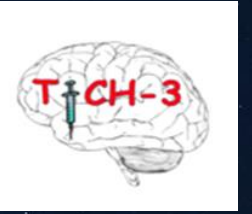




University of
Nottingham

UK | CHINA | MALAYSIA



ISRCTN97695350

**TRANEXAMIC ACID
FOR INTRACEREBRAL
HAEMORRHAGE:
TICH-3 TRIAL**

**Finland
Investigators**

Professor Nikola Sprigg

On behalf TICH-3 Trial Team

30/05/2023



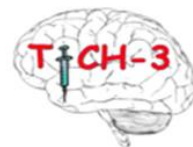


Funding:



- 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

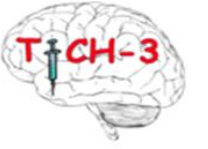


FUNDED BY

NIHR | National Institute for
Health and Care Research



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
- Future planning



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>

BACKGROUND

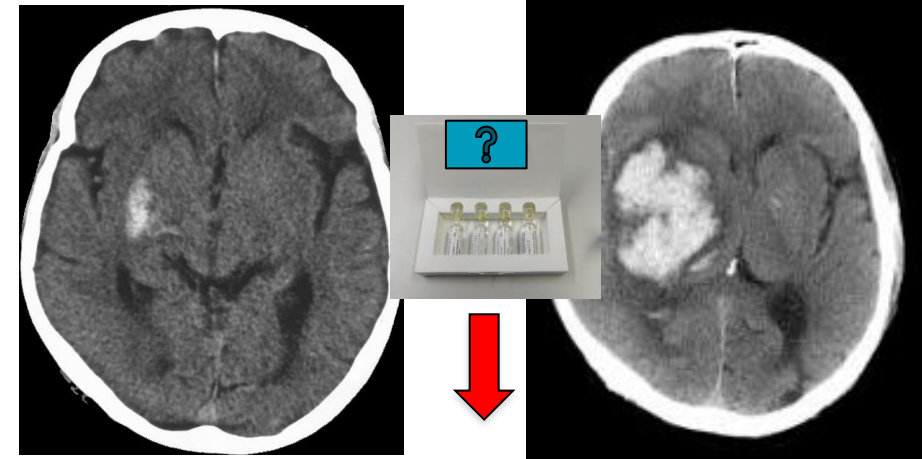


Intracerebral Haemorrhage (ICH)



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	3400
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 approved on 19.04.2023



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: 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 site in Finland

Helsinki University Hospital

National Coordinator: Daniel Strbian

Coordinating study nurse: Saija Eirola



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 (SA04).**
- Massive ICH (usually when haematoma volume > 60ml)
- Severe coma, Glasgow Coma Scale <5
- Decision for palliative (end of life) care



TICH-3: Eligibility Criteria



Sisäänottokriteerit:

- i. Ikä \geq 18 vuotta.
- ii. Aika akuutin spontaanin ICH:n oireiden alkamisesta \leq 4,5 tuntia.
- iii. ICH vahvistettu kuvantamistutkimuksella.
- iv. Jos oireiden alkamisaikaa ei tiedetä, on aikaraja 4,5 tuntia oireiden toteamisesta, eikä potilaalla saa olla poissulkukriteerejä.
- v. Potilaat, jotka käyttävät suoria oraalisia antikoagulantteja, voidaan ottaa mukaan tutkimukseen.
- vi. Tietoinen suostumus (EU) N:o 536/2014 35 artiklan mukaisesti.

Poissulkukriteerit:

- i. Tunnettu indikaatio TXA-hoitoon (esim. traumaattinen aivoverenvuoto).
- ii. Vasta-aihe TXA-hoidolle hoitavan lääkärin arvion mukaan (TXA:n riski arvioidaan suuremmaksi kuin siitä saatava hyöty):
 - a. Akuutti kouristelu.
 - b. Akuutti laskimo- tai valtimotromboosi.
 - c. Yliherkkyys TXA:lle tai suolaliuokselle.
 - d. Tiedossa oleva rakenteellinen poikkeavuus, kuten valtimo-laskimoepämuodostuma, aneurysma tai kasvain. Rakenteellista poikkeavuutta ei tarvitse poissulkea ennen randomisointia, mutta jos sellainen on tiedossa, potilasta ei tule ottaa tutkimukseen.
- iii. Käytössä oleva hoitotason antikoagulaatio lukuun ottamatta suoria oraalisia antikoagulantteja.
- iv. Massiivinen ICH, johon hemostaattinen hoito vaikuttaa turhalta (tavallisesti silloin, kun hematooman tilavuus $>$ 60 ml).
- v. Syvä tajuttomuus (Glasgow Coma Scale $<$ 5).
- vi. Potilaan osalta tehty päätös palliatiivisesta hoidosta ja aktiivisen hoidon lopettamisesta.



