University of Nottingham
UK | CHINA | MALAYSIA

ISRCTN97695350

TRANEXAMIC ACID FOR INTRACEREBRAL HAEMORRHAGE: TICH-3 TRIAL

Italy Investigators

Professor Nikola Sprigg

On behalf TICH-3 Trial Team

26/04/2023

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

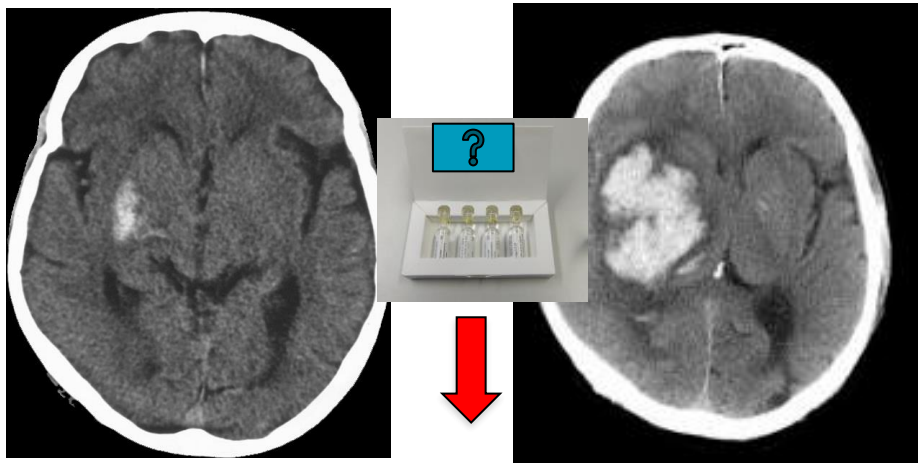
- A short 3 ½ minute video is available to introduce team members to the TICH-3 trial
  http://tich-3.ac.uk/docs/#Videos

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.

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-2 https://doi.org/10.1016/S0140-6736(18)31033-X

Key changes from TICH-2

Target participants most likely to benefit

Change	TICH-2	TICH-3
Primary outcome	Function day 90	Death by day 7 Function day 180
Recruitment target	2000	5500
Recruitment time	8 hours since onset	4.5 hours since onset
Baseline ICH volume	No maximum	Exclude massive (usually Haematoma Volume> 60ml)
Consent	Written consent	Oral consent –followed by written consent
Randomisation	On-line	Simple – lowest pack number

Other TXA in ICH trials

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

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

PROTOCOL

EU Protocol v4.2 approved on 19.04.2023

TICH-3 Synopsis

ICH emergency condition - facilitate rapid enrolment

Design: Double blind randomised clinical trial, pragmatic streamlined design

Participants: Inclusion: < 4.5 hours of stroke onset

Exclusion: Massive ICH (Glasgow Coma Scale < 5 or Haematoma Volume > 60ml)

Consent: Rapid emergency process – oral consent followed by written consent

Intervention: Tranexamic 1g IV bolus added to 100ml sodium chloride over 10 mins then 1g added to 250ml sodium chloride infusion over 8hrs or saline by identical regime
Given alongside standard ICH care, including BP lowering as per clinical guidelines[1]

Randomisation: Simple - use the lowest available treatment pack number

Primary Outcome: Early death (day 7)

Secondary outcome: Function-Shift analysis modified Rankin Scale day at 6 months

Sample size: 5500 (3900 UK and 1900 Internationally)

Cost/funder: UK NIHR plus others internationally

Duration: 7.25 years - Aim start UK recruitment early 2022

1: https://www.nice.org.uk/guidance/ng128/chapter/Recommendations

TICH-3 Italy - National Coordinator - Dr Alfonso Ciccone

Bari	AOU Consorziale Policlinico Bari	Dr Marco Petruzzellis
Cagliari (AOU)	AOU Cagliari - Policlinico Monserrato Duilio Casula	Dr Marta Melis
Cagliari (Brotzu)	Azienda Ospedaliera G. Brotzu	Dr Jessica Moller
Carpi	Ospedale Ramazzini AUSL Modena	Dr Luca Vaghi
Cremona	ASST di Cremona	Dr Bruno Censori
Firenze	Azienda Ospedalierio Universitaria Careggi	Dr Patrizia Nencini
Genova	IRCCS Ospedale Policlinico San Martino	Dr Laura Malfatto
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Milano (Niguarda)	ASST Grande Ospedale Metropolitano Niguarda	Dr Cristina Motto
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Napoli (Nord)	Presidio Ospedaliero Santa Maria delle Grazie - ASL Napoli 2 Nord	Dr Francesco Barbato
Novara	Azienda Ospedaliero Universitaria Maggiore della Carità	Dr Roberto Tarletti
Palmero (Paolo Giacconne)	Azienda Ospedaliera Universitaria Policlinico Paolo Giacconne Palermo	Dr Paolo Aridon
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Roma (Tor Vergata)	Policlinico Tor Vergata	Prof Marina Diomedi
Taranto	Ospedale SS. Annunziata ASL Taranto	Dr Giovanni Boero
Trieste	Azienda Sanitaria Universitaria Guiliano Isontina	Dr Marcello Naccarato

TICH-3: Eligibility Criteria

Criteri di inclusione:
i. Adulti (≥ 18 anni)
ii. Presentarsi entro 4,5 ore dall'insorgenza di ICH spontanea acuta
iii. ICH confermata tramite imaging cerebrale
iv. Quando l'insorgenza dei sintomi è sconosciuta, il paziente deve trovarsi entro 4,5 ore dalla scoperta dei sintomi e non avere altri criteri di esclusione.
v. I pazienti in terapia con anticoagulanti orali diretti possono essere inclusi
vi. Consenso informato secondo l'articolo 35 del (UE) n. 536/2014
vii. Si prega di consultare il documento separato per i descrittori specifici dei paesi dell'UE - vedere l'Appendice 2 e il documento Parte II

Criteri di esclusione:
viii. Paziente con un'indicazione raccomandata nota per il trattamento con TXA (ad esempio lesioni cerebrali traumatiche).
ix. I pazienti con controindicazioni alla TXA a giudizio del medico curante devono essere esclusi. Cioè quando la controindicazione supera il rischio di somministrare TXA a un paziente come trattamento di emergenza per ICH:
a. Crisi epilettiche attive
b. Diagnosi attuale di trombosi venosa o arteriosa acuta
c. Ipersensibilità alla TXA o soluzione fisiologica
d. Pazienti con nota anomalia strutturale sottostante come malformazione artero-venosa, aneurisma, tumore. Un'anomalia strutturale sottostante non deve essere esclusa prima dell'arruolamento, ma se nota, i pazienti non devono essere arruolati.
x. Paziente noto per essere in terapia anticoagulante al momento dell'arruolamento, con l'eccezione degli anticoagulanti orali diretti (i pazienti in terapia con anticoagulanti orali diretti non sono esclusi).
xi. ICH massivo per cui il trattamento emostatico sembra inutile (Questo avverrebbe normalmente quando il volume dell'ematoma è stimato superiore a 60 ml)
xii. Coma grave (Glasgow Coma Scale <5)
xiii. Decisione già presa per le cure palliative (fine della vita) con ritiro del trattamento attivo

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

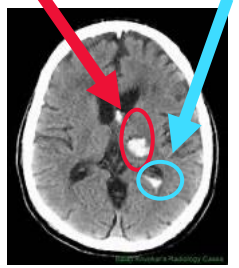
Can TICH-3 participants be co-enrolled to the Annexa-4 trial?

No, if they have been recruited for the ANNEXA-4 trial they cannot be recruited for TICH 3.

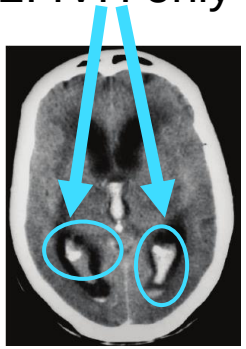
Eligibility: Frequently asked questions

- 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 undertake by a medically qualified doctor under the clinical trials regulations.

1. ICH and IVH



2. IVH only



Final decision on eligibility rests with treating physician

Investigator questions

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

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

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

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

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

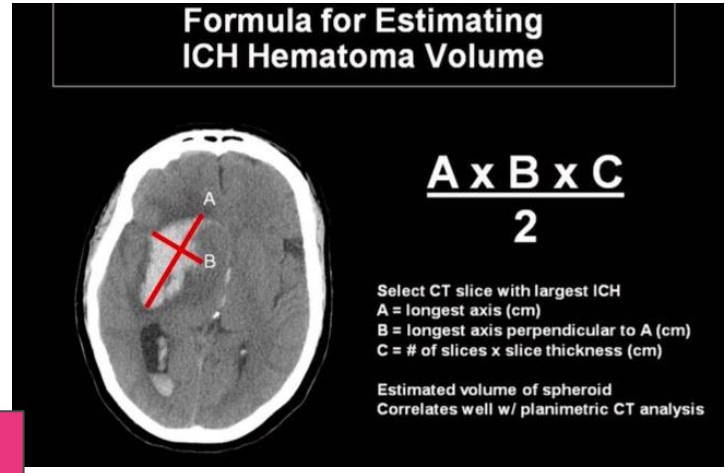
- Yes – they should take as long as they need, but need to explain to them that in other bleeding conditions TXA is more effective if given as soon as possible after stroke onset, when the risk of bleeding (haematoma expansion) is greatest. If they cannot decide within the 4.5hours since stroke onset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

Haematoma volume measurement

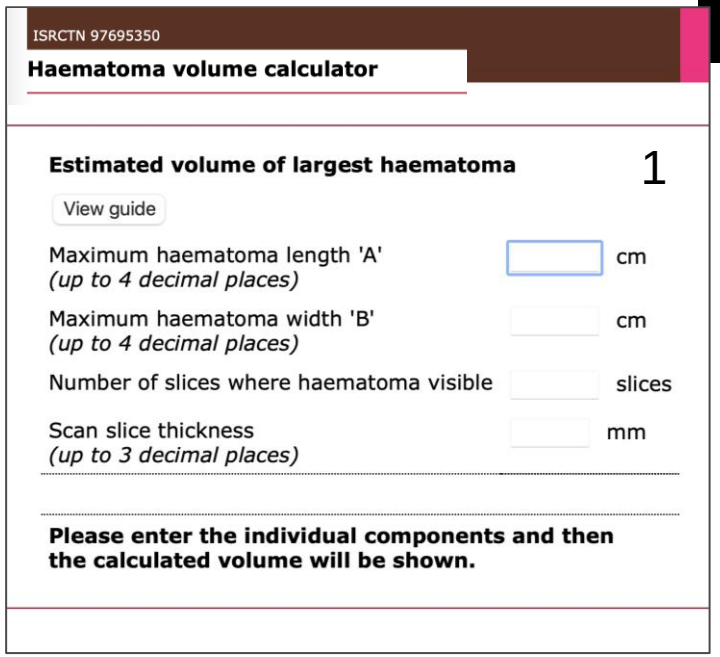
Exclude patients with massive haematoma (usually >60ml)

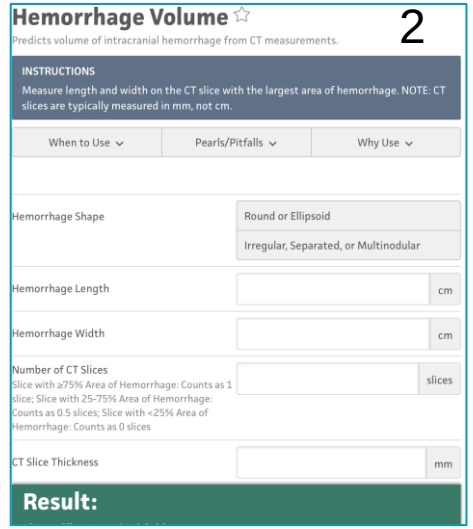
1. If CT scan uses automated haematoma volume software – patient can be enrolled if HