University of Nottingham
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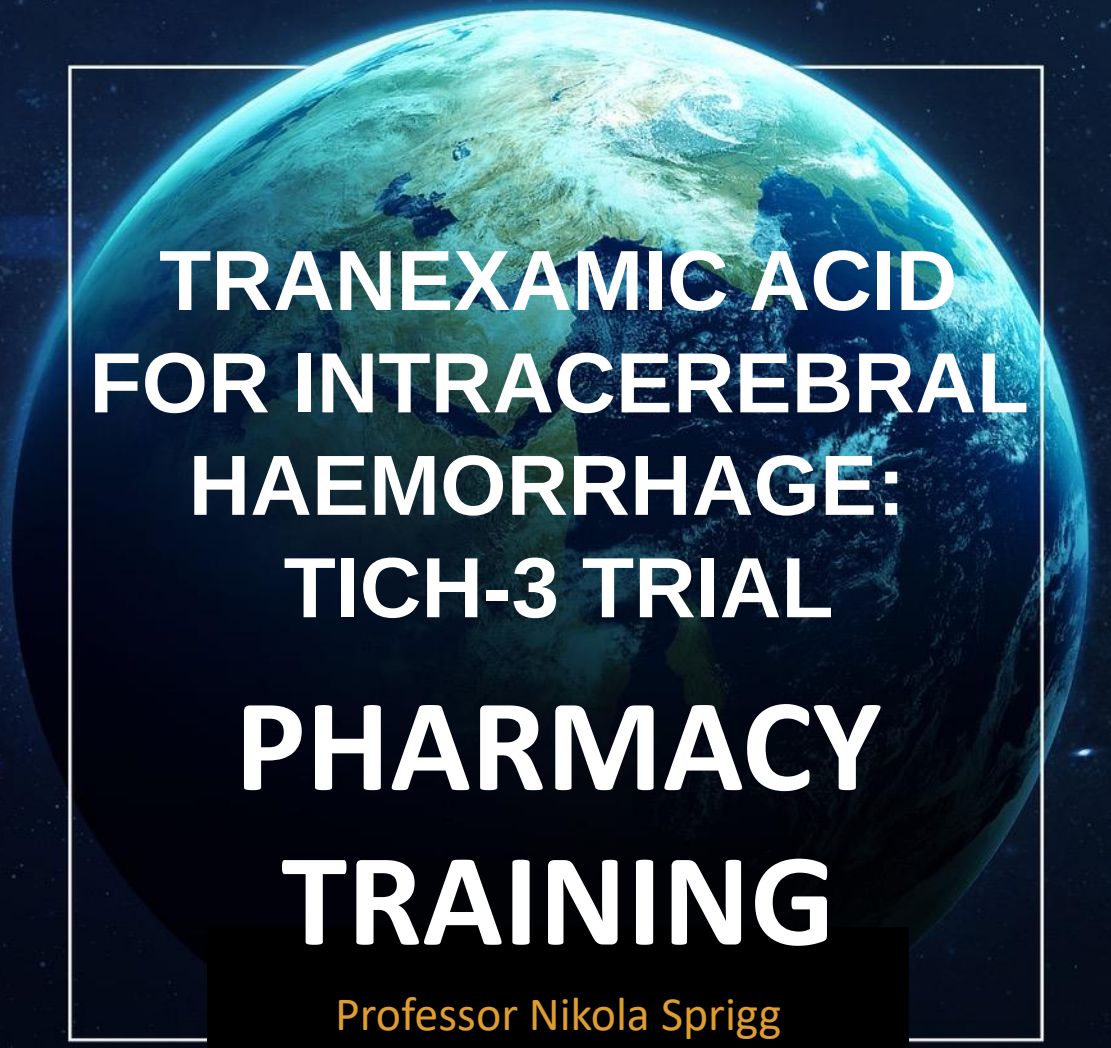


TRANEXAMIC ACID FOR INTRACEREBRAL HAEMORRHAGE: TICH-3 TRIAL

PHARMACY TRAINING

Professor Nikola Sprigg

On behalf TICH-3 Trial Team

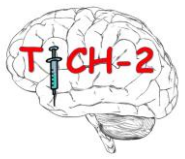
Final v2.0 30/01/2023

Disclosures

Nikola Sprigg

- Chief investigator for TICH-2 funded by National Institute of Health Research Health Technology Assessment (NIHR HTA project code 11_129_109)

- Chief investigator for DASH funded by National Institute of Health Research Research for Patient Benefit (RfPB)



FUNDED BY
NIHR | National Institute for Health and Care Research

Aims and Objectives

- Background
- Study design
- Randomisation
- QR code randomisation alert
- Drug storage and administration

Please complete training log of all attendees with signatures

BACKGROUND

Impact of Intracerebral Haemorrhage

- 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
- ICH-related death and disability set to rise due to ageing population
- There is no effective drug treatment for ICH
- A significant proportion of patients get worse – haematoma expansion

Tranexamic Acid

- TXA and recombinant factor VIIa are both haemostatic agents. TXA acts through antifibrinolytic mechanisms and recombinant factor VIIa is a procoagulant, so they have different risk-benefit profiles. Factor VIIa, has been associated with a reduction in haematoma expansion but an increased risk of arterial occlusive events.
- 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.
- Post-hoc 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.
- 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.
- 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 AIMS

TICH-3 Synopsis

Pragmatic randomised clinical trial

Design: RCT double blind study streamlined design

Participants: Inclusion: < 4.5 hours onset

Exclusion: Massive ICH (usually GCS < 5 or HV > 60ml)

Consent: Rapid emergency process

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]

Comparator: Saline identical regime

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

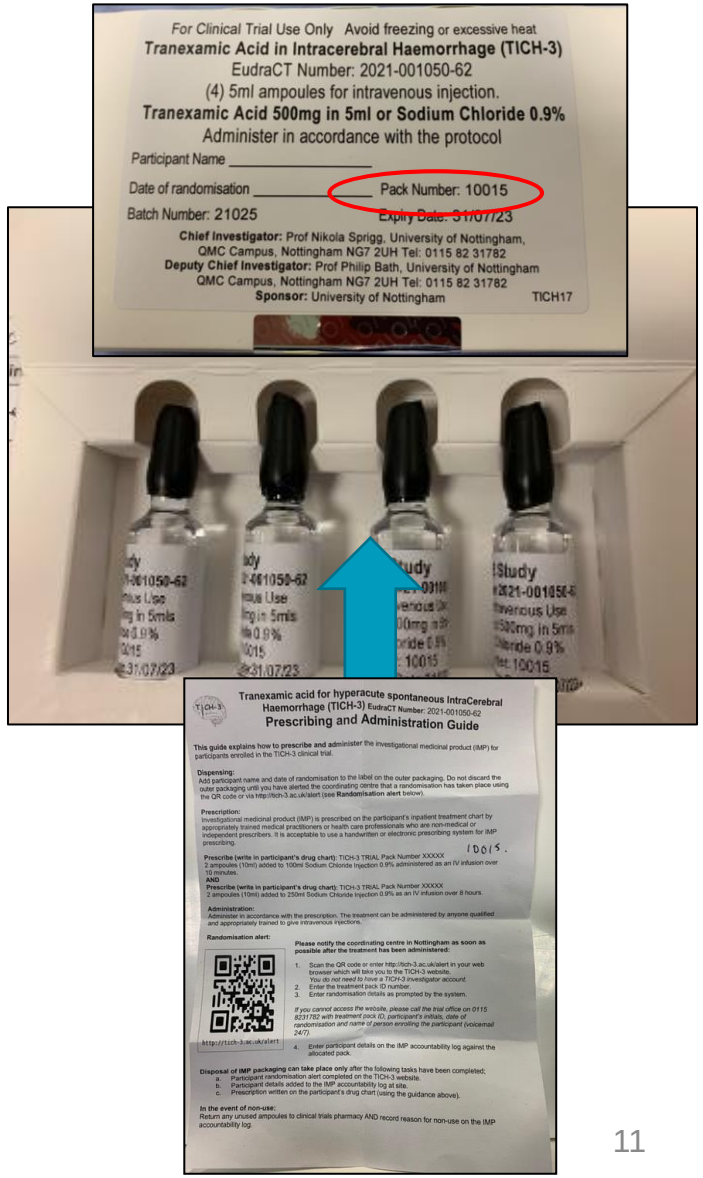
Exclusion criteria

- 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

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 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.
Do not need to be on delegation log to prescribe

Prescribe (write in participants drug chart):

