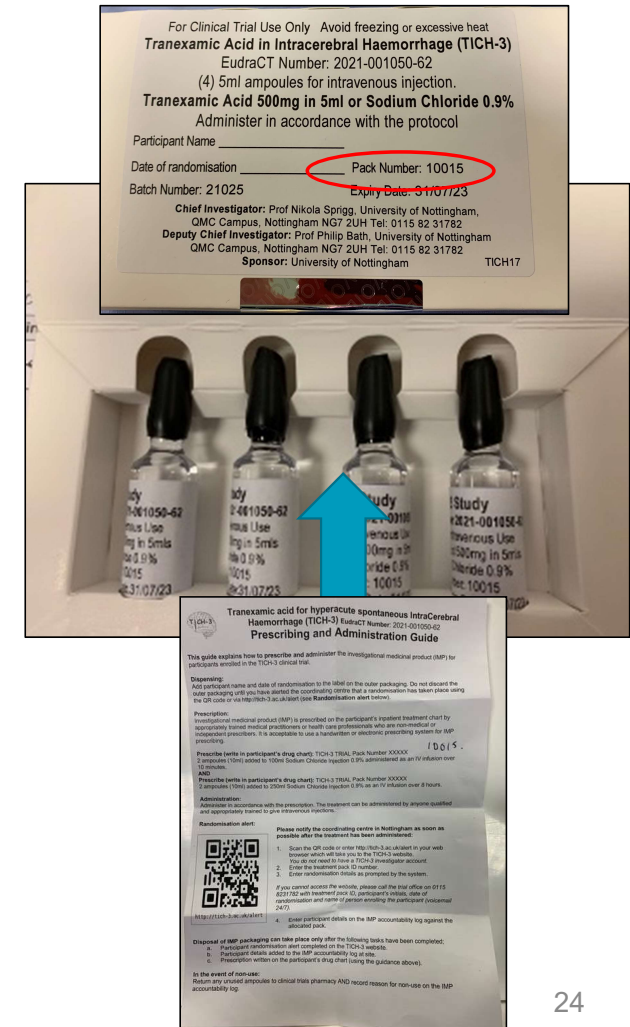
RANDOMISATION



Randomisation



- 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: 2021-001050-82

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
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
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.

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



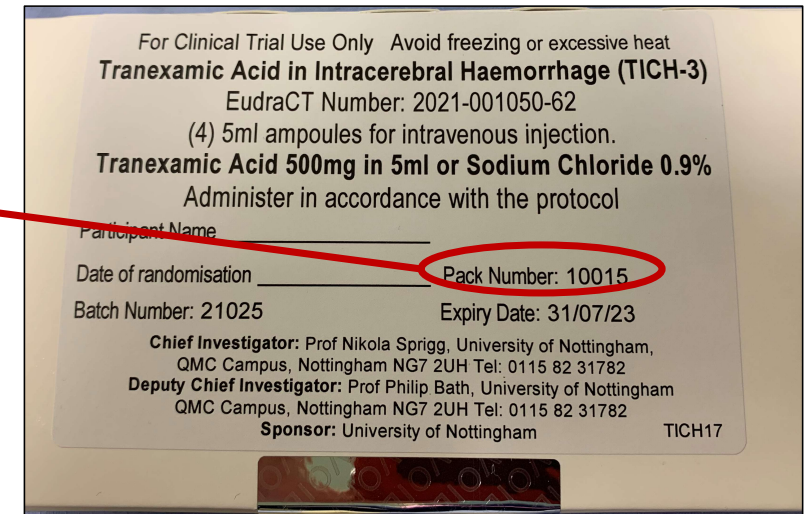
Let us know about a new TICH-3 participant

Treatment pack ID:

Participant's initials:
(2 or 3 letters)

Your initials:
(2 or 3 letters)

For initials, please use first letters from forename then surname and enter a dash (-) if no middle initial



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

Please confirm that the TICH-3 participant was randomised at the hospital shown below.

