University of Nottingham
UK | CHINA | MALAYSIA

ISRCTN97695350

TRANEXAMIC ACID FOR INTRACEREBRAL HAEMORRHAGE: TICH-3 TRIAL

WARD TRAINING

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On behalf TICH-3 Trial Team

Final v1.1 08/03/2024

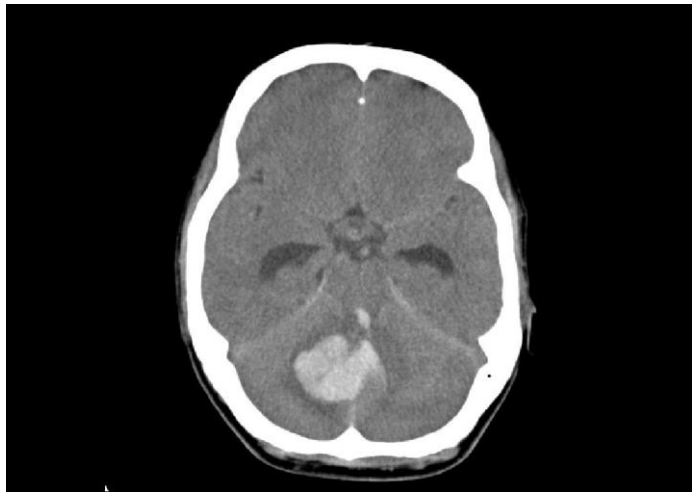
Introduction

- TICH-3 is a double-blinded, randomised study recruiting patients with confirmed Intracerebral Haemorrhage (ICH)
- Participants must be randomised within 4.5 hours of stroke onset (or symptom discovery following wake-up)
- Participants will also receive usual Standard of Care e.g. blood pressure lowering treatment, DOAC reversal with PCC, referral to neurosurgery

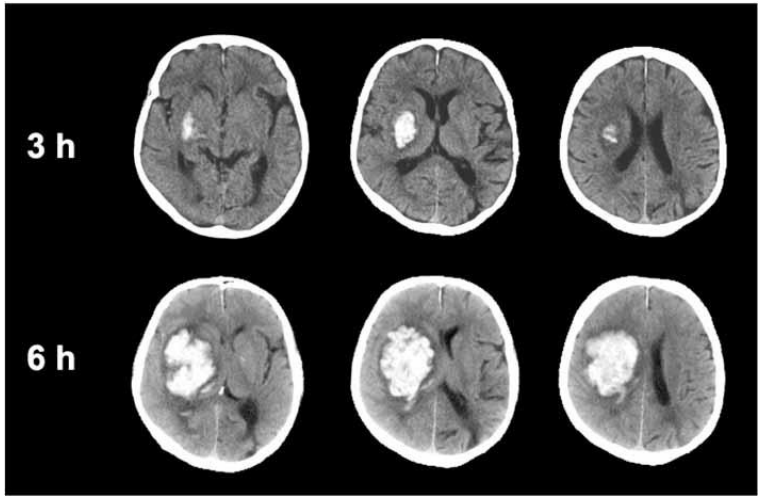
Rationale

- 1.7 million strokes worldwide per year with a mortality of over 40%
- 10,000+ people suffered an Intracerebral Haemorrhage (ICH) last year in England
- There is no effective drug treatment to stop continued bleeding (haematoma growth) after ICH
- Tranexamic acid (TXA) reduces bleeding and death in other emergency bleeding conditions

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



Case courtesy of Dr Farzad Pirzad, Radiopaedia.org, rID: 9620



Bornes, Troy & Butcher, Ken. (2009). Management of Hypertension in the Acute Phase of Stroke. Current Hypertension Reviews. 5.

