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ISRCTN97695350

TRANEXAMIC ACID FOR INTRACEREBRAL HAEMORRHAGE: TICH-3 TRIAL

INVESTIGATOR TRAINING:

Enrolling investigators & Emergency department

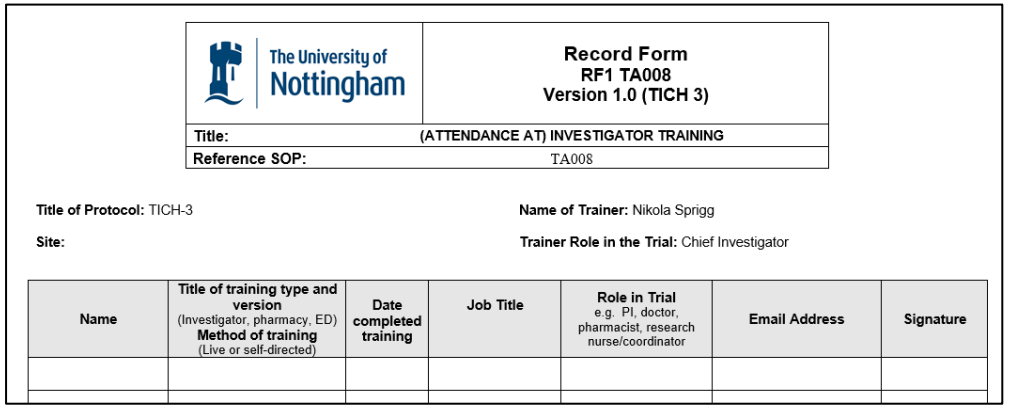
Professor Nikola Sprigg

On behalf TICH-3 Trial Team

Final v1.6 06/07/2022

Aims and Objectives

- Intracerebral haemorrhage and haematoma expansion
- Tranexamic acid
- Study design
- Inclusion and exclusion criteria
- Consent process
- Randomisation and randomisation alert
- Drug administration
- Safety monitoring



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

Name of Trainer: Nikola Sprigg

Site:

Trainer Role in the Trial: Chief Investigator

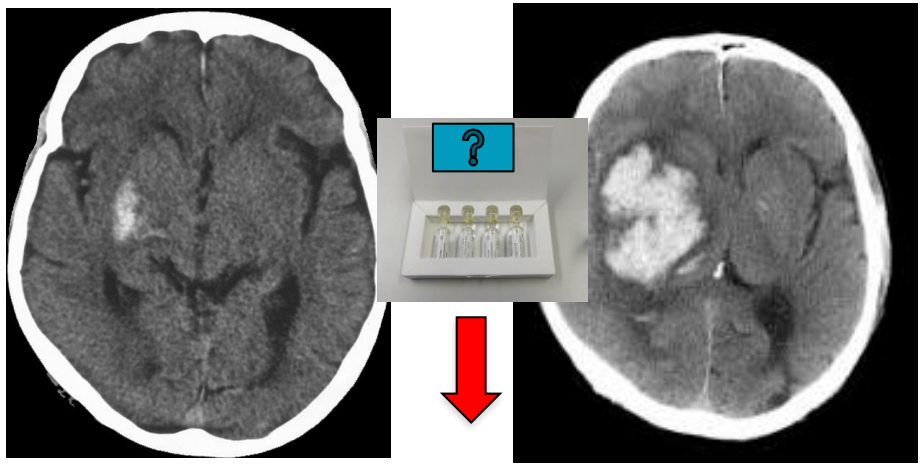
Name	Title of training type and version (Investigator, pharmacy, ED) **Method of training** (Live or self-directed)	Date completed training	Job Title	Role in Trial e.g. PI, doctor, pharmacist, research nurse/coordinator	Email Address	Signature

Please complete training log after completing to be added to the TICH-3 delegation log

Intracerebral Haemorrhage

Intracerebral haemorrhage can be devastating

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



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

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

Tranexamic Acid

- 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.
- Use of TXA after acute ICH was tested in TICH-1 which assessed the feasibility of a larger trial. The administration of TXA was feasible and well tolerated and led to TICH-2.
- 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-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 then 1g infusion 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 start UK recruitment early 2022

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 ischaemic stroke (haemorrhagic transformation of infarct, HTI) or thrombolysis or venous infarct is NOT spontaneous ICH

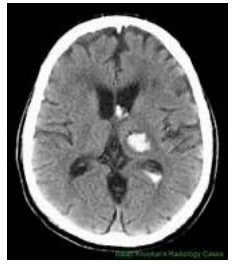
Exclusion criteria

- Known indication for TXA treatment (e.g. traumatic brain injury).
- Known contra-indication for TXA treatment (e.g. seizures)
- Known to be taking anticoagulation at time of enrolment
- Massive ICH (usually when haematoma volume > 60ml)
- Severe coma, Glasgow Coma Scale <5
- Decision for palliative (end of life) care

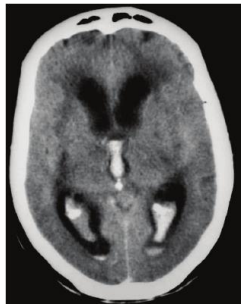
Eligibility: Frequently asked questions

- 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
- If patient had a seizure in the past?
  Active seizures are a contraindication to tranexamic acid. Previous seizures e.g.
  recent likely to be a contraindication isolated proved seizure in past may not be decision rests with treating physician
- 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.
- Known to be taking prophylactic enoxaparin?
  Can be enrolled – to be excluded needs to be treatment dose anticoagulation
- 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 atereriopathy due to hypertension or cerebral amyloid angiopathy

1. ICH and IVH



2. IVH only



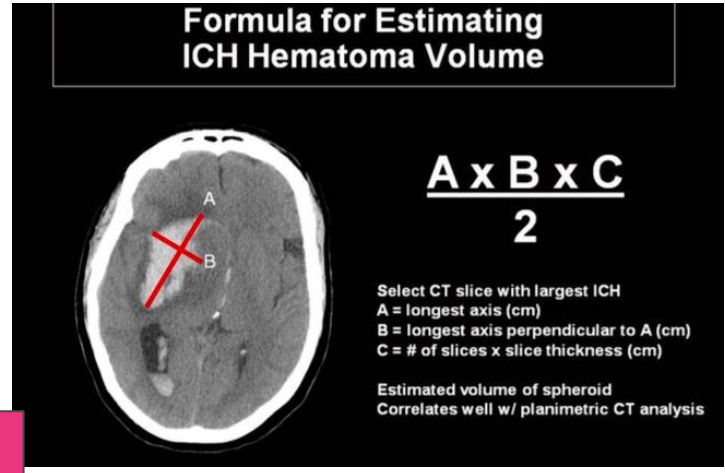
Final decision on eligibility rests with treating physician

Haematoma volume measurement

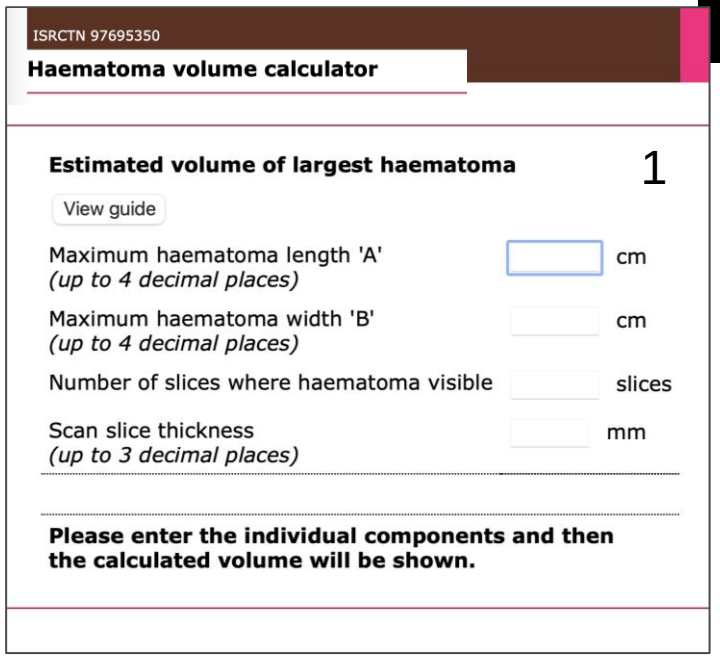
Exclude patients with massive haematoma (usually >60ml)

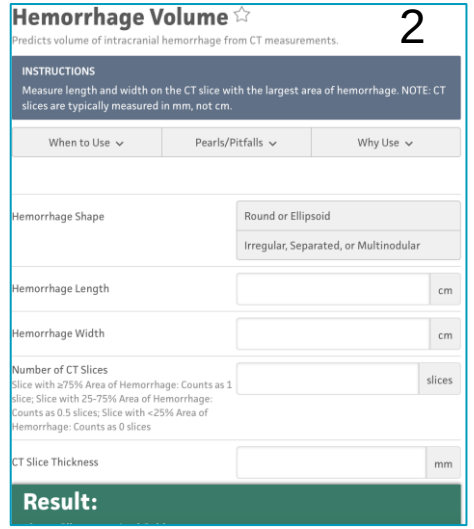
1. If CT scan uses automated haematoma volume software – patient can be enrolled if HV not greater than 60mls
2. Calculate HV manually using TICH-3 HV=ABC/2 calculator on the website[1] or alternatives e.g. mdcalc app[2] Dimensions can be obtained from neuroradiology or measured directly.
3. If ABC/2 not possible: measure the maximum length of the haematoma. Exclude - if max length A > 5cm

- 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

Emergency Consent Process

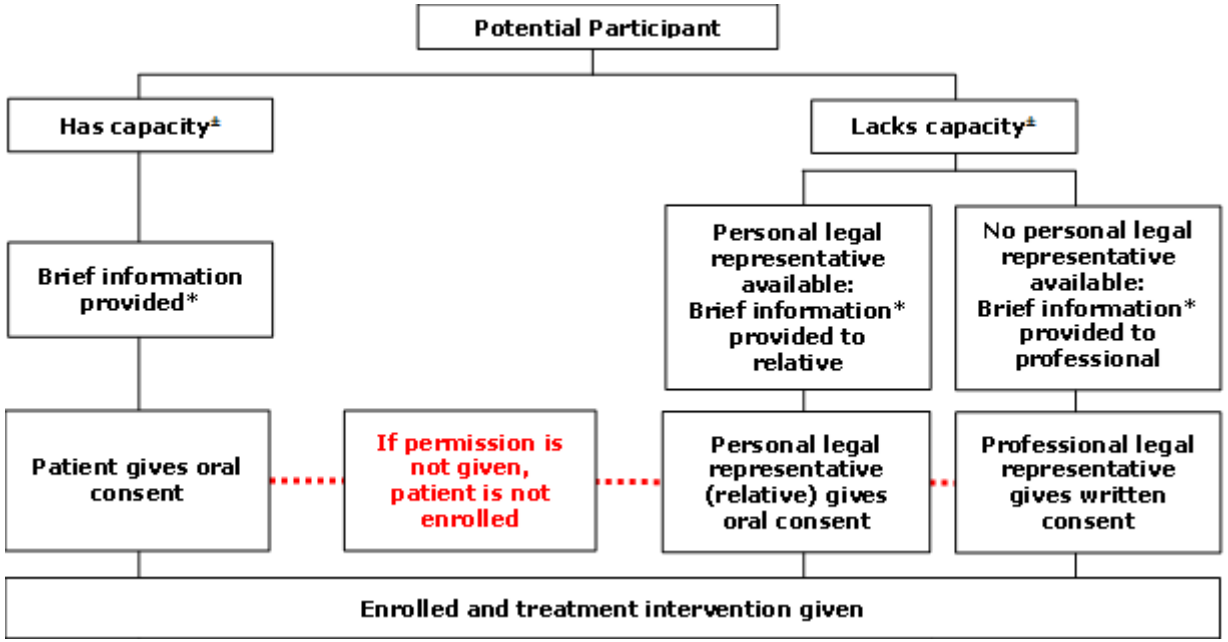
Rapid consent process, initially verbal consent

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

<u>Hierarchy approach in UK</u>

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.
- 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

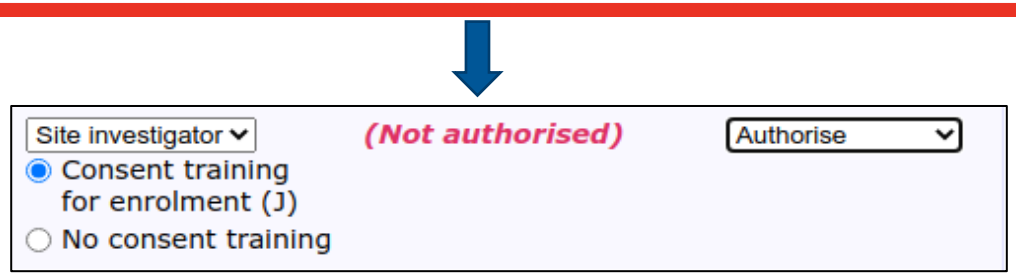
± Assessment of capacity is the responsibility of the treating physician

Delegated roles for consent: J and Z

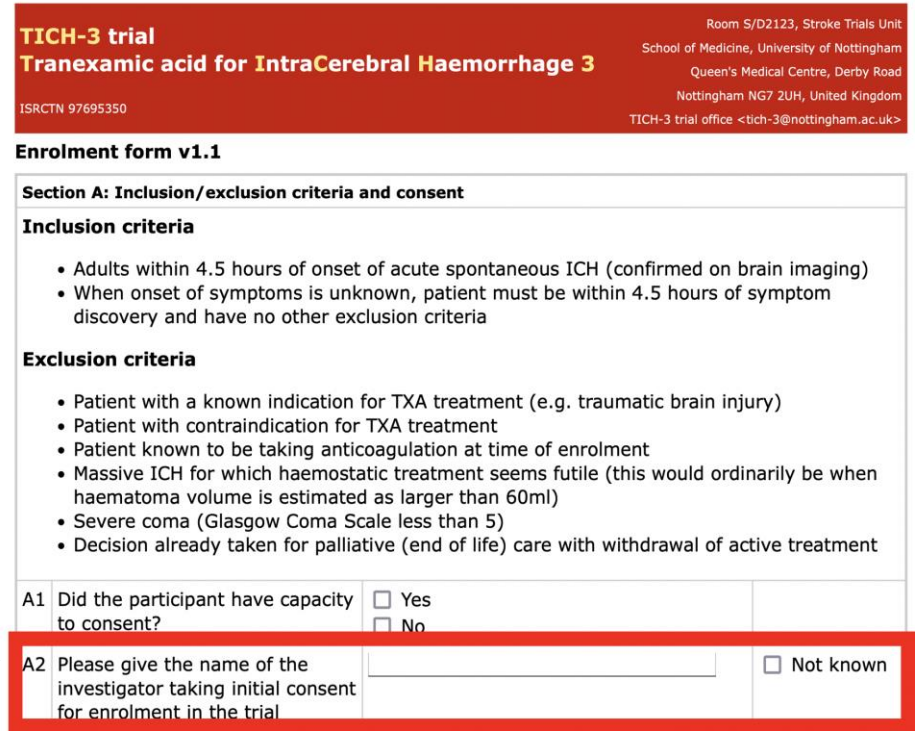
Person taking initial consent must be delegated role J

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



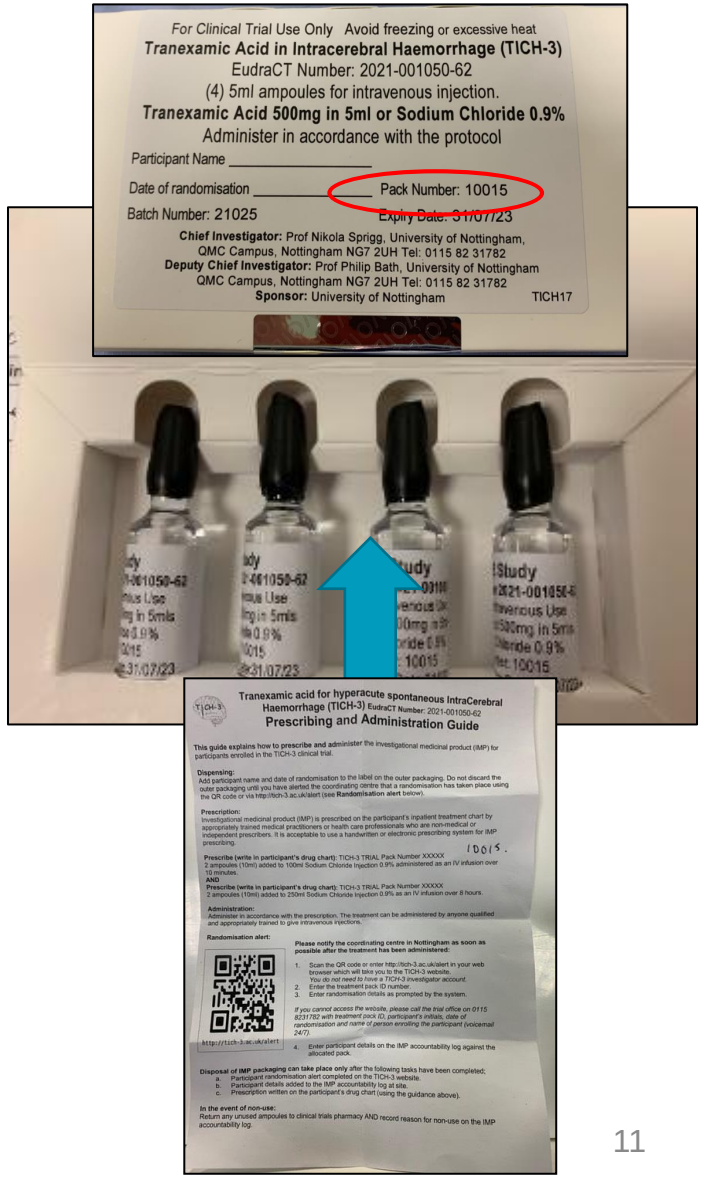
Person taking written consent must be delegated role Z

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**

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 selects 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.

Prescribe (write in participants 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.

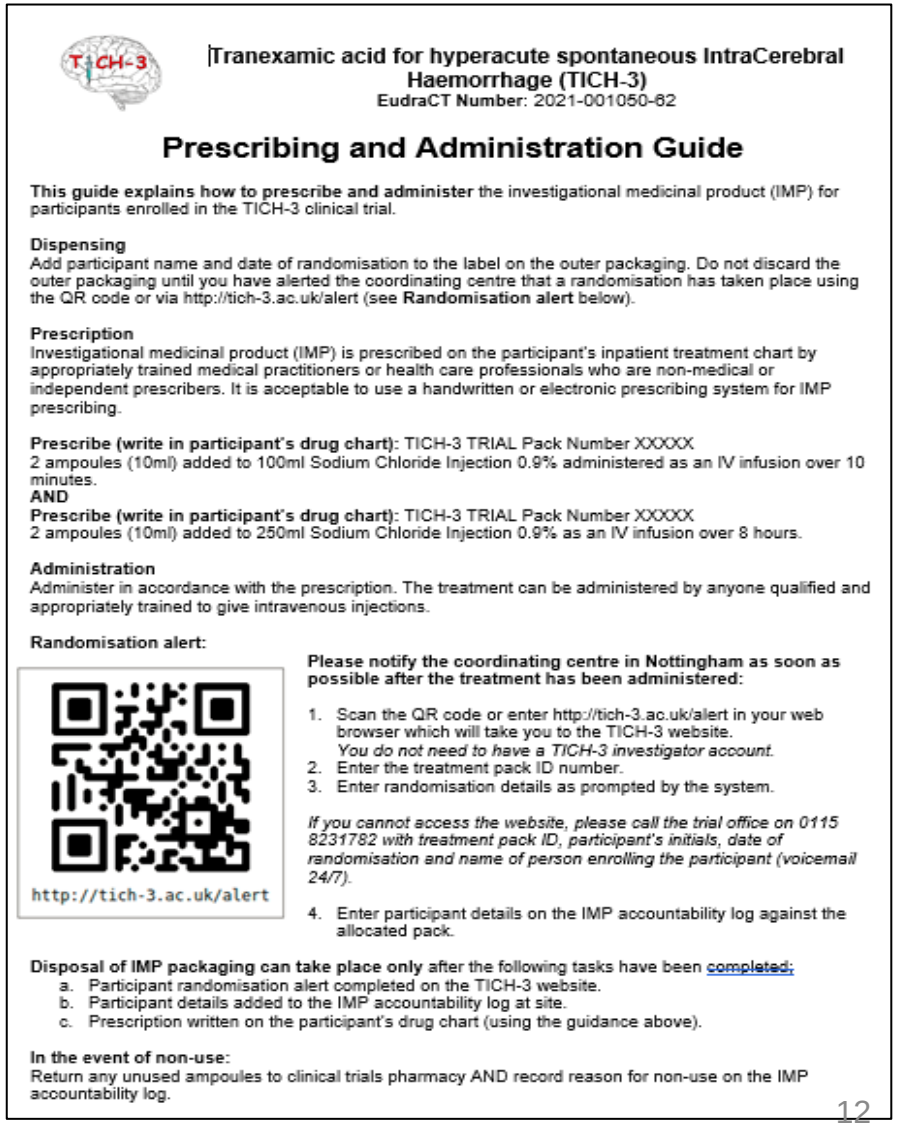
AND

TICH-3 TRIAL Pack Number XXXXX

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.



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.

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 WPD020 (Destruction of IMP).

Broken after randomisation, **before treatment**:

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

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

✓Administer as much drug as possible

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

x Do not open another treatment pack

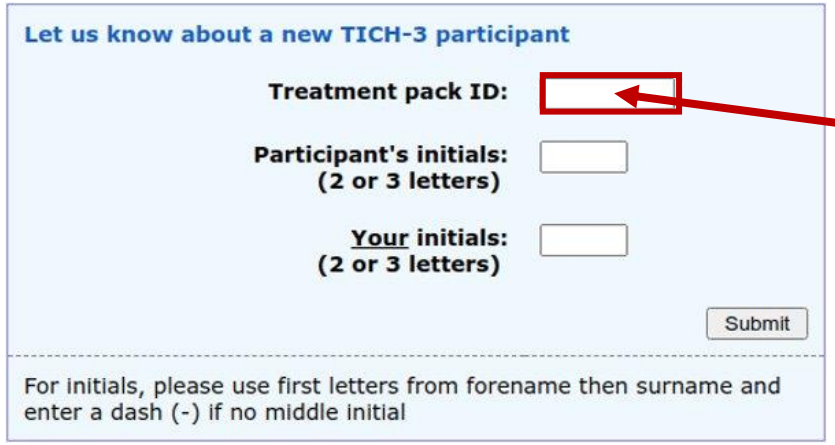
Always record broken vials on the inventory or accountability log as appropriate

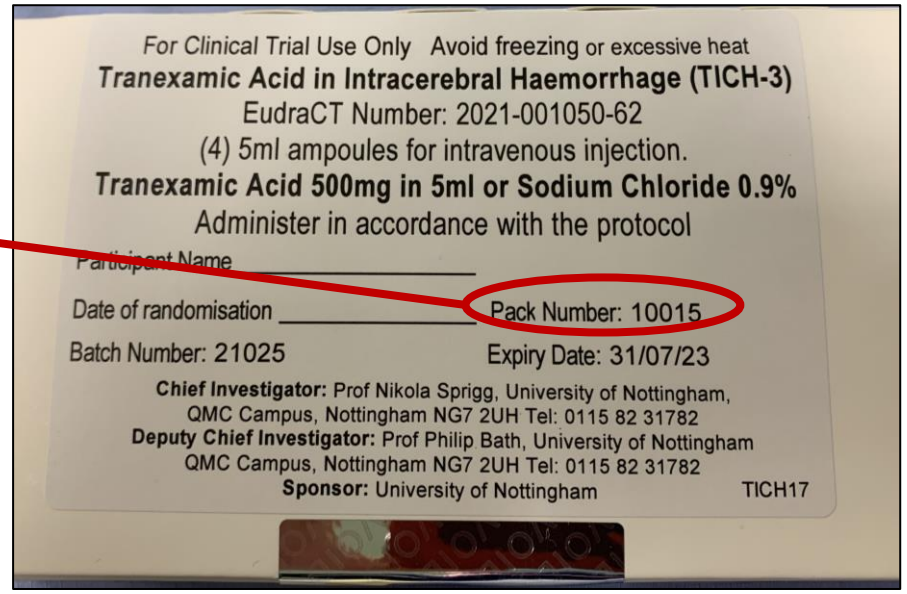
Randomisation Alert

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/



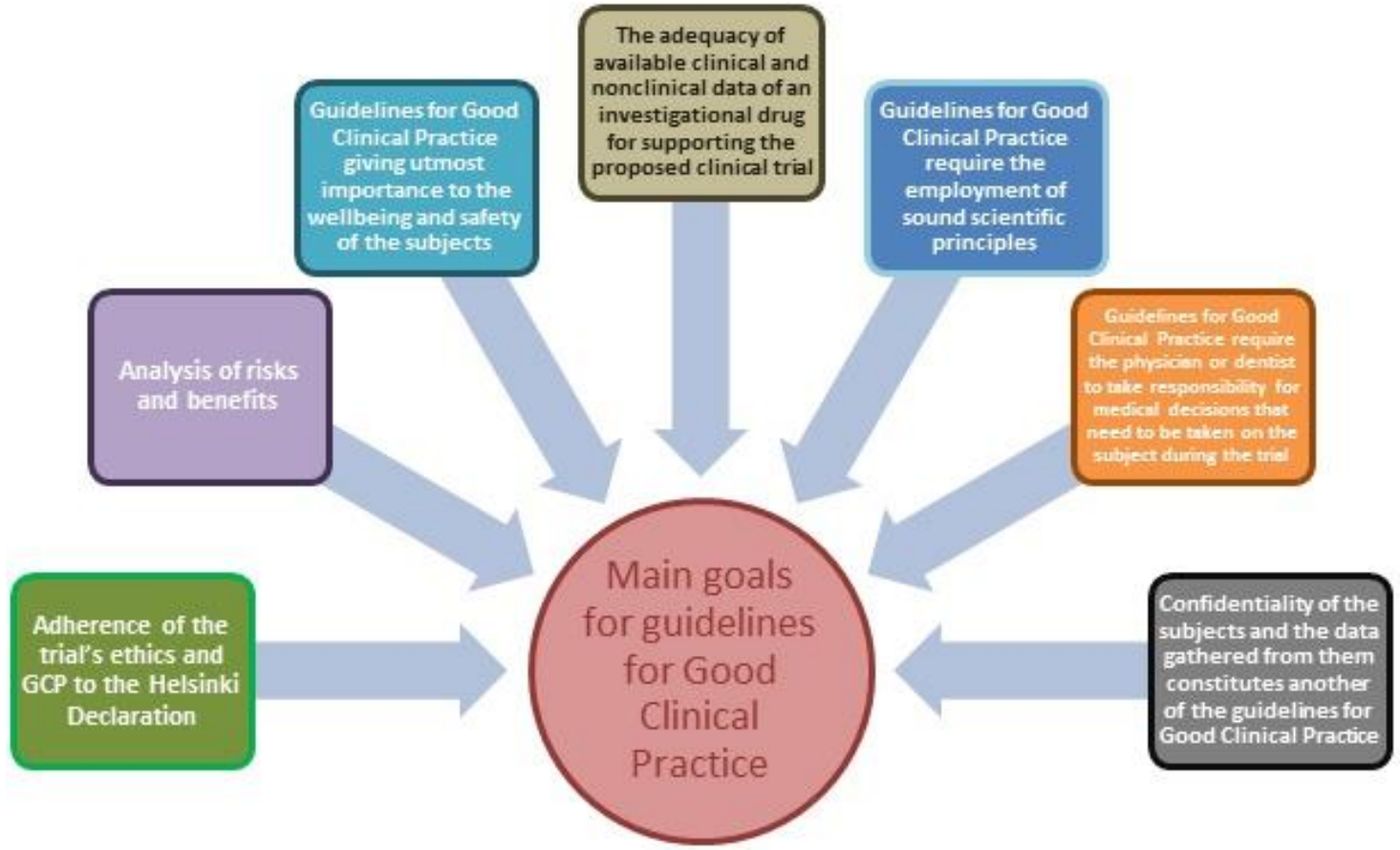


2. Investigator will then confirm that the participant was randomised at the hospital shown in the alert box.

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

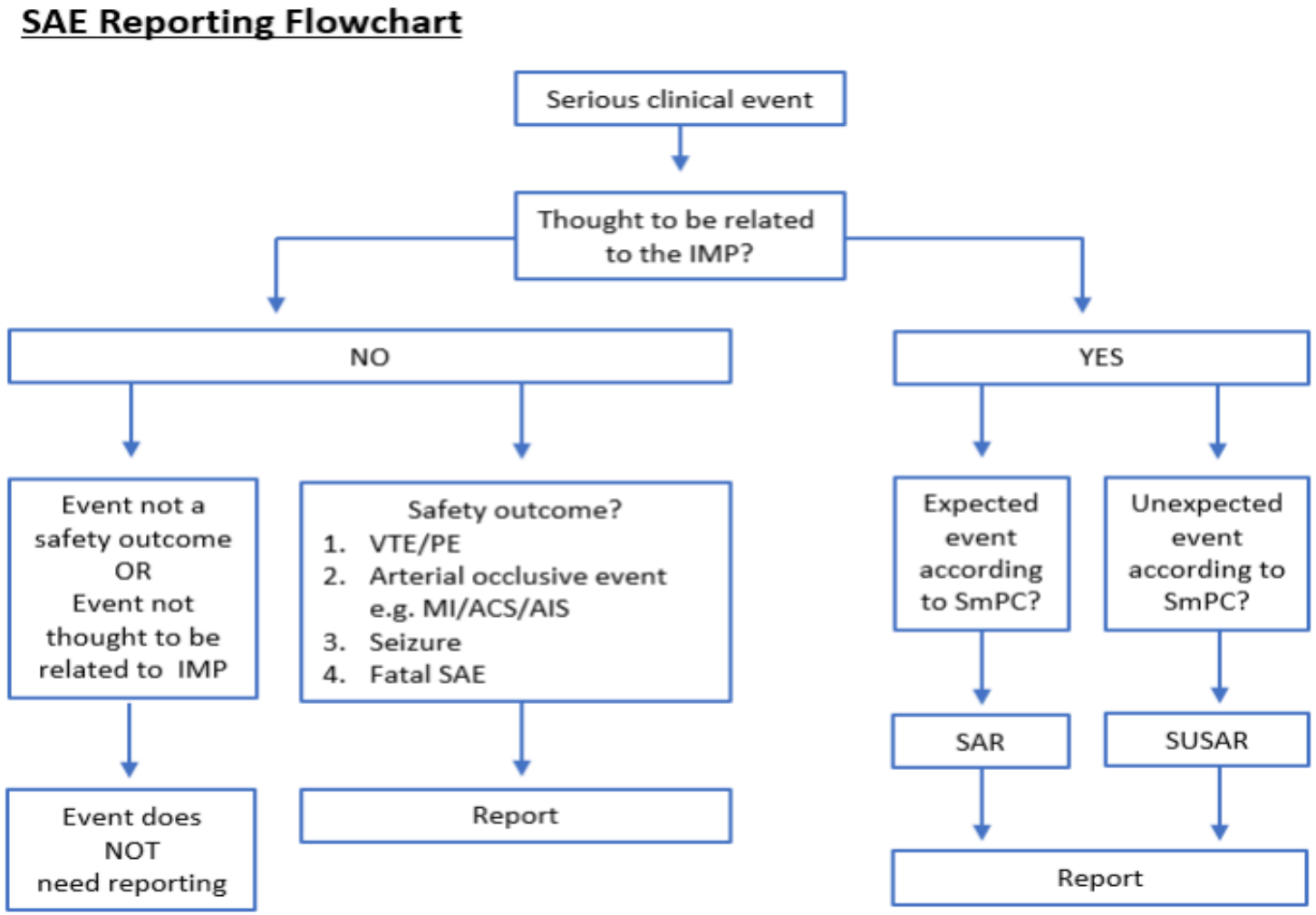
Serious adverse reactions (SAR) or Suspected Unexpected Serious Adverse Reactions (SUSAR):

- 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



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 (or print them).

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

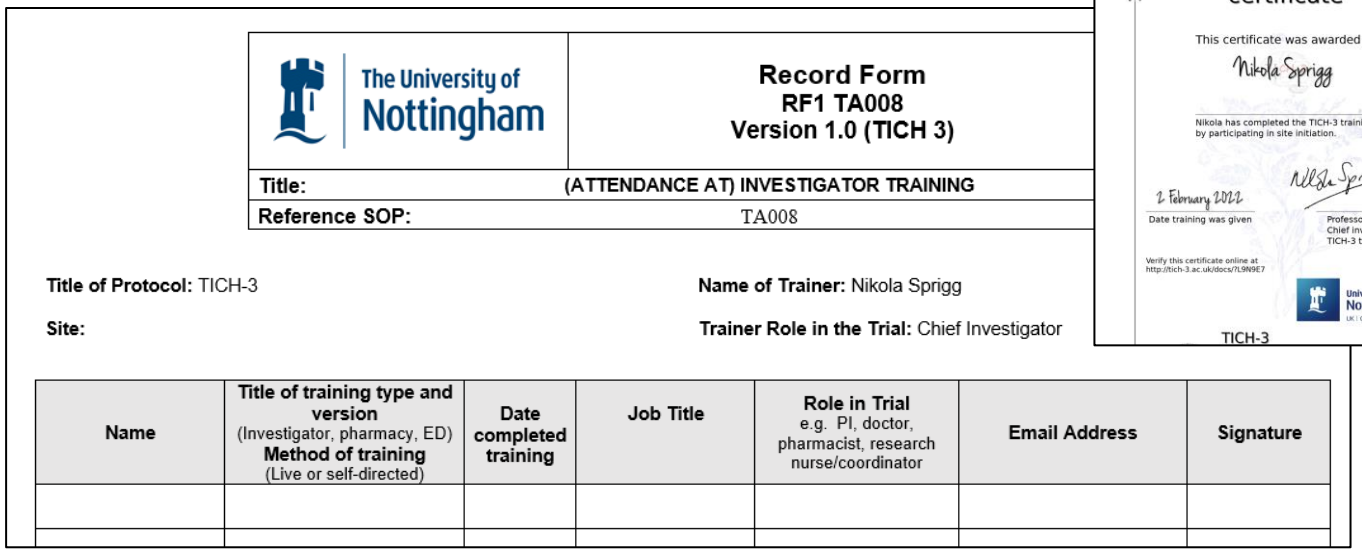
+44 (0)7798 670 726 +44 (0)7810 540 604

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

Training and delegation log

- Please complete the investigator training log and return via email to the coordinating centre
- The coordinating centre will then create an investigator account on the TICH-3 website
- Investigators will receive an email to confirm that they want to be an investigator in the TICH-3 trial
- Local PI will then be notified via email and will then countersign the investigator on the online delegation log
- A short 3 ½ minute video is available for ED training http://tich-3.ac.uk/docs/#Videos



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

Name of Trainer: Nikola Sprigg

Site:

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

Print this certificate or go to the TICH-3 start page

TICH-3 training certificate

This certificate was awarded to

Nikola Sprigg

Nikola has completed the TICH-3 training by participating in site initiation.

2 February 2022

Date training was given

Professor Nikola Sprigg
Chief Investigator
TICH-3 trial

Verify this certificate online at http://tich-3.ac.uk/docs/7L9N9E7

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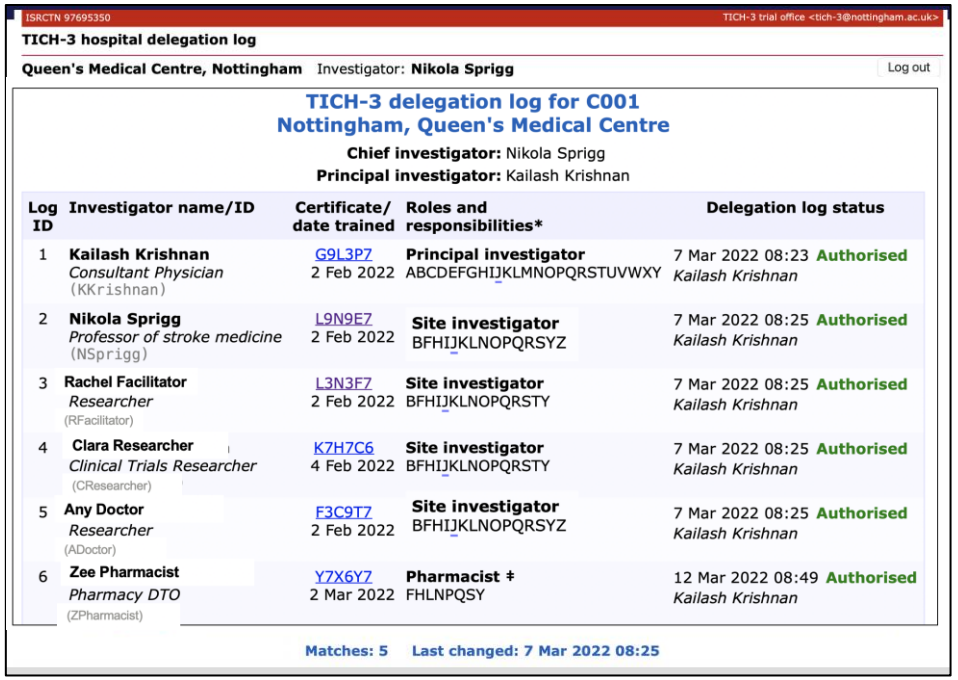
TICH-3



ISRCTN 97695350 — TICH-3 trial office <tich-3@nottingham.ac.uk>

TICH-3 hospital delegation log

Queen's Medical Centre, Nottingham Investigator: **Nikola Sprigg** Log out

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*

Matches: 5 **Last changed: 7 Mar 2022 08:25**

University of Nottingham Trial Team

Name	Role	Contact Information
Brittany Dutton	Clinical Trials Manager (UK Site Recruitment)	E: brittany.dutton2@nottingham.ac.uk
Joseph Dib	Clinical Trials Manager (International Site Recruitment)	E: joseph.dib4@nottingham.ac.uk
Olivia Matthews	Follow Up Coordinator	E: olivia.matthews@nottingham.ac.uk
Kerry Larkin	Follow Up Coordinator	E: kerry.larkin@nottingham.ac.uk
Nikola Sprigg	Chief Investigator	E: nikola.sprigg@Nottingham.ac.uk

Trial Coordinating Centre contact information:

+44(0)115 823 1782

TICH-3@nottingham.ac.uk

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THANK YOU!

Any questions?

TICH-3@nottingham.ac.uk

Audit list of updates to training presentations

Previous versions

Version 1.4 25/05/2022

- Broken vials slide changed from protocol violation to ‘Record on day 7 form that participant does not receive all of the randomised treatment as per protocol and explain why’
- Added link for ED training video
- Eligibility criteria slide added ‘Note - ICH secondary to ischaemic stroke (haemorrhagic transformation of infarct, HTI) or thrombolysis or venous infarct is NOT spontaneous ICH’
- Key points slide - HV < 60mls corrected to HV > 60mls
- Eligibility FAQ slide added Can patients with venous infarction or haemorrhagic transformation of infarct (HTI) be enrolled? No, these are secondary causes of ICH and should not be included. The inclusion criteria requires that thehaemorrhage is thought to be spontaneous at time of enrolment and Can patients that have a bleed after thrombolysis be enrolled? No, this is not a spontaneous haemorrhage

Version 1.5 13/06/2022

- Inform investigators re sponsors SOPS – GCP breach slide 16

This Version 1.6 06/07/2022

- SAE example given e.g. HE

This version 1.7 28/07/2022

- Added SAE flowchart
- Deleted some duplicate FAQ questions and added FAQ recurrent bleeds