Centre ID: **C001**

City/name: **NOTTINGHAM, Nottingham DEMO Hospital**

Country: **United Kingdom**



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
- ✓ Enter a protocol violation for 'participant does not receive all of the randomised treatment as per protocol'.
- ✗ 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

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





GCP training



Free GCP training - In English, French and Spanish



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





Safety Events, SARS and SUSARS



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

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

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

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

- All events suspected to be related to the IMP will be assessed for seriousness, expectedness and causality by local investigator. Section 4.8 of the SmPC, date of last revision 02 February 2021, will act as the **Reference Safety Information**: Tranexamic Acid <https://Tranexamic Acid SmPC 20210202 REVISION.pdf>

Serious Adverse Events (SAEs) that are not safety outcomes, SARS or SUSARS should not be reported

E.g. Neurological deterioration, haematoma expansion, cerebral oedema that is NOT thought to be related to the IMP, and does not result in death does not need to be reported as an SAE

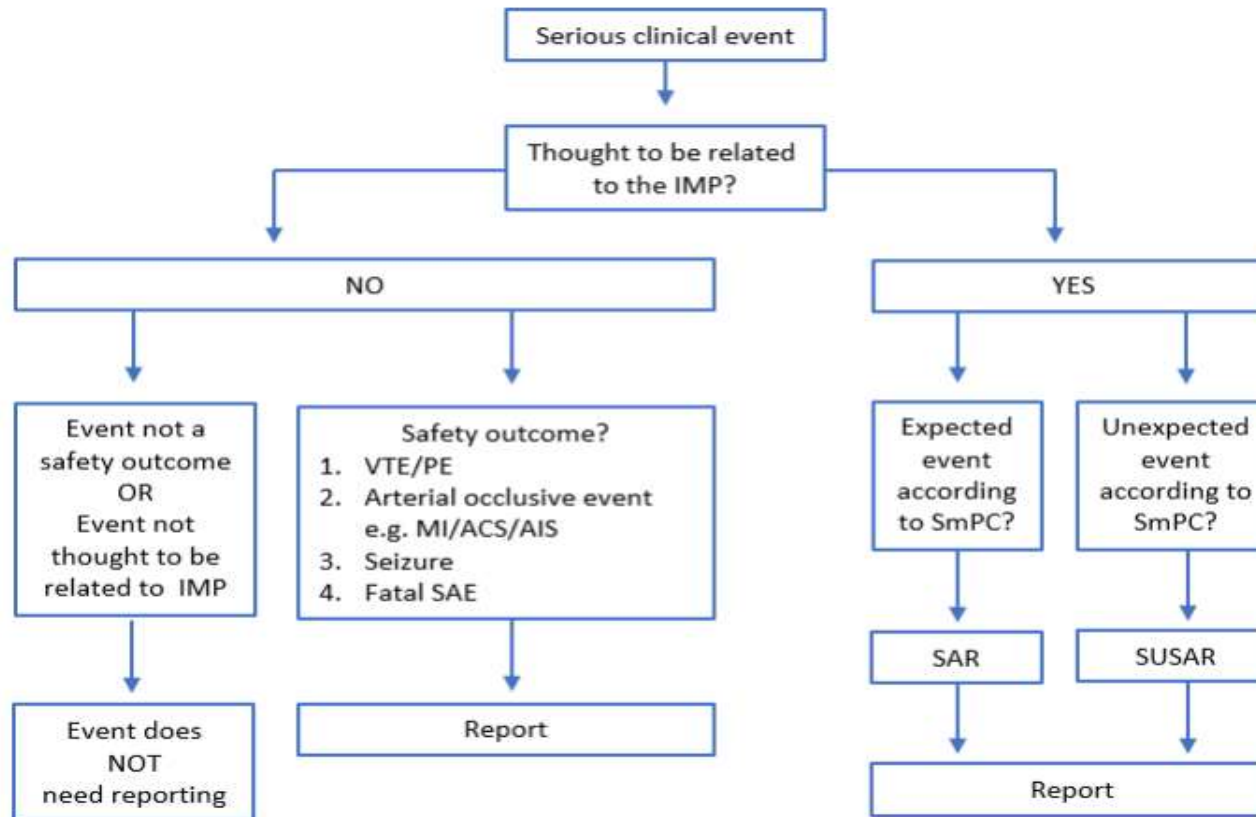
The PI must review and sign off SAE's – recommend print off and file SAE form in site file after sign off by PI



SAE Reporting Flowchart



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	<input type="checkbox"/> Not related
	<input type="checkbox"/> Improbable
	<input type="checkbox"/> Possible
	<input type="checkbox"/> Probable
	<input type="checkbox"/> 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	<input type="checkbox"/> SAR
	<input type="checkbox"/> SAE
	<input type="checkbox"/> 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)



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

Suspected SUSARs

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

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

A12a Clinical outcome of this event	<input type="checkbox"/> Resolved <input type="checkbox"/> Event ongoing <input type="checkbox"/> Recovered with sequelae <input type="checkbox"/> Died
A12b If event ongoing or recovered with sequelae, please provide details	<input type="text"/>

A4 Please describe the event, e.g. new limb weakness, crushing chest pain, bleeding gums, rash	<input type="text"/>
Note: Death is an end result, not an independent event	

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

For urgent medical enquiries (including [unblinding](#)), and for randomisation problems, you can contact the following emergency mobile numbers. Please ensure that you have these written down.

+44 (0)7725 580 092	+44 (0)7736 843 592
+44 (0)7798 670 726	+44 (0)7810 540 604



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.

IMP AND PHARMACY



Storage of IMP

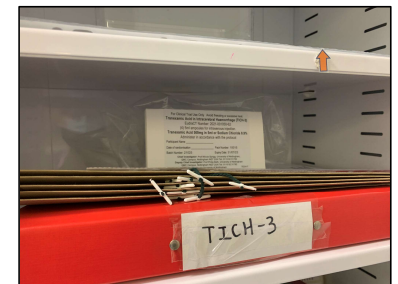


Temperature monitoring is not required. The packs will be stored at room temperature and protected from excessive heat and freezing.

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.





Drug dispatch: International



- 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 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	<input type="checkbox"/> 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	



Monitoring of IMP



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

The IMP will be shipped from Sharp directly to the site's pharmacy. The pharmacy will complete the inventory log and part of the accountability log and then distribute to the research team with the IMP to be placed in the agreed storage location (discussed and agreed when completing the assessment and monitoring of IMP storage form).

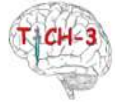
Once the IMP is in the storage location, pharmacy/research team will need to login to the TICH-3 web site and mark the treatment packs as available for randomisation.

The following forms are downloadable from the TICH-3 website and form part of the pharmacy's site file;

1. Assessment and Monitoring of IMP Storage – to be completed prior to initiation
2. Inventory Log – to be completed by pharmacy when IMP arrives at site
3. IMP Accountability Log – to be completed by research team when IMP is used at site
4. IMP Check – to be completed by research team to ensure IMP all present and accounted for




IMP Paperwork (1): Set up, IMP receipt



Assessment and monitoring of remote IMP storage

1

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 should be followed:		
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 and monitoring of remote IMP storage

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.

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

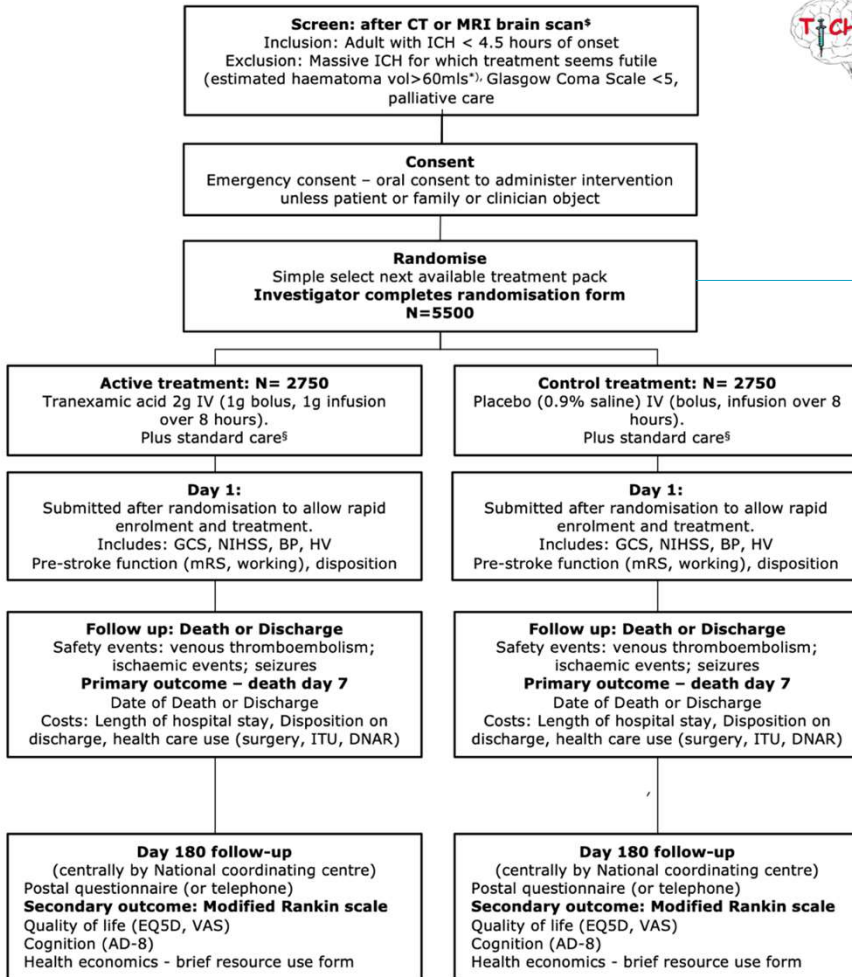
DATA COLLECTION



Trial Flow Chart:



TICH-3 Flow chart Protocol v1.3 4.Mar 21



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

Randomisation alert

Enrolment form

Contact details form

Day 7 follow-up
AND
Discharge/death

(See separate guidance for completion of these eCRFs)



Logging onto TICH-3 website



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>

Please log in if you need the TICH-3 emergency contact numbers. The recruitment total for the trial to date is: 0

Login using the Investigator ID, password issued to you by the [TICH-3 trial office](#).
If you have forgotten your login details then please [click here](#).

TICH-3 investigator ID:

Password:

Please ensure that your web browser has both cookies and JavaScript enabled.

NOTE: Serious Adverse Events (SAEs) – we have a legal responsibility to collect all safety events occurring within the first 7 days after randomisation (including SARs/SUSARs/fatal SAEs).

Safety events include: venous thromboembolism; ischaemic events (arterial thrombosis at any site, ischaemic stroke, transient ischaemic attack, peripheral artery embolism, myocardial infarction, acute coronary syndrome) and seizures.

Please remember that fatal SAEs need to be reported until discharge from hospital, even if this is after 7 days. Please assess if expected according to SmPC: <https://medicines.org.uk/emc/product/1220/smpc>

Investigators have a legal responsibility to report applicable SAEs to the chief investigator within 24 hours.

[Documents](#)
[Switch to mobile site](#)

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>

Logged in as: Nikola Sprigg <nikola.sprigg@nottingham.ac.uk> ([update email address](#))

For urgent medical enquiries (including [unblinding](#)), and for randomisation problems, you can contact the following emergency mobile numbers. Please ensure that you have these written down.

+44 (0)7725 580 092 +44 (0)7736 843 592
 +44 (0)7798 670 726 +44 (0)7810 540 604

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

- Coordinating centre will set up an account for investigators – we need the completed attendance at investigator training log completed (electronic signatures are accepted) and returned to us via email to know who needs logins for the TICH-3 website and subsequently added to the delegation log
- Additional investigators can be added later
- PI must activate before site can recruit
- Password reset on-line



Adding a new participant to the database



1. Complete randomisation alert

2. Add new participant

3. Need treatment pack ID number

4. Confirm randomisation site

5. Complete enrollment form

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

Participant list
 Queen's Medical Centre, Nottingham Investigator: Nikola Sprigg

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

Add a new participant Non-participant protocol violations (0)

Total number of trial participants recruited at this centre: 0
 Local time: 24 Mar 2022 10:14 GMT

1: Nottingham, Queen's Medical Centre

1. Please indicate which treatment pack was used

Treatment pack ID

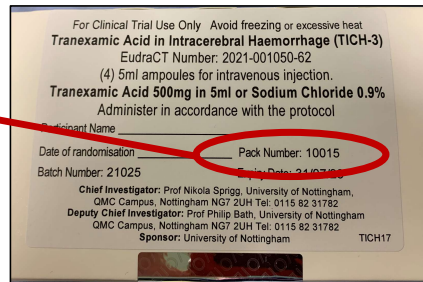
2. Please confirm that the correct hospital has been selected

Hospital C001 Queen's Medical Centre Stroke Office
 Room 2149, D Floor, South Block
 Queen's Medical Centre
 Derby Road
 Nottingham
 United Kingdom

Local time 10:10 GMT, 24 Mar 2022
 (Europe/London)

Yes, randomise at hospital C001 No, select another centre

The enrolment form **does not** support draft records.
 The form **must** be submitted completely, otherwise the data will be lost.



This will be a record of a manual randomisation already performed for treatment pack ID 10015.
 The next available trial number will be used for this participant.

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 [Select...] [Select...]

Section B: Participant details

B1 Initials 3 letters from forenames then surname, or 2 separated by a hyphen (-)

B2 Date of birth (dd-mmm-yyyy) - Day - - Month - - Year -

B3 Sex Male Female

B4 Date/time of onset of index stroke (dd-mmm-yyyy hh:mm 24hr) - Day - - Month - - Year - : :



Enrolment, Day 7 follow-up and Discharge/death eCRF (2)



Enrolment eCRF

TICH-3 trial
Tranexamic acid for IntraCerebral Haemorrhage 3

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>

ISRCTN 97695350

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?	<input type="checkbox"/> Yes <input type="checkbox"/> No
A2	Please give the name of the investigator taking initial consent for enrolment in the trial	<input type="text"/> <input type="checkbox"/> Not known

Section B: Participant details

B1	Initials <i>3 letters from forenames then surname, or 2 separated by a hyphen (-)</i>	<input type="text"/>
B2	Date of birth <i>(dd-mmm-yyyy)</i>	D ____ / M ____ / Y ____
B3	Sex	<input type="checkbox"/> Male <input type="checkbox"/> Female
B4	Date/time of onset of index stroke <i>(dd-mmm-yyyy hh:mm 24hr)</i>	D ____ / M ____ / Y ____ H ____ : M ____
B5	Date/time of randomisation <i>(dd-mmm-yyyy hh:mm 24hr)</i> <i>If unknown, please use date/time of first dose</i>	D ____ / M ____ / Y ____ H ____ : M ____
B6	Allocated treatment pack ID	<input type="text"/>

Day 7 follow-up eCRF

TICH-3 trial
Tranexamic acid for IntraCerebral Haemorrhage 3

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>

ISRCTN 97695350

Day 7 follow-up form v1.0

Section A: Day 7 follow-up

A1	Participant status	<input type="checkbox"/> Alive and in hospital <input type="checkbox"/> Discharged prior to day 7 <input type="checkbox"/> Withdrawn from follow-ups <input type="checkbox"/> Died
A2a	Was all randomised treatment received?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not known
A2b	Date/time of first dose <i>(dd-mmm-yyyy hh:mm 24hr)</i>	D ____ / M ____ / Y ____ H ____ : M ____ <input type="checkbox"/> Not done <input type="checkbox"/> Not known
A2c	Explanation if treatment not received or data missing	<input type="text"/> <input type="checkbox"/> Not applicable
<i>Systolic / diastolic</i>		
A3	Please enter BP recorded closest to 6 hours after stroke onset	<input type="text"/> / <input type="text"/> <input type="checkbox"/> Not done <input type="checkbox"/> Not known
A4a	Blood pressure on day 7 - reading 1	<input type="text"/> / <input type="text"/> <input type="checkbox"/> Not done <input type="checkbox"/> Not known
A4b	Blood pressure on day 7 - reading 2	<input type="text"/> / <input type="text"/> <input type="checkbox"/> Not done <input type="checkbox"/> Not known