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.

If the patient has already been given the IMP, and a deferred consent is used, the relatives can take as long as they need to make the decision.



Haematoma volume measurement - FINLAND



Exclude patients with massive haematoma (usually >60ml)

1. Your automated software –is not currently validated for HV measurement
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
 - IVH volume should not be included in the measurement
 - 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.

ISRCTN 97695350

Haematoma volume calculator

Estimated volume of largest haematoma 1

[View guide](#)

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

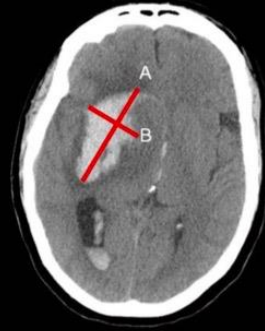
Maximum haematoma width 'B' cm
(up to 4 decimal places)

Number of slices where haematoma visible slices

Scan slice thickness mm
(up to 3 decimal places)

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

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

Hemorrhage Volume

Predicts volume of intracranial hemorrhage from CT measurements.

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
Slice with ≥75% Area of Hemorrhage: Counts as 1 slices
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



Consent Process - FINLAND



Step 1

1. Acute intracerebral haemorrhage confirmed by imaging
2. Screening for eligibility for TICH-3
3. Written informed consent
 - a) from patient
 - b) from witness, if patient cannot write, but can give oral consent
 - c) from next-of-kin
4. If informed consent cannot be obtained, investigator makes the decision to enroll the patient (deferred consent)
5. Randomisation
6. Administration of IMP

Step 2 after point 4. in Step 1

- a) patient regains capacity immediately
 - written informed consent from patient
 - from witness if patient cannot write, but can give oral consent
- b) patient does not regain capacity
 - written informed consent from next-of-kin
 - i. patient regains capacity
 - written informed consent from patient
 - ii. patient does not regain capacity
 - written informed consent from next-of-kin is final

EMERGENCY SITUATION, DEFERRED CONSENT

- If a written informed consent cannot be obtained from the participant or his/her relative in the acute stage, a study investigator can make the decision to enroll the participant after carefully weighing the risks and benefits.
- In that case a deferred consent will be sought from the participant or his/her relative as soon as possible.
- The participant may decline to participate or withdraw his/her consent without giving a reason at any time during the study.



Documenting Consent

Yes



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

For example:

- Patient meets criteria for TICH-3 and gives oral consent, witness (e.g. staff nurse) signs the consent form
- Patient meets criteria for TICH-3, but lacks capacity, wife provides written consent
- Patient meets criteria for TICH-3, but lacks capacity, attempt to contact relative with no response so study investigator makes the decision to enrol the patient to the study
 - Deferred consent obtained from the participant, witness, or relative



Delegated roles for consent: J and Z

Person taking 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**

Site investigator ▾ (Not authorised) Authorise ▾

Consent training for enrolment (J)

No consent training

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

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? Yes No

A2 Please give the name of the investigator taking initial consent for enrolment in the trial Not known

Person taking follow-on consent must be delegated role Z

(will not be used in Finland - written consent will be obtained prior to enrolment and therefore follow-on consent not required).

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**



Consent by a witness or a relative



Consent by a witness

In this scenario, the participant has capacity to consent for enrolment orally, but cannot sign the consent form. The consent is then handwritten by a witness who is not involved in the study. As soon as the participant regains capacity to write, or a relative becomes available, they should provide the written informed consent.

Consent by a relative

In this scenario, the participant has no capacity to consent for enrolment. The consent is then handwritten by a relative. As soon as the participant regains capacity, he/she should provide the written informed consent. The same form is also used for a deferred consent, i.e. after the IMP has already been given.

HUS 7 (8)

TUTKITTAVAN SUOSTUMUS TICH-3-TUTKIMUKSEEN OSALLISTUMISESTA

Tutkimuksen nimi: Traneksaamihappo akuutin spontaanin aivoverenvuodon hoidossa (TICH-3)
EU-tutkimusnumero: 2022-500587-35-01
HYKS Meilahden tornisairaala, Neurologian AVH-tutkimusyksikkö

Minua on pyydetty osallistumaan yllä mainittuun tieteelliseen tutkimukseen, jonka tarkoituksena on selvittää, ehkäisekö traneksaamihappo-niminen lääke aivoverenvuodon kasvua ja voiko se siten vähentää aivoverenvuodon aiheuttaman vammaan vakavuutta.

Olen lukenut ja ymmärtänyt saamani tutkimustiedotteen ja annan suostumukseni sen mukaiseen tutkimukseen. Olen saanut tiedotteesta riittävästi tietoa tutkimuksesta ja sen yhteydessä suoritettavista tietojen keräämisestä, käsitteistä ja luovuttamisesta. Tiedotteen sisältö on kerrottu minulle myös suullisesti ja olen saanut riittävän vastauksen kaikkiin tutkimusta koskeviin kysymyksiini.

Tiedot antoi AVH-tutkimusyksikön tutkijalääkäri _____.

Minulla on ollut riittävästi aikaa harkita tutkimukseen osallistumista. Olen saanut riittävät tiedot tutkimuksen tarkoituksesta ja sen toteutuksesta, tutkimuksen hyödyistä ja riskeistä sekä oikeuksista. Minua ei ole painostettu eikä houkuttelu osallistumaan tutkimukseen.

Tiedän, että tietojani käsitellään luottamuksellisesti, eikä niitä luovuteta sivullisille. Ymmärrän, että tässä tutkimuksessa henkilötietojani tallennetaan EU:n ja ETA:n ulkopuolella Iso-Britanniassa toimivan tutkimuksen toimeksiantajan ylläpitämään tutkimusrekisteriin. Tietojani tallennetaan ainoastaan tieteellisiin tutkimustarkoituksiin varten. Tiedotni tallennetaan koodattuna asianmukaisiin suojatuihin käytäisiin.

Olen tietoinen siitä, että henkilötietojani voidaan käsitellä myös kotimaisen ja ulkomaisen viranomaisen suorittaman tarkastuksen, tutkimusinstituutin kuuluttamattoman tutkimuksen säännönmukaista laadunvalvontaa tekevän henkilön (tutkimusmonitorin) ja/tai toimeksiantajan edustajan suorittaman laadunvarmistustoiminnan yhteydessä.

Ymmärrän, että tähän tutkimukseen osallistuminen on vapaaehtoista. Olen selvillä siitä, että minulla on oikeus kieltäytyä osallistumasta tutkimukseen. Voin myöhemmin halutessani myös keskeyttää tutkimuksen tai peruuttaa suostumukseni milloin tahansa syytä ilmoittamatta, eivätkä ne vaikuta kohteluuni tai saamaani jatkohoitoon millään tavalla. Olen tietoinen siitä, että mikäli keskeytän tutkimuksen tai peruutan suostumukseni, minusta ei tämän jälkeen tallenneta mitään tietoa tutkimusrekisteriin, mutta keskeyttäminen ja suostumukseni peruuttaminen mennessä kerättyjä tietoja käytetään osana tutkimusta.

Tiedän, että tutkimukseen osallistumisesta ei makseta korvausta.

Allekirjoituksellani vahvistan osallistumiseni tähän tutkimukseen ja suostun vapaaehtoisesti tutkimushenkilöksi.

Tutkittavan allekirjoitus _____ Päiväys _____
Nimensehvennys _____ Tutkittavan henkilötunnus _____

TICH-3 - Tutkittavan tiedote ja suostumus / v1.3 / 08.05.2023

HUS 8 (8)

Riippumaton todistaja

Mikäli tutkittava antaa suostumuksensa, mutta ei pysty itse allekirjoittamaan suostumusta, suostumuksen voi allekirjoittaa tutkimuksesta riippumaton todistaja.

Todistajan allekirjoitus _____ Päiväys _____
Nimensehvennys _____

Suostumus vastaanotettu

Tutkijalääkärim allekirjoitus _____ Päiväys _____
Nimensehvennys _____

Alkuperäinen allekirjoitettu asiakirja jää tutkijalääkärim arkistoon ja kopio allekirjoitetusta suostumuksesta annetaan tutkittavalle.

TICH-3 - Tutkittavan tiedote ja suostumus / v1.3 / 08.05.2023

HUS 7 (8)

OMAISEN SUOSTUMUS TICH-3-TUTKIMUKSEEN OSALLISTUMISESTA

Tutkimuksen nimi: Traneksaamihappo akuutin spontaanin aivoverenvuodon hoidossa (TICH-3)
EU-tutkimusnumero: 2022-500587-35-01
HYKS Meilahden tornisairaala, Neurologian AVH-tutkimusyksikkö

Omaistani on pyydetty osallistumaan yllä mainittuun tieteelliseen tutkimukseen, jonka tarkoituksena on selvittää, ehkäisekö traneksaamihappo-niminen lääke aivoverenvuodon kasvua ja voiko se siten vähentää aivoverenvuodon aiheuttaman vammaan vakavuutta.

Olen lukenut ja ymmärtänyt saamani tutkimustiedotteen ja annan omaiseni puolesta suostumukseni mukaiseen tutkimukseen. Olen saanut tiedotteesta riittävästi tietoa tutkimuksesta ja sen yhteydessä suoritettavista tietojen keräämisestä, käsitteistä ja luovuttamisesta. Tiedotteen sisältö on kerrottu minulle myös suullisesti ja olen saanut riittävän vastauksen kaikkiin tutkimusta koskeviin kysymyksiini.

Tiedot antoi AVH-tutkimusyksikön tutkijalääkäri _____.

Minulla on ollut riittävästi aikaa harkita omaiseni osallistumista tutkimukseen. Olen saanut riittävät tiedot tutkimuksen tarkoituksesta ja sen toteutuksesta, tutkimuksen hyödyistä ja riskeistä sekä omaiseni oikeuksista. Minua ei ole painostettu eikä houkuttelu allekirjoittamaan suostumusta. Olen tietoinen siitä, että päätös osallistua tutkimukseen on omaiseni tahdon mukainen. Omaiseni allekirjoittama suostumukseni itse heti, kun hänen kunnossaan sen sallii.

Tiedän, että omaiseni tietojani käsitellään luottamuksellisesti, eikä niitä luovuteta sivullisille. Ymmärrän, että tässä tutkimuksessa omaiseni henkilötietoja tallennetaan EU:n ja ETA:n ulkopuolella Iso-Britanniassa toimivan tutkimuksen toimeksiantajan ylläpitämään tutkimusrekisteriin. Tietoja tallennetaan ainoastaan tieteellisiin tutkimustarkoituksiin varten. Omaiseni tiedot tallennetaan koodattuna asianmukaisiin suojatuihin käytäisiin.

Olen tietoinen siitä, että omaiseni henkilötietoja voidaan käsitellä myös kotimaisen ja ulkomaisen viranomaisen suorittaman tarkastuksen, tutkimusinstituutin kuuluttamattoman tutkimuksen säännönmukaista laadunvalvontaa tekevän henkilön (tutkimusmonitorin) ja/tai toimeksiantajan edustajan suorittaman laadunvarmistustoiminnan yhteydessä.

Ymmärrän, että omaiseni osallistuminen tutkimukseen on vapaaehtoista. Olen selvillä siitä, että hänellä, ja minulla hänen puolestaan, on oikeus kieltäytyä tutkimukseen osallistumisesta, keskeyttää tutkimuksen osallistumisensa tai peruuttaa suostumuksensa milloin tahansa syytä ilmoittamatta ilman, että se vaikuttaa hänen kohteluunsa tai saamaansa jatkohoitoon millään tavalla. Jos hätätilatutkimuksen luonteen takia lääke- tai plasebohoito on jo annettu, omaiseni ei tallenneta mitään uutta tietoa tutkimusrekisteriin kieltäytymisen/suostumukseni peruuttamisen jälkeen (ml. 6 kk:n seuranta). Olen tietoinen siitä, että mikäli omaiseni, tai minä hänen puolestaan, keskeyttää tutkimuksen tai peruuttaa suostumuksensa, hänen tai keskeyttämisensä tai suostumukseni peruuttamisensa mennessä kerättyjä tietoja käytetään osana tutkimusta.

Tiedän, että tutkimukseen osallistumisesta ei makseta korvausta.

Omaisen tiedot _____ Päiväys _____
Nimensehvennys _____

TICH-3 - Omaisen tiedote ja suostumus, hätätilatutkimus / v1.3 / 08.05.2023

HUS 8 (8)

Allekirjoituksellani vahvistan omaiseni osallistumisen tähän tutkimukseen.

Tutkittavan nimi _____ Tutkittavan henkilötunnus _____

Omaisen allekirjoitus _____ Päiväys _____
Nimensehvennys _____ Sukide tutkittavaan _____

Suostumus vastaanotettu

Tutkijalääkärim allekirjoitus _____ Päiväys _____
Nimensehvennys _____

Alkuperäinen allekirjoitettu asiakirja jää tutkijalääkärim arkistoon ja kopio allekirjoitetusta suostumuksesta annetaan omaiselle.

TICH-3 - Omaisen tiedote ja suostumus, hätätilatutkimus / v1.3 / 08.05.2023



Written follow on consent

- 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.
- 2 copies of consent form – 1 for patient, 1 for study team.
- Please localise the consent forms and participant information sheets at R:\HEL_Nsk_AVH\TICH-3\TIEDOTE- JA SUOSTUMUSLOMAKKEET
- Trial documentation can be found at <https://stroke.nottingham.ac.uk/sif/docs/?sid=TICH-3>

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

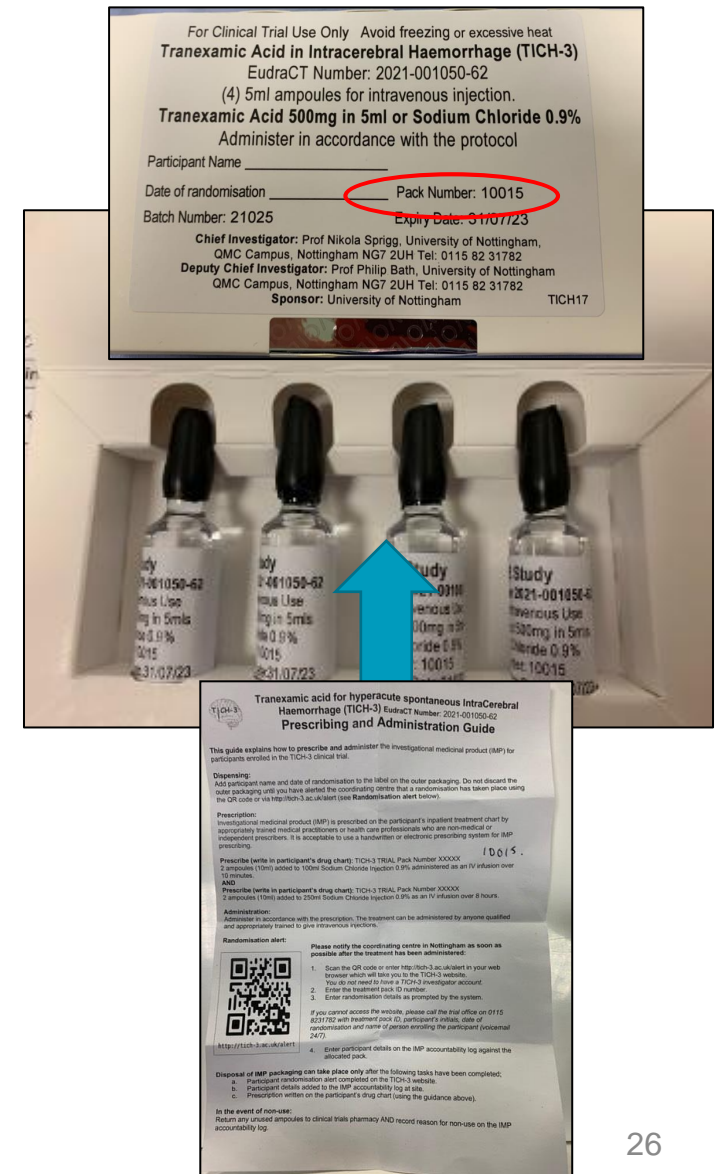
RANDOMISATION



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:



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.

<http://tich-3.ac.uk/alert>

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



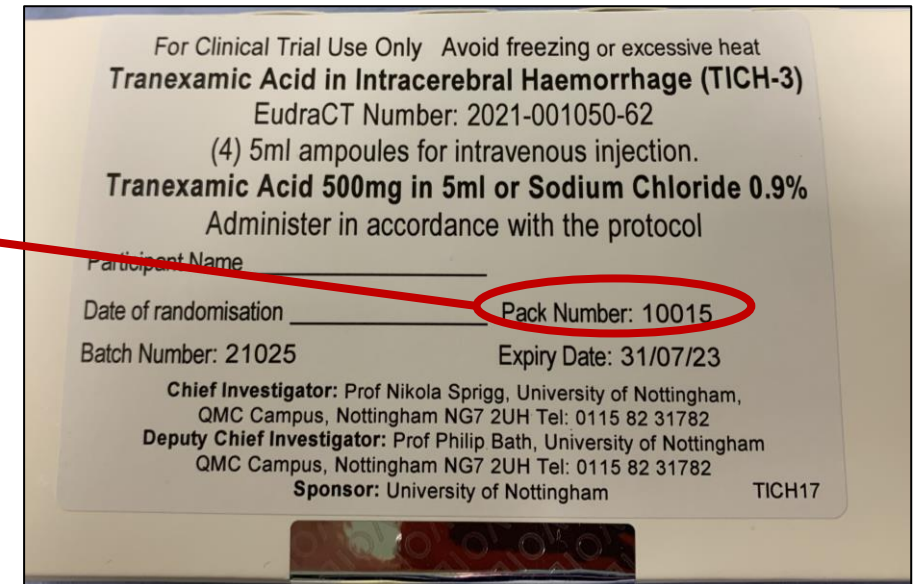
Let us know about a new TICH-3 participant

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 cause of death



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

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

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



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).

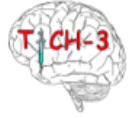
Once the IMP is in the storage location, pharmacy/research team will need to login to the TICH-3 web site and mark the treatment packs as available for randomisation.

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

2



IMP Paperwork (2): Ongoing



<h3 style="margin: 0;">3</h3> <p style="margin: 0; font-size: small;">Tranexamic acid for IntraCerebral Haemorrhage (TICH-3) IMP Accountability Log Tranexamic acid or placebo, 4 x 5ml ampoule treatment pack</p>								
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

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.

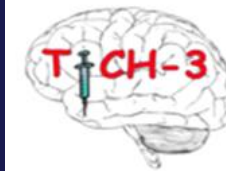
The inventory logs, completed accountability logs and IMP check should be stored in your site file. We do not require these to be uploaded to the TICH-3 website or sent to us unless requested.

<h2 style="margin: 0;">IMP Check</h2> <p style="margin: 0; font-size: x-small;">** CHECKS MUST BE COMPLETED AT LEAST MONTHLY **</p>		<h3 style="margin: 0;">4</h3>
<p>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.</p> <p>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.</p>		
Study Title:	Tranexamic acid for hyperacute spontaneous IntraCerebral Haemorrhage (TICH-3)	
EudraCT No:	2021-001050-62	
Site:		
Principal Investigator:		
DATE/TIME	SIGNATURE	COMMENTS

DATA COLLECTION



Trial Flow Chart:



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



Screen: after CT or MRI brain scan*
 Inclusion: Adult with ICH < 4.5 hours of onset
 Exclusion: Massive ICH for which treatment seems futile (estimated haematoma vol>60mls*), Glasgow Coma Scale <5, palliative care

Consent
 Emergency consent – oral consent to administer intervention unless patient or family or clinician object

* In Finland; consent by patient, witness, or relative – or in emergency, decision to enrol by study investigator followed by deferred consent

Randomise
 Simple select next available treatment pack
Investigator completes randomisation form
N=5500

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

Randomisation alert

Active treatment: N= 2750
 Tranexamic acid 2g IV (1g bolus, 1g infusion over 8 hours).
 Plus standard care[§]

Control treatment: N= 2750
 Placebo (0.9% saline) IV (bolus, infusion over 8 hours).
 Plus standard care[§]

Day 1:
 Submitted after randomisation to allow rapid enrolment and treatment.
 Includes: GCS, NIHSS, BP, HV
 Pre-stroke function (mRS, working), disposition

Day 1:
 Submitted after randomisation to allow rapid enrolment and treatment.
 Includes: GCS, NIHSS, BP, HV
 Pre-stroke function (mRS, working), disposition

Enrolment form

Follow up: Death or Discharge
 Safety events: venous thromboembolism; ischaemic events; seizures
Primary outcome – death day 7
 Date of Death or Discharge
 Costs: Length of hospital stay, Disposition on discharge, health care use (surgery, ITU, DNAR)

Follow up: Death or Discharge
 Safety events: venous thromboembolism; ischaemic events; seizures
Primary outcome – death day 7
 Date of Death or Discharge
 Costs: Length of hospital stay, Disposition on discharge, health care use (surgery, ITU, DNAR)

Contact details form

Day 7 follow-up
 AND
 Discharge/death

Day 180 follow-up
 (centrally by National coordinating centre)
 Postal questionnaire (or telephone)
Secondary outcome: Modified Rankin scale
 Quality of life (EQ5D, VAS)
 Cognition (AD-8)
 Health economics - brief resource use form

Day 180 follow-up
 (centrally by National coordinating centre)
 Postal questionnaire (or telephone)
Secondary outcome: Modified Rankin scale
 Quality of life (EQ5D, VAS)
 Cognition (AD-8)
 Health economics - brief resource use form

(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.

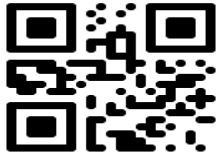
+44 (0)7725 580 092 +44 (0)7736 843 592
 +44 (0)7798 670 726 +44 (0)7810 540 604

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



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

1. Complete randomisation alert

2. Add new participant

TICH-3 trial
Tranexamic acid for IntraCerebral Haemorrhage 3

ISRCTN 97695350

Participant list

Queen's Medical Centre, Nottingham Investigator: Nikola Sprigg

« [Back to start page](#)

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

Refresh

Find centre

Filter trial number(s):

Add a new participant

[Non-participant protocol violations](#) (0)

Total number of trial participants recruited at this centre: 0

1: Nottingham, Queen's Medical Centre

Local time: 24 Mar 2022 10:14 GMT

3. Need treatment pack ID number

1. Please indicate which treatment pack was used

Treatment pack ID

2. Please confirm that the correct hospital has been selected

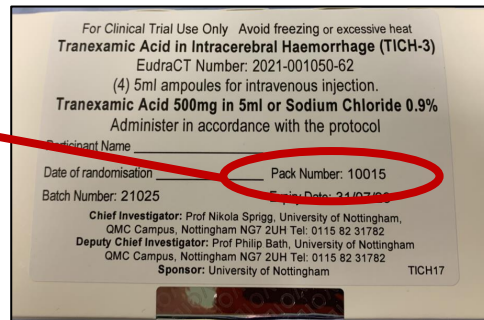
Hospital C001 **Queen's Medical Centre** Stroke Office
Room 2149, D Floor, South Block
Queen's Medical Centre
Derby Road
Nottingham
United Kingdom

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.



4. Confirm randomisation site

5. Complete enrollment form

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?	<input type="radio"/> Yes <input type="radio"/> No	
A2	Please give the name of the investigator taking initial consent for enrolment in the trial	<input type="text" value="[Select...]"/>	<input type="text" value="[Select...]"/>

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>	<input type="text" value="- Day -"/> <input type="text" value="- Month -"/> <input type="text" value="- Year -"/>
B3	Sex	<input type="radio"/> Male <input type="radio"/> Female
B4	Date/time of onset of index stroke <i>(dd-mmm-yyyy hh:mm 24hr)</i>	<input type="text" value="- Day -"/> <input type="text" value="- Month -"/> <input type="text" value="- Year -"/> : <input type="text" value=""/> : <input type="text" value=""/>




Contact Details Form



⚠ Identifying information **MUST NOT** be entered into this pseudonymised database for TICH-3. You can use the secure vault (see below) to provide us with the participant's contact details and other identifying information, which will be encrypted and stored separately.

i You can also use the secure vault to upload required documents for the selected participant. Please indicate the document type below, or use the 'Multiple document types' option (if you have a mix of documents in one file). If your file isn't a PDF or image, please 'print' it to a PDF first.

Please choose a data type to access the secure vault

 (*) applicable type only

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

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

< [Return to TICH-3 trial site](#)



TICH-3 – Tranexamic acid for IntraCerebral Haemorrhage 3



The information you enter into the form below will be encrypted and stored in the secure vault, held separately from the pseudonymised database used for TICH-3 CRFs.

New TICH-3 participant contact details

This page will expire in 14 minutes and 50 seconds

A A A A A A
B B B B B B
C C C C C C
D D D D D D
E E E E E E
F F F F F F
G G G G G G
H H H H H H
I I I I I I
J J J J J J
K K K K K K
L L L L L L
M M M M M M
N N N N N N
O O O O O O
P P P P P P
Q Q Q Q Q Q
R R R R R R
S S S S S S
T T T T T T
U U U U U U
V V V V V V
W W W W W W
X X X X X X
Y Y Y Y Y Y
Z Z Z Z Z Z

Please complete as much of this form as possible.

- Please make sure to include the participant's telephone number, which is required for follow-ups.

Form submitted by:

TICH-3 participant ID: **C**■■■■-■■■■-■■■■ (female, 94 years old)

Surname:

Forename(s):

Middle initials:

Permanent address:

Post code:

Country:

Follow-up telephone number:

Temporary residence:

Alternate telephone number:

Email address:

Date of birth: / / (dd/mm/yyyy)

NHS/CHI/H+C number:

Hospital number:

Name of hospital ward(s):
(not hospital name)

Place of birth:

GP title/name:

GP practice name:

GP address:

GP post code:

GP telephone:

Comments:



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

Enrolment form v1.1

Section A: Inclusion/exclusion criteria and consent

Inclusion criteria

- Adults within 4.5 hours of onset of acute spontaneous ICH (confirmed on brain imaging)
- When onset of symptoms is unknown, patient must be within 4.5 hours of symptom discovery and have no other exclusion criteria

Exclusion criteria

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

A1 Did the participant have capacity to consent? Yes No

A2 Please give the name of the investigator taking initial consent for enrolment in the trial Not known

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) D ____ / M ____ / Y ____

B3 Sex Male Female

B4 Date/time of onset of index stroke (dd-mmm-yyyy hh:mm 24hr) D ____ / M ____ / Y ____
H ____ : M ____

B5 Date/time of randomisation (dd-mmm-yyyy hh:mm 24hr) D ____ / M ____ / Y ____
If unknown, please use date/time of first dose H ____ : M ____

B6 Allocated treatment pack ID

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

Day 7 follow-up form v1.0

Section A: Day 7 follow-up

A1 Participant status Alive and in hospital
 Discharged prior to day 7
 Withdrawn from follow-ups
 Died

A2a Was all randomised treatment received? Yes No Not known

A2b Date/time of first dose (dd-mmm-yyyy hh:mm 24hr) D ____ / M ____ / Y ____
H ____ : M ____ Not done Not known

A2c Explanation if treatment not received or data missing Not applicable

Systolic / diastolic

A3 Please enter BP recorded closest to 6 hours after stroke onset / Not done Not known