Streamlined Recruitment Process

- Patient suspected of suffering a stroke
- CT/MRI scan shows bleeding and is within 4.5 hours of symptom discovery
- Contact local Research Coordinating Team or TICH-3 trained Medic if out-of-hours
- **Confirm eligibility** can be completed by any clinician they do not need to be on the TICH-3 delegation log
- **Delegated investigator** obtains initial oral consent, consent process just needs to be documented in the medical record. We also allow remote recruitment over phone/telemedicine. If no relatives, then ask an independent doctor and use brief consent form to document.
- **Lowest numbered TICH-3 treatment pack** is prescribed and administered by appropriate staff (they do not need to be on the delegation log or GCP trained)
- **Alert coordinating centre** that patient has been enrolled into the trial using the randomisation alert on the prescribing and administration guide
- Research team will obtain follow on written consent when next on site

TICH-3 Eligibility Criteria

Inclusion criteria

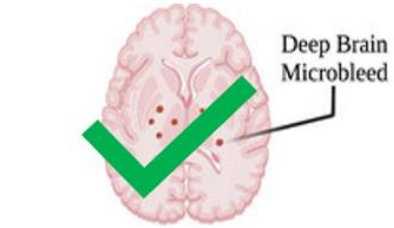
- Spontaneous ICH (confirmed on brain imaging) < 4.5 hours of onset

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

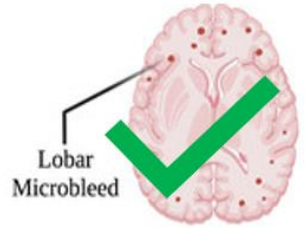
IMP treatment should be started within the 4.5 hours inclusion window.

Exclusion criteria

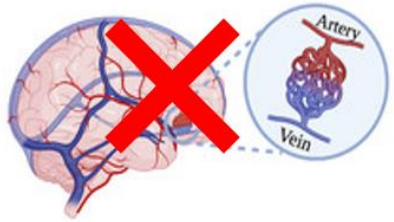
- Known indication for TXA treatment (e.g. traumatic brain injury) *or* contra-indication for TXA treatment (e.g. active seizures) *in view of treating physician*
- Patient known to be taking therapeutic anticoagulation with warfarin or low molecular weight heparin at time of enrolment. **(DOAC is permitted)**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



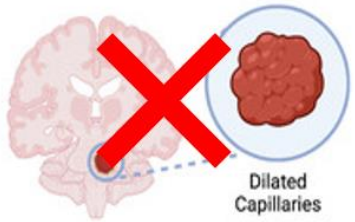
Hypertension Microangiopathy



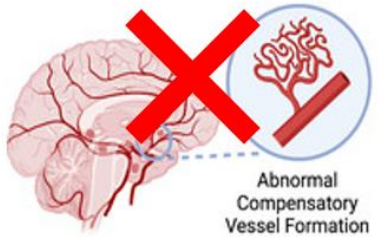
Cerebral Amyloid Angiopathy



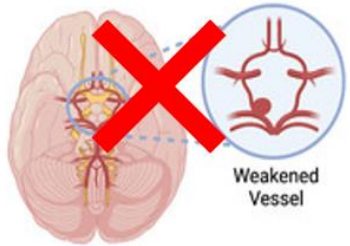
Arteriovenous Malformation



Cavernous Angioma



Moyamoya Disease



Aneurysm

Emergency Consent Process

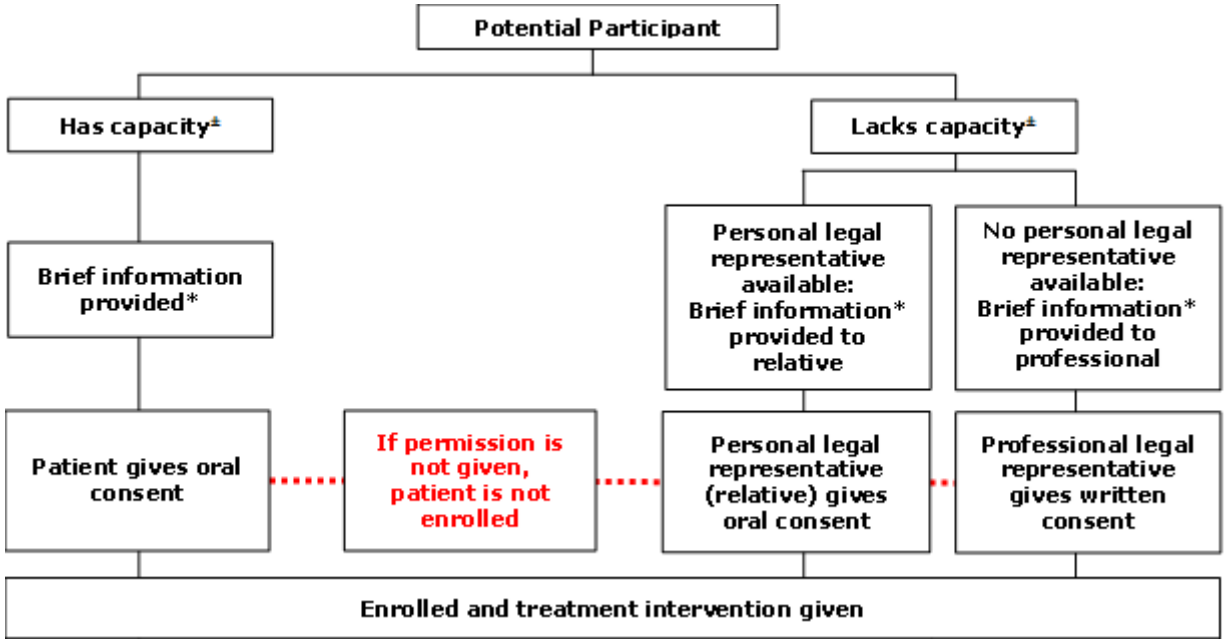
Rapid consent process, initially verbal consent