Section B: Treatment during first 6 hours

B1a	Was BP-lowering treatment given in the first 6 hours?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not known
B1b	If yes, which antihypertensive drugs were given in the first 6 hours?	<input type="checkbox"/> Glyceryl trinitrate (GTN) - patch <input type="checkbox"/> Glyceryl trinitrate (GTN) - IV <input type="checkbox"/> Sodium nitroprusside <input type="checkbox"/> Other nitrate therapy (e.g. ISDN/ISMN) <input type="checkbox"/> Urapidil <input type="checkbox"/> Labetalol <input type="checkbox"/> Other beta-blocker (e.g. atenolol, propranolol, bisoprolol) <input type="checkbox"/> Calcium channel blocker (e.g. nifedipine, amlodipine) <input type="checkbox"/> Diuretic (e.g. bendroflumethiazide, indapamide, hydrochlorothiazide) <input type="checkbox"/> Not applicable <input type="checkbox"/> Not known

Discharge/death eCRF

TICH-3 trial
Tranexamic acid for IntraCerebral Haemorrhage 3

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 Nottingham NG7 2UH, United Kingdom
 TICH-3 trial office <tich-3@nottingham.ac.uk>

ISRCTN 97695350

Discharge or death in hospital form v1.0

For participants with a long stay in hospital, this form is to be completed by day 180 (or as close as possible).

Section A: Discharge/death details		
A1	Date of discharge or death <i>(dd-mmm-yyyy)</i>	D ____ / M ____ / Y ____
A2a	Discharge disposition	<input type="checkbox"/> Home - independent, alone <input type="checkbox"/> Home - independent, with partner/family/friend <input type="checkbox"/> Warden-aided flat <input type="checkbox"/> Residential home <input type="checkbox"/> Home - needing care <input type="checkbox"/> Carer's home <input type="checkbox"/> Respite care <input type="checkbox"/> Care home <input type="checkbox"/> Nursing home <input type="checkbox"/> Rehabilitation hospital <input type="checkbox"/> In hospital <input type="checkbox"/> Died <input type="checkbox"/> Other <input type="checkbox"/> Not known
A2b	Did the participant return to their original place of residence? <i>If died, please select 'No'</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not known
A3	Please list any other trials into which the participant was co-enrolled	<input type="text"/> <input type="checkbox"/> Not applicable <input type="checkbox"/> Not known
A4a	What was the final diagnosis of the randomising event?	<input type="checkbox"/> Intracerebral haemorrhage with no known underlying cause <input type="checkbox"/> Intracerebral haemorrhage with underlying cause <input type="checkbox"/> Ischaemic stroke with haemorrhagic transformation <input type="checkbox"/> Ischaemic stroke without haemorrhagic transformation <input type="checkbox"/> Non-stroke/other <input type="checkbox"/> Not known



Enrolment, Day 7 follow-up and Discharge/death eCRF (1)



- 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				✓ There are no active data queries			
Local time: 6 Apr 2022 13:13 BST				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 patients 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 e.g. If participant dies at day 2 you still need to complete day 7 form and discharge/death form
- If repatriated before day 7 please complete forms early and then check if patient still alive at day 7 and enter data

****Only trial team members signed off on the delegation log can enter data****



Uploading Consent forms



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.



Day 180 Form

To be conducted by Co-National Coordinator

To be confirmed if this is by post, phone or face to face

Includes

- Modified Rankin scale
- EQ-5D
- AD-8 cognition score

We will need to delegate follow up coordinator role to someone with appropriate access to complete forms on line

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 <mszh@nottingham.ac.uk>

Day 180 follow-up form - POSTAL VERSION v1.0

When you were in hospital approximately 180 days ago either you, or someone on your behalf, gave permission for you to participate in a clinical trial called TICH-3. This would have happened when you first attended hospital following your stroke.