A4a Blood pressure on day 7 - reading 1 / Not done Not known

A4b Blood pressure on day 7 - reading 2 / Not done Not known

Section B: Treatment during first 6 hours

B1a Was BP-lowering treatment given in the first 6 hours? Yes No Not known

B1b If yes, which antihypertensive drugs were given in the first 6 hours? Not applicable Not known

- Glyceryl trinitrate (GTN) - patch
- Glyceryl trinitrate (GTN) - IV
- Sodium nitroprusside
- Other nitrate therapy (e.g. ISDN/ISMN)
- Urapidil
- Labetalol
- Other beta-blocker (e.g. atenolol, propranolol, bisoprolol)
- Calcium channel blocker (e.g. nifedipine, amlodipine)
- Diuretic (e.g. bendroflumethiazide, indapamide, hydrochlorothiazide)

Discharge/death 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
 ISRCTN 97695350
 TICH-3 trial office <tich-3@nottingham.ac.uk>

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 (dd-mmm-yyyy) D ____ / M ____ / Y ____

A2a Discharge disposition Home - independent, alone Not known
 Home - independent, with partner/family/friend
 Warden-aided flat
 Residential home
 Home - needing care
 Carer's home
 Respite care
 Care home
 Nursing home
 Rehabilitation hospital
 In hospital
 Died
 Other

A2b Did the participant return to their original place of residence? Yes No Not known
If died, please select 'No'

A3 Please list any other trials into which the participant was co-enrolled Not applicable Not known

A4a What was the final diagnosis of the randomising event? Intracerebral haemorrhage with no known underlying cause Not known
 Intracerebral haemorrhage with underlying cause
 Ischaemic stroke with haemorrhagic transformation
 Ischaemic stroke without haemorrhagic transformation
 Non-stroke/other



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 -

*** Consent forms to be filed on site.**

Unanonymised consent forms can not be uploaded on TICH 3 website.



Day 180 Form

To be conducted by Co-National Coordinator

- Modified Rankin Scale (mRS)
- Quality of life (EQ-5D-5L)
- Thinking and memory (AD-8)

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](#)
- [IMP 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 ABCDEFGHIJKL <u>M</u> NOPQRSTUVWXYZ	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 BFHIJKL <u>N</u> OPQRSYZ	7 Mar 2022 08:25 Authorised <i>Kailash Krishnan</i>
3	Rachel Facilitator <i>Researcher</i> (R Facilitator)	L3N3F7 2 Feb 2022	Site investigator BFHIJKL <u>N</u> OPQRSTY	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 BFHIJKL <u>N</u> OPQRSTY	7 Mar 2022 08:25 Authorised <i>Kailash Krishnan</i>
5	Any Doctor <i>Researcher</i> (A Doctor)	F3C9T7 2 Feb 2022	Site investigator BFHIJKL <u>N</u> OPQRSYZ	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>

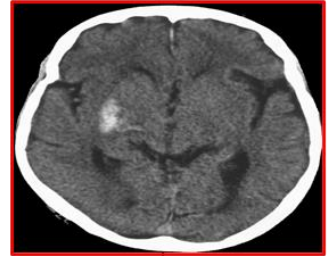
SUMMARY



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)
- 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: [Select...] ▼

Submit

* - includes pharmacy technician

CONTACT INFORMATION



University of Nottingham Trial Team



Name	Role	Contact Information
Chaamanti Menon	Clinical Research Fellow	E: chaamanti.menon@nottingham.ac.uk
Joseph Dib	Clinical Trials Manager (International Site Recruitment)	E: joseph.dib4@nottingham.ac.uk
Tiffany Hamilton	Senior Clinical Trials Manager	E: Tiffany.hamilton@nottingham.ac.uk
Nikola Sprigg	Chief Investigator	E: nikola.sprigg@Nottingham.ac.uk

Trial Coordinating Centre contact information:



+44(0)115 823 1782



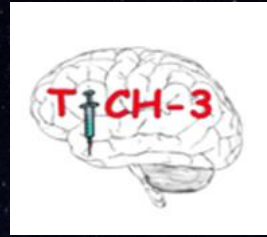
MS-TICH-3-Inter@nottingham.ac.uk



University of
Nottingham

UK | CHINA | MALAYSIA

FUNDED BY
NIHR National Institute for
Health and Care Research



Kiitos
Kysymyksiä?



Meeting Notes

- Site confirmed they will use ABC/2 to determine haematoma volume.
- Not permitted to include participant's initials in Finland – to put N/A.
- To discuss – how consent forms will be monitored as site will not be uploading them to secure vault due to regulations in Finland.
- Day 180 – likely to be 3 people performing the day 180 questionnaire, which will usually be done face-to-face or by phone. Daniel to confirm in advance of first follow-up.
- Ethical conditions are all in place and approved – Daniel can now begin the process for applying for local approval