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

Hierarchy approach in UK

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

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



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

± Assessment of capacity is the responsibility of the treating physician

Professional legal representative consent by an independent doctor

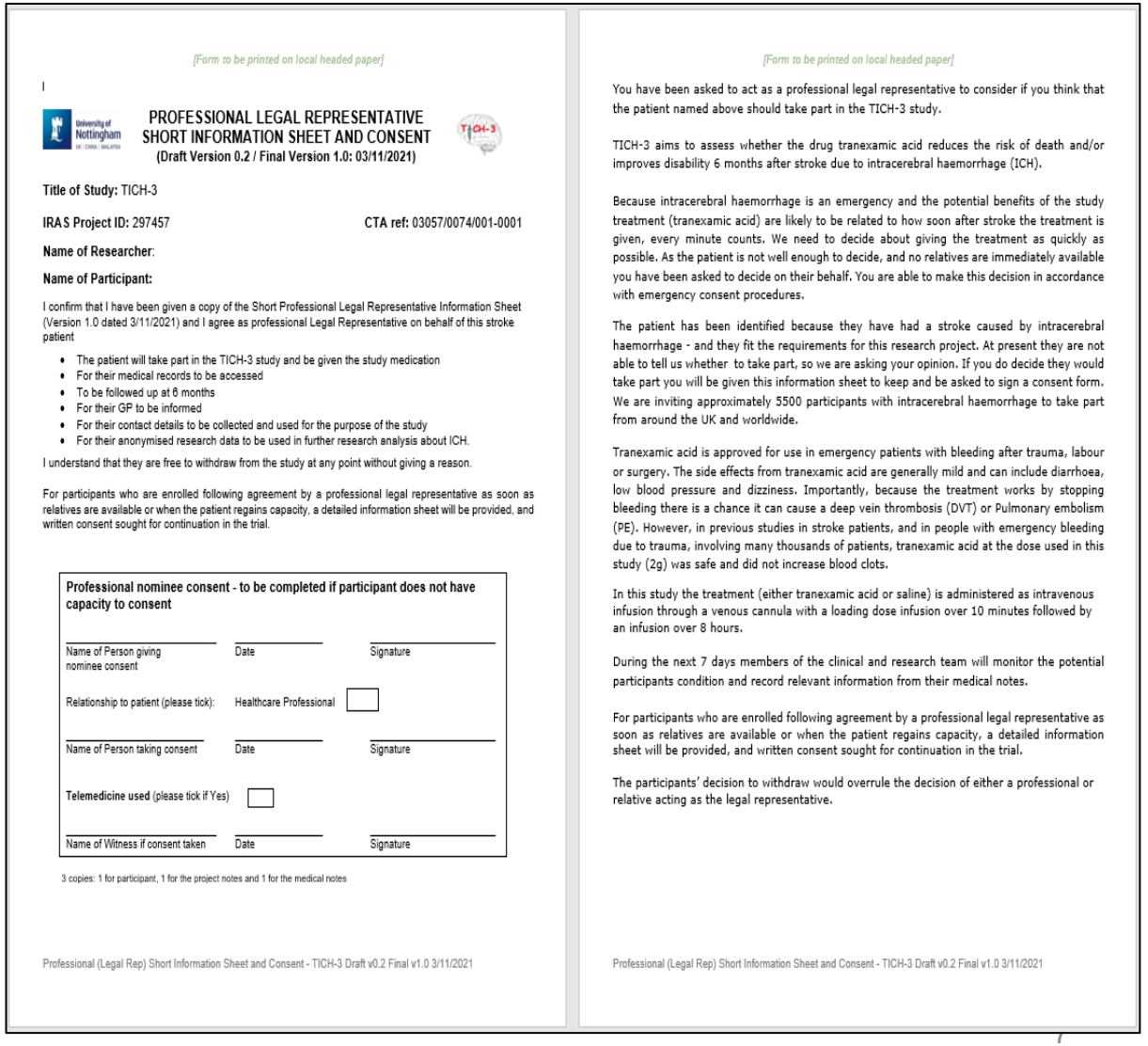
If patient does not have capacity to consent and no relatives are contactable then an independent doctor can act as professional legal representative for the patient.

Enrolment consent by independent doctor

Short Information Sheet and Consent form should be used (pictured to the right). In this scenario the professional legal representative enrolment consent is handwritten.

Informing relatives

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



[Form to be printed on local headed paper]

I

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

Remote recruitment

Eligibility

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

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

Consent

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

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

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

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

TICH-3 Treatment Packs

- Temperature monitoring is not required. The packs will be stored at room temperature and protected from excessive heat and freezing
- TICH-3 treatment packs contain 4 ampoules: Tranexamic Acid **OR** Sodium Chloride (placebo)
- The IMP is stored in a secure, limited access storage area, this could be in the A&E, stroke ward or thrombolysis bag
- Ensure all members of the local team are aware of where the IMP and related documents (consent forms/PIS) are stored
- Local site is responsible for the accountability and monitoring of the IMP
- Research Coordinators will carry out checks monthly to ensure all treatment packs are sealed and accounted for
- TICH-3 drug should **NEVER** be given to patients that are not enrolled in to the TICH-3 trial
- To randomise open the next lowest numbered treatment pack

Prescribing and Administering the IMP

Prescribing the IMP

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

Prescribe (write in participants drug chart):

TICH-3 - TRIAL Pack Number XXXXX

TRANEXAMIC ACID OR PLACEBO

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

AND

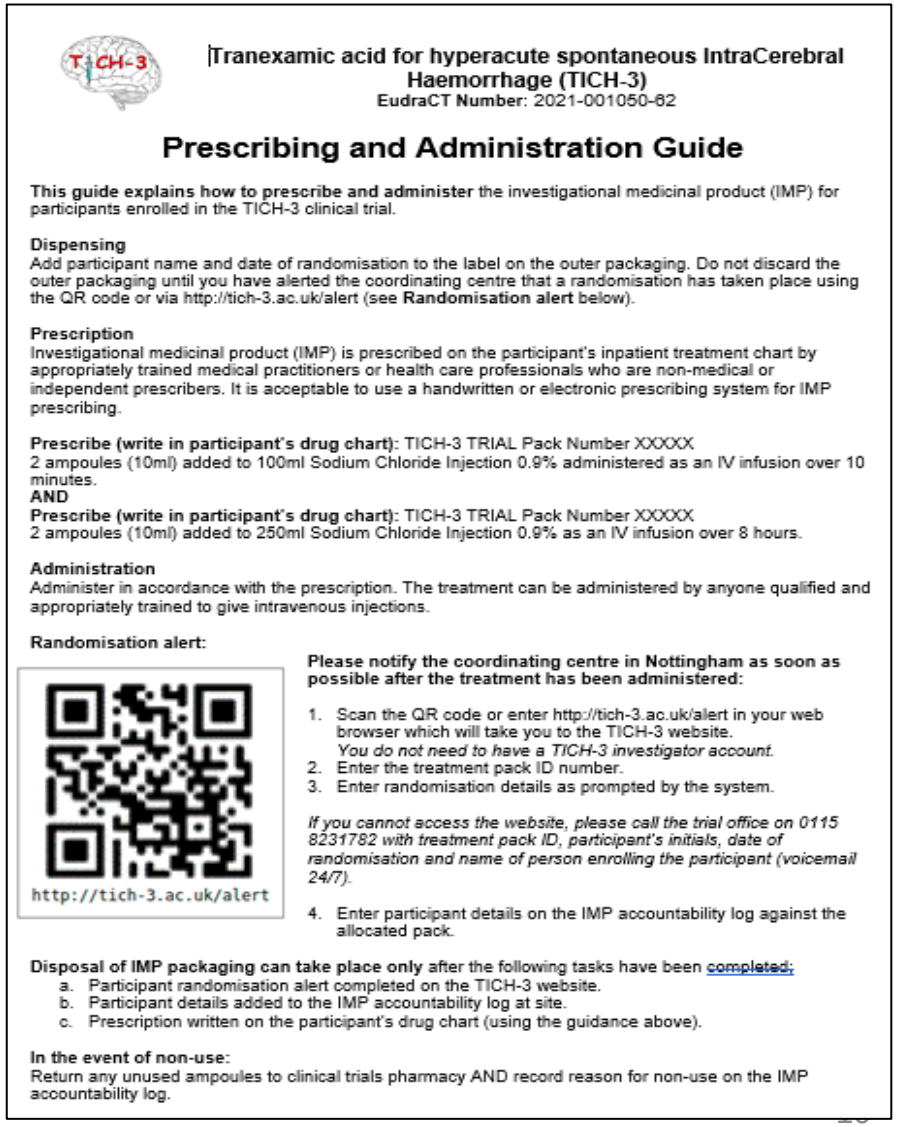
TICH-3 TRIAL Pack Number XXXXX

TRANEXAMIC ACID OR PLACEBO

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

Administering the IMP

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



Tranexamic acid for hyperacute spontaneous IntraCerebral Haemorrhage (TICH-3)
EudraCT Number: 2021-001050-62

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. 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/

Let us know about a new TICH-3 participant

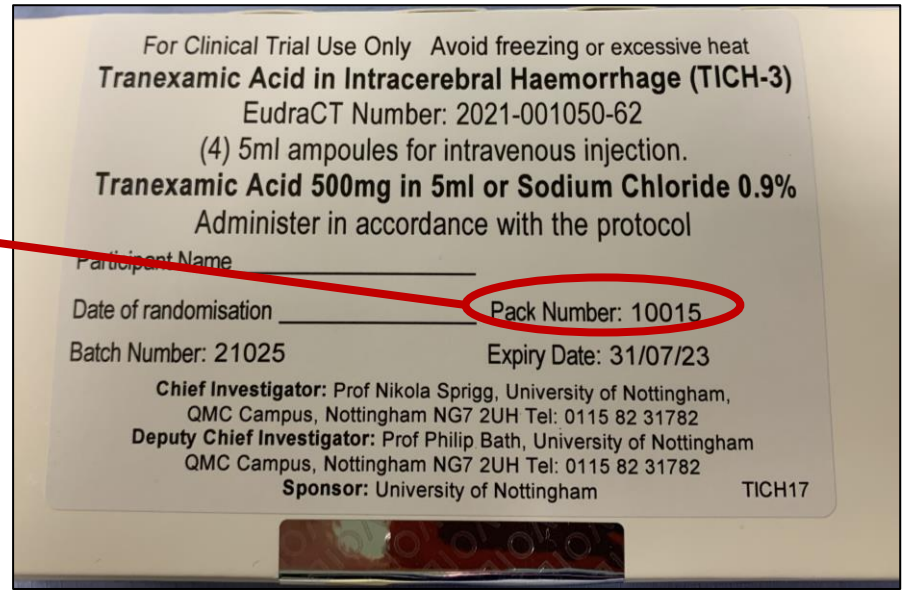
Treatment pack ID:

Participant's initials:
(2 or 3 letters)

Your initials:
(2 or 3 letters)

Submit

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**

Confirm Cancel

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

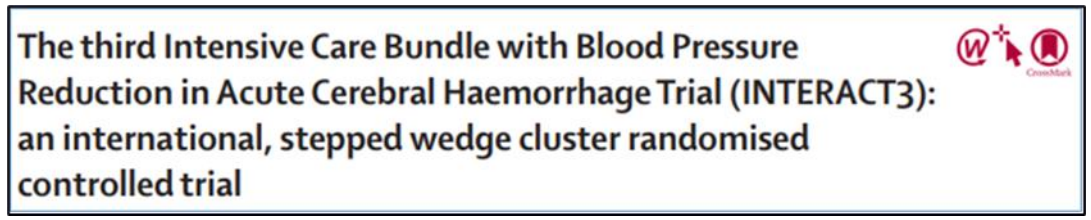
Standard of care for ICH – ABC ICH bundle of care

- All participants should receive standard care for ICH as per the local clinical pathway and guidelines. This is likely to include referral to a stroke unit and components of ABC-ICH

✓ **A**nticoagulation reversal

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

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


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

✓ **C**onsideration 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

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.

- Try to contact the clinician that enrolled the patient if available

- If TICH-3 trained investigators are not available, the emergency numbers should be used for further guidance. Please make sure these numbers are noted down with the TICH-3 treatment packs for if required in an emergency.

> 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

- For non-emergency queries the TICH-3 office can also be contacted on 0115 823 1782 between 8am and 5pm Monday – Friday

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 (IC now 2 – 31 days)

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)

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

NEW CO-ENROLMENT AGREEMENT IMPLEMENTED FOR NEW TRIALS, does not need localising at each site, the master agreement signed by the 2 trials CIs – please get in touch to discuss any co-enrolment.

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

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

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

Further Information and Getting Involved

- The NIHR provides free Good Clinical Practice training and further information
- You can self-register using your NHS email via the this link:

  https://portal.nihr.ac.uk/register?app=LMS

- The TICH-3 documents page provides further guidance documents https://stroke.nottingham.ac.uk/sif/docs/?sid=TICH-3

- Contact your local Stroke Research Team if you are interested in becoming a TICH-3 investigator

University of Nottingham Trial Team

Name	Role	Contact Information
Brittany Hare	Clinical Trials Manager (UK Site Recruitment)	E: brittany.hare@nottingham.ac.uk
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Trial Coordinating Centre contact information:

+44(0)115 823 1782

TICH-3@nottingham.ac.uk

University of Nottingham
UK | CHINA | MALAYSIA

THANK YOU!

Any questions?

TICH-3@nottingham.ac.uk

Audit list of updates to training presentations

This version 1.1 08/03/2024

- Added information new co-enrolment agreement process and currently have this agreed MARCH trial