It is important that we now collect information on how well you have recovered from your stroke. The following questionnaire asks important questions and we would be grateful if you would complete it to the best of your ability. For each question, please choose the answer that applies to you and put a tick in the box next to it. If you are unsure which answer to choose, please tick the box that seems closest. Even if you feel that the questions do not apply to you please would you answer them, as it will help us to answer important questions about strokes.

Some questions deal with personal matters. Your name and address will **not** be stored on a database with your answers, and we will keep the information that you give us in absolute confidence.

If you would prefer to speak to us and answer the questions by telephone, then please call the number provided on the covering letter. We can call you straight back to pay for the call. Alternatively, please post this questionnaire in the provided self-addressed envelope.

It is important that answers are given for all questions, to ensure completeness of data collection.

Section A: Basic information

A1 Date of completion
(dd-mmm-yyyy)

D ____ / M ____ / Y ____

LOCAL SITE FILE



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.

Print this certificate or [go to the TICH-3 start page](#)



For site initiation we require a minimum 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 <i>Consultant Physician</i> (K Krishnan)	G9L3P7 2 Feb 2022	Principal investigator ABCDEFGHIJKLMNOPQRSTUVWXYZ	7 Mar 2022 08:23 Authorised <i>Kailash Krishnan</i>
2	Nikola Sprigg <i>Professor of stroke medicine</i> (N Sprigg)	L9N9E7 2 Feb 2022	Site investigator BFHIJKLNOPQRSYZ	7 Mar 2022 08:25 Authorised <i>Kailash Krishnan</i>
3	Rachel Facilitator <i>Researcher</i> (R Facilitator)	L3N3F7 2 Feb 2022	Site investigator BFHIJKLNOPQRSTY	7 Mar 2022 08:25 Authorised <i>Kailash Krishnan</i>
4	Clara Researcher <i>Clinical Trials Researcher</i> (C Researcher)	K7H7C6 4 Feb 2022	Site investigator BFHIJKLNOPQRSTY	7 Mar 2022 08:25 Authorised <i>Kailash Krishnan</i>
5	Any Doctor <i>Researcher</i> (A Doctor)	F3C9T7 2 Feb 2022	Site investigator BFHIJKLNOPQRSYZ	7 Mar 2022 08:25 Authorised <i>Kailash Krishnan</i>
6	Zee Pharmacist <i>Pharmacy DTO</i> (Z Pharmacist)	Y7X6Y7 2 Mar 2022	Pharmacist # FHLNPQSY	12 Mar 2022 08:49 Authorised <i>Kailash Krishnan</i>

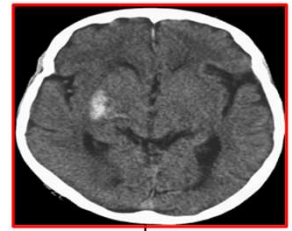
SUMMARY



TICH-3 Key Points



- 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



Verbal permission



Randomisation Alert



Written consent

Primary outcome:
Mortality day 7

Secondary:
mRS day 180





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****



What happens next?

- CTIS approval – Part I regulatory approval received 20/4/2023
- Part II Approved 26/04/2023
- Finalise contracts with each site
- Investigators will be added to the delegation log after completing the training log
- Please complete the investigator training log and return via email to the coordinating centre
- Or use the self referral form: <http://tich-3.ac.uk/?ZSelfRef>
- IMP will be sent to designated sites

Self-referral checklist

Please read through the following points carefully and indicate which are applicable, then submit at the bottom.

- I am a hospital researcher, administrator, pharmacist* or radiologist.
- I have completed the TICH-3 trial training.
- I have my signed work CV.
- I have a GCP certificate.
- I do **not** already have a TICH-3 account.
(If you do, please contact the co-ordinating office when another hospital needs to be added to your account).
- I declare my intention to participate in the TICH-3 trial.

Your country:

Submit

* - includes pharmacy technician

CONTACT INFORMATION



University of Nottingham Trial Team



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**Thank you
Any Questions?**