TICH-3 - TRIAL Pack Number XXXXX

TRANEXAMIC ACID OR PLACEBO

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

AND

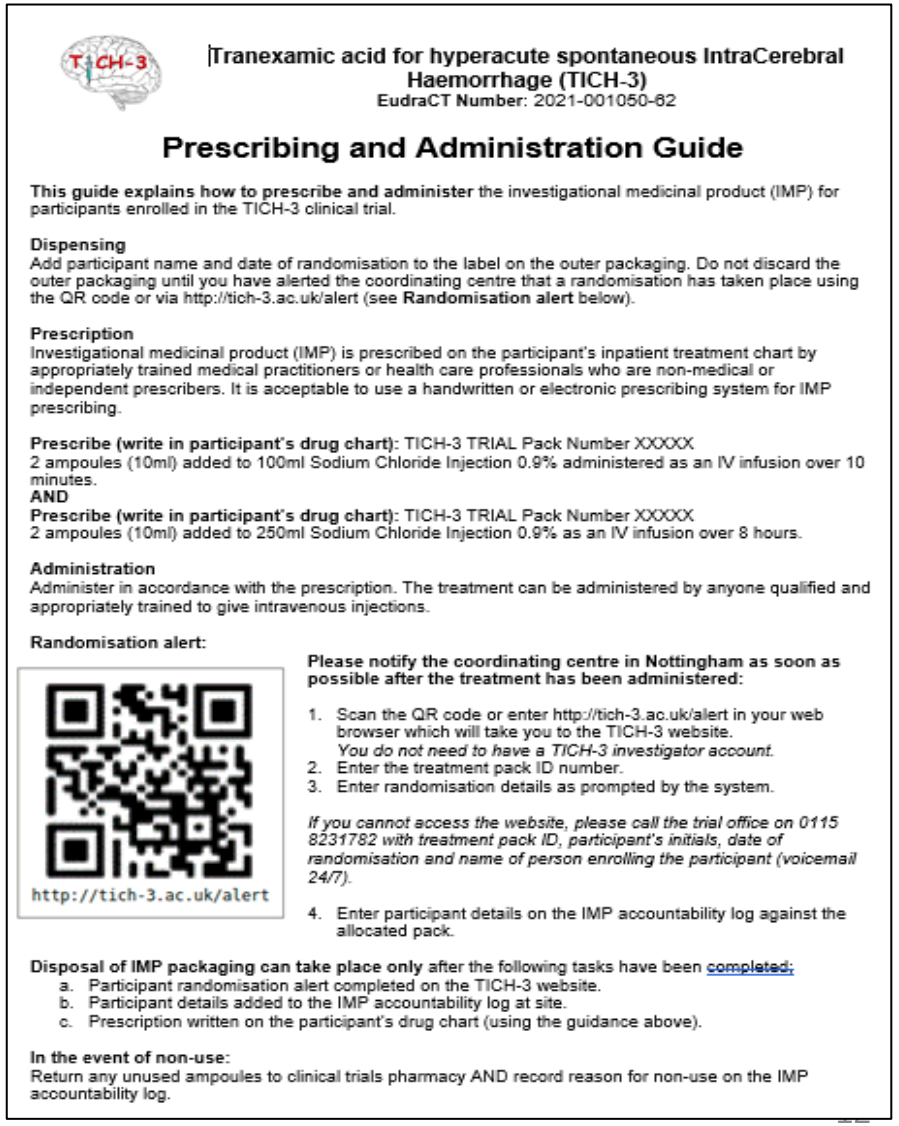
TICH-3 TRIAL Pack Number XXXXX

TRANEXAMIC ACID OR PLACEBO

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

Administering the IMP

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



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

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 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

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.

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 time to ensure IMP all present and accounted for

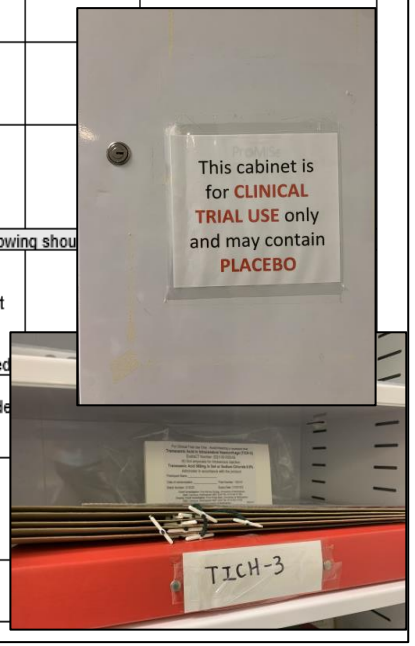
IMP Paperwork (1): Set up, IMP receipt

1

Assessment and monitoring of remote IMP storage

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

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



1. Assessment 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.

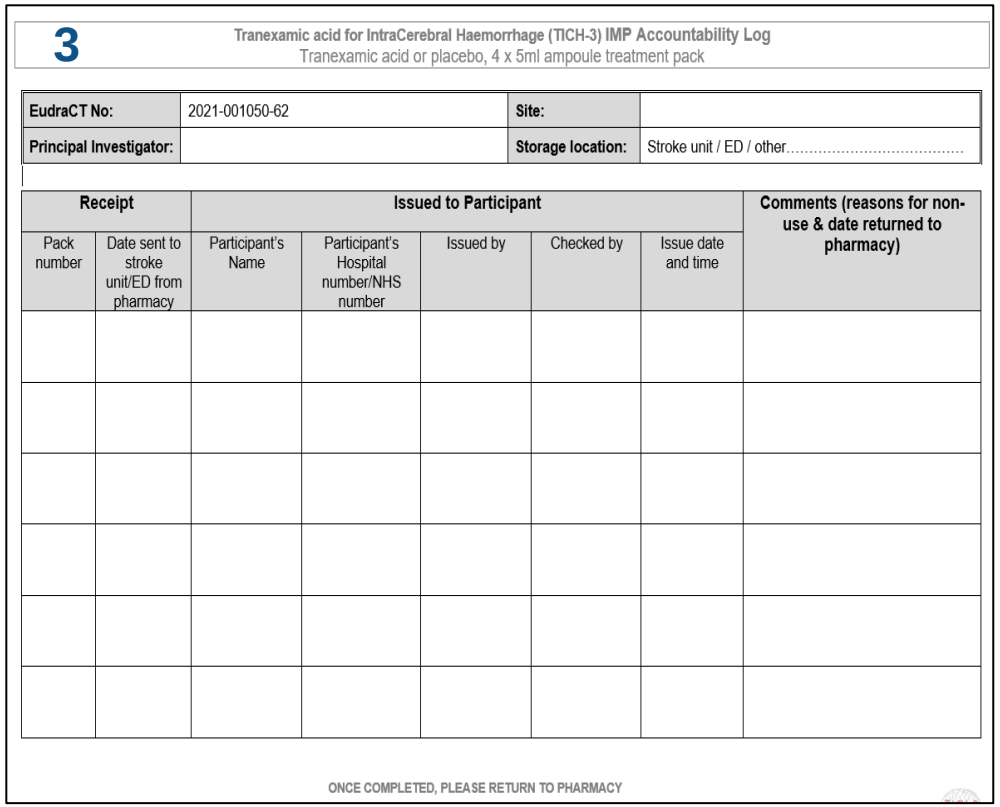
2

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

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

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

IMP Paperwork (2): Ongoing



3

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

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

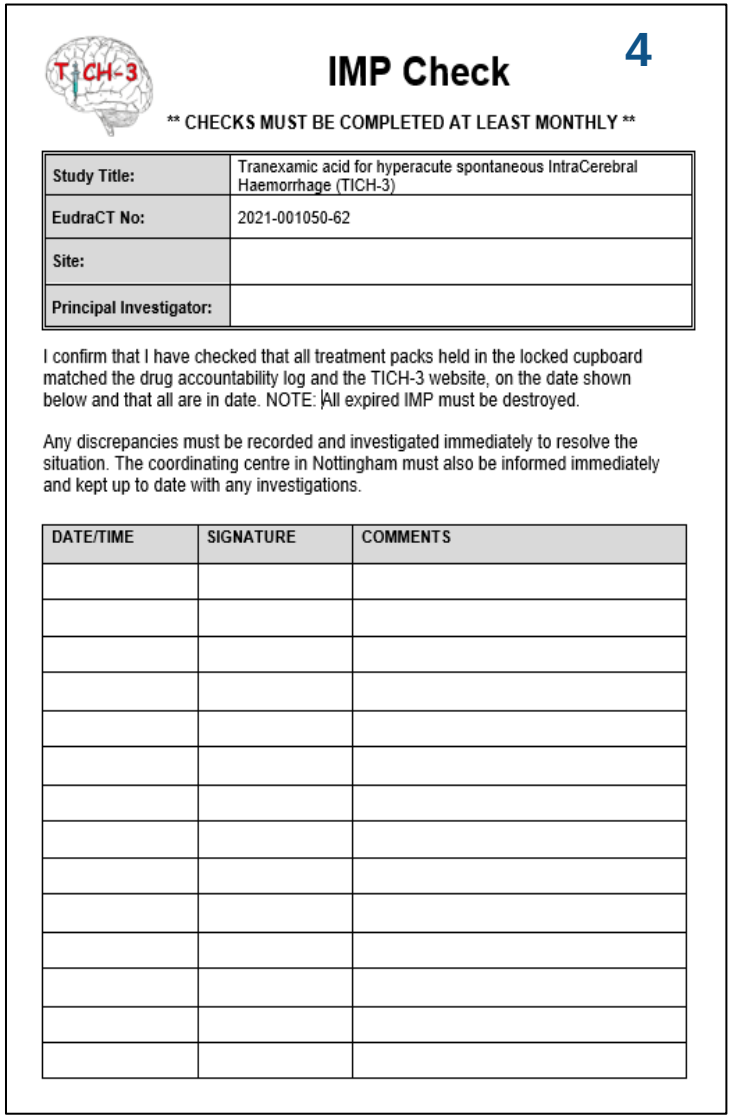
Receipt		Issued to Participant					Comments (reasons for non-use & date returned to pharmacy)
Pack number	Date sent to stroke unit/ED from pharmacy	Participant's Name	Participant's Hospital number/NHS number	Issued by	Checked by	Issue date and time	

ONCE COMPLETED, PLEASE RETURN TO PHARMACY

3. IMP Accountability Log

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

4. IMP Check



4

IMP Check

** CHECKS MUST BE COMPLETED AT LEAST MONTHLY **

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

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

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

DATE/TIME	SIGNATURE	COMMENTS

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

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

Drug dispatch

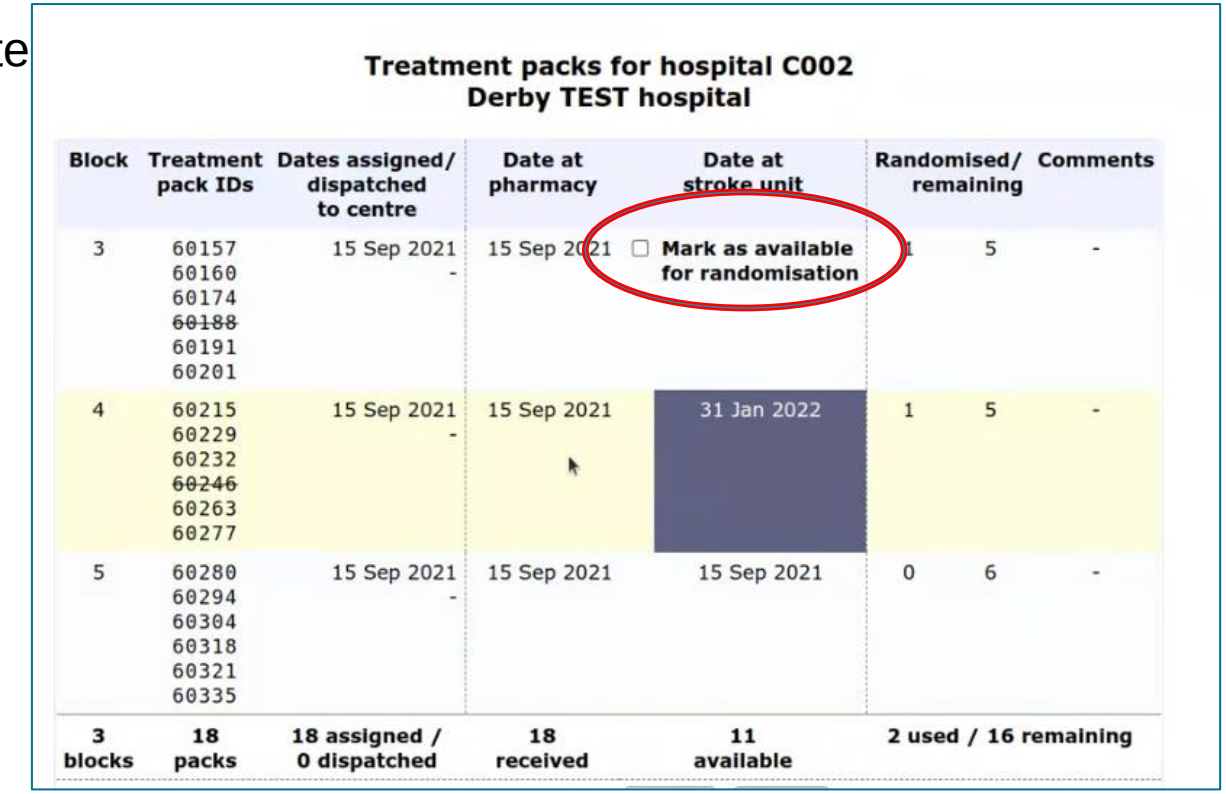
- Coordinating centre will order drug for dispatch once site is nearly ready to commence recruitment
- Blinded treatment packs will be randomly assigned to sites in blocks of 6 treatment packs

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

  > No deliveries out of hours/weekends

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

- Investigator needs to ‘mark available for randomisation’ on TICH-3 website
- Coordinating centre will re-order/issue when stock running low or when drug due to expire



Treatment packs for hospital C002
Derby TEST hospital

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

IMP Procedures

Emergency recall of IMP

TICH-3 IMP has been sourced, manufactured, packaged and assembled via a technical agreement with Sharp who hold an MIA(IMP) licence, recall may be required for defects in any of the following:

- raw materials
- finished IMP
- containers and packaging
- labelling
- assembly process, including blinding and randomisation
- storage conditions

In event of an emergency recall the coordinating centre will contact the local team immediately by phone and/or email. The process is required to be documented.

Destruction procedures of IMP

Destroy locally if unused or expired IMP to be destroyed at local site, we will monitor centrally and instruct sites to destroy at closedown or if IMP expired. If you could just keep a record of what has been sent for destruction on the accountability log.

PHARMACY SITE FILE

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

Local Site File Contents

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

TICH-3 trial – Tranexamic acid for IntraCerebral Haemorrhage 3

Trial documents

Emergency contacts

This page does not provide the emergency mobile numbers.

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

Approved protocol

- Protocol Final v1.0 03.11.2021 fully signed.pdf

Expression of interest

- Online expression of interest form

Trial documents

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

UK site training

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

Information sheets and consent forms

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

Pharmacy documents

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

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

Any 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, equally if any colleague leaves the team the PI is required to sign and date 'role finished' against their name.

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

- Principal Investigator
- Research Nurse/coordinator
- Pharmacist

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

Electronic Delegation Log

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

Chief investigator: Nikola Sprigg

Principal investigator: Kailash Krishnan

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

Delegated roles:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

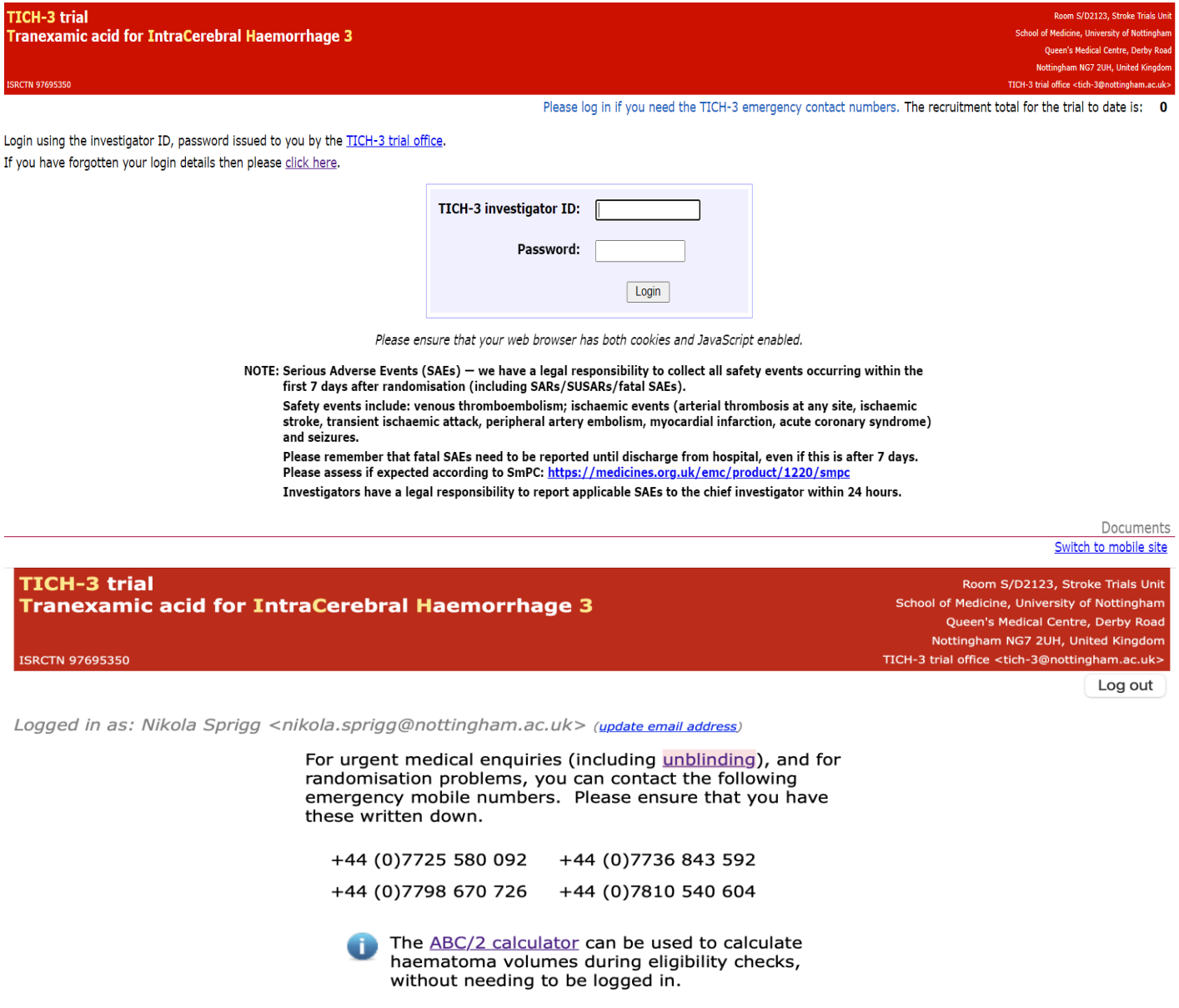
X. Responsibility for data monitoring. **PI, DPI**

Others as locally applicable or trial specific (list)

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

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

Logging onto TICH-3 website

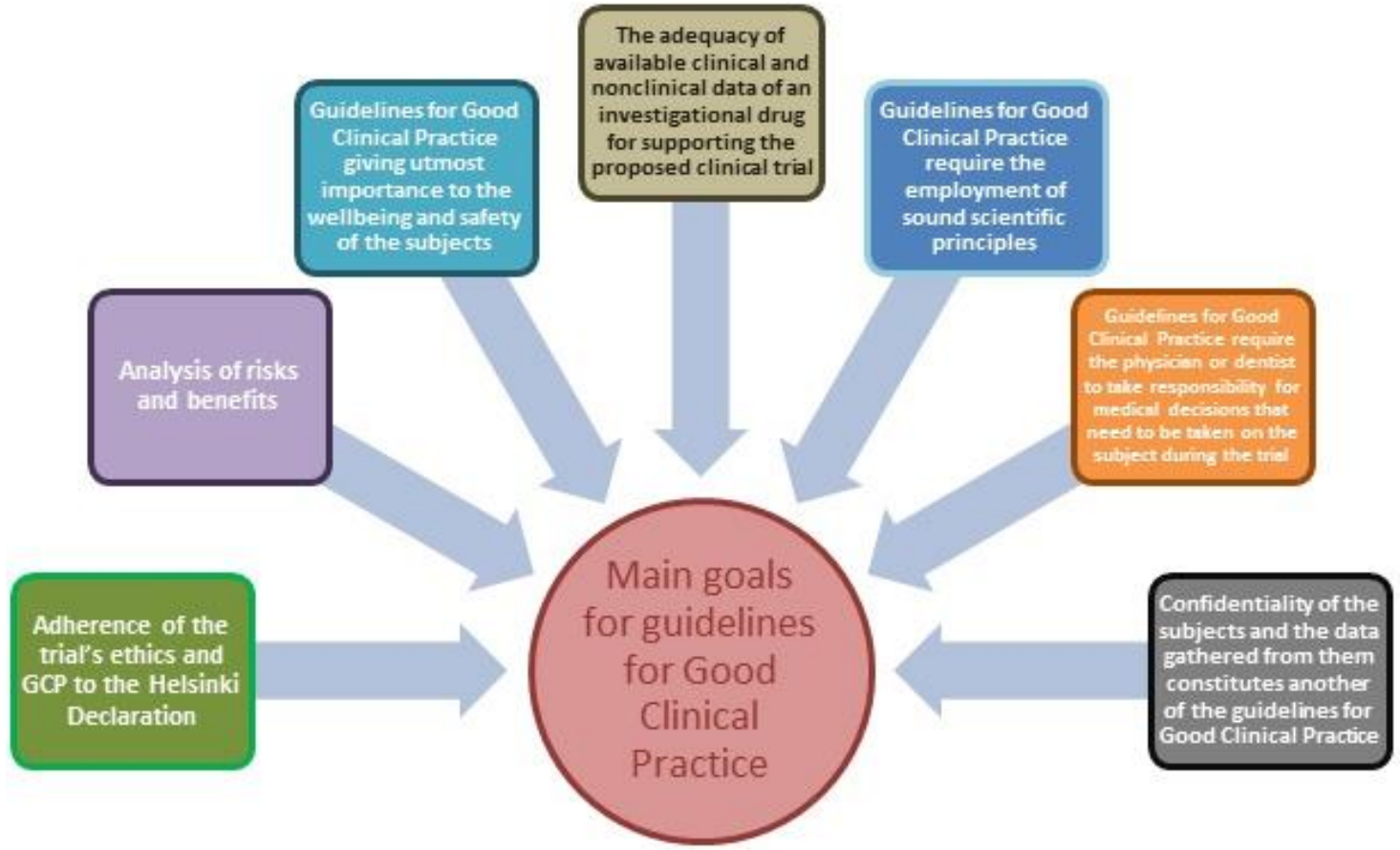


- Coordinating centre will set up an account for investigators – we need the completed attendance at investigator training log completed (electronic signatures are accepted) and returned to us via email to know who needs logins for the TICH-3 website and subsequently added to the delegation log
- Additional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

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, SAEs AND SUSARs

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):

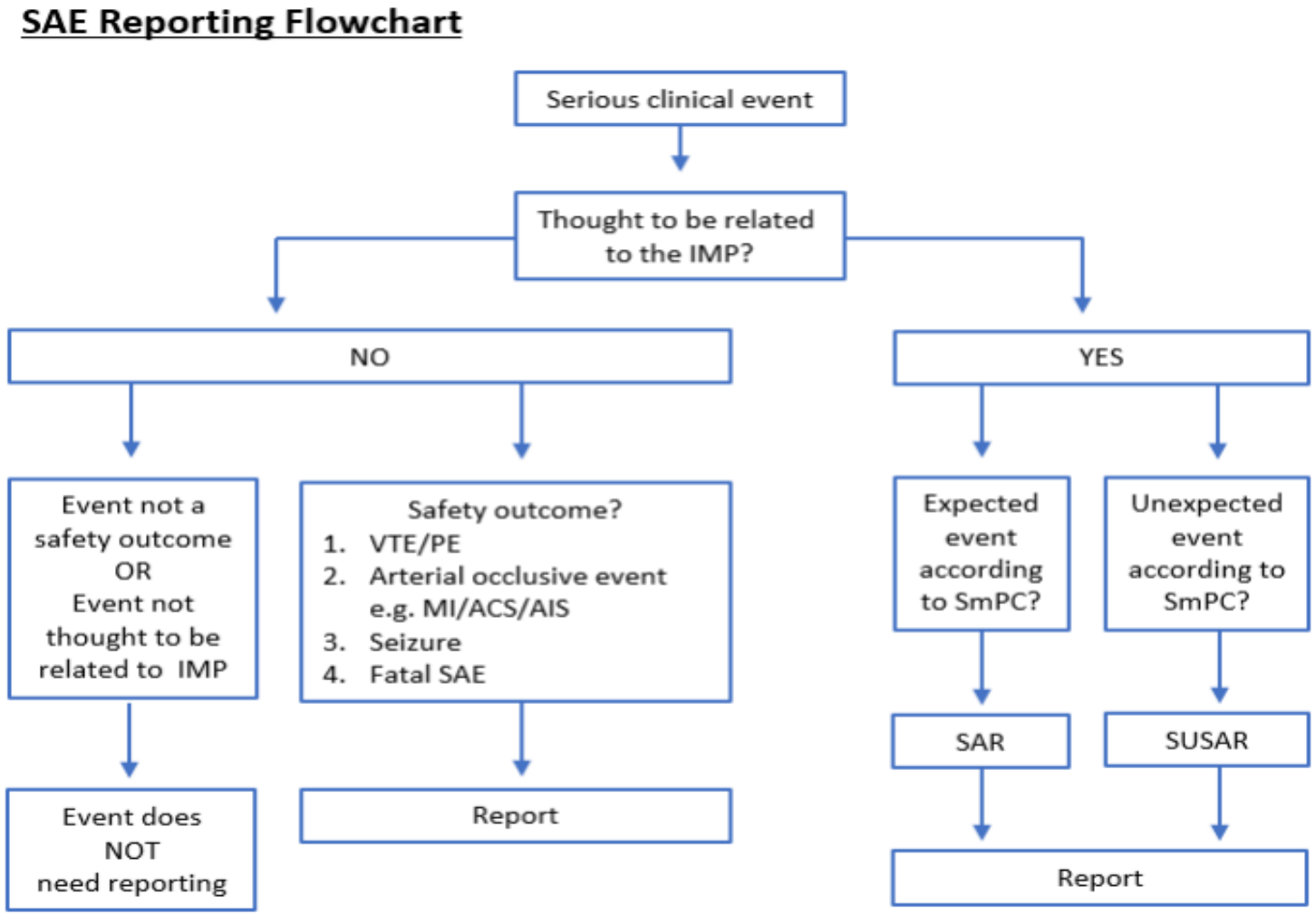
- All events suspected to be related to the IMP will be assessed for seriousness, expectedness and causality by local investigator. Section 4.8 of the SmPC, date of last revision 02 February 2021, will act as the **Reference Safety Information:** Tranexamic Acid https://Tranexamic Acid_SmPC_20210202_REVISION.pdf

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.

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

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

SUMMARY

ACTION – Return Training Log

- Please complete the investigator training log and return via email to the coordinating centre
  Click here for direct download of training log
- Or use the self referral form: http://tich-3.ac.uk/?ZSelfRef

- Team members who could not attend live training can access training slides from TICH-3 website https://stroke.nottingham.ac.uk/tich-3/docs/#UK_site_training

  There are 3 versions of the training slides

  1. Investigator training which gives a detailed description of the whole trial process, intended for the PI and research nurses/coordinators. There is also a video of this training.
  2. Enrolling investigator training this streamlined training is intended for team members who will only be taking enrolment consent i.e. consultants
  3. Pharmacy training this streamlined training is intended for members of pharmacy team

- A short 3 ½ minute video is available to introduce team members to the TICH-3 trial
  http://tich-3.ac.uk/docs/#Videos

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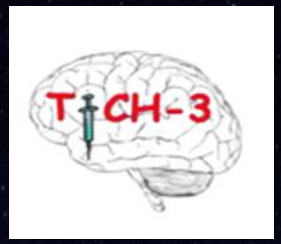

THANK YOU!

Any questions?

Audit list of updates to training presentations

Previous versions

Version 1.2 30/03/22:

- Link for NIHR account for GCP training added
- Trial team updated

Version 1.3 27/04/2022

- NIHR logo updated
- Slide 32 Safety reporting – clarified that only events related to IMP need assessing for expectedness and SMPC link to PDF updated
- Added that TXA is not standard of care for ICH
- Need for PI to countersign SAEs added to slide 23

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

Version 1.5 13/06/2022

- Inform investigators re sponsors SOPS – GCP slide and pharmacy site file slide

Version 1.6 06/07/2022

- SAE example given e.g. HE

Version 1.7 28/07/2022

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

This version 2.0 30/01/2023

- Amended exclusion criteria that patients on DOACs at time of ICH are now eligible
- Updated prescription example so its states tranexamic acid or placebo
- Added link for self referral form to get team members onto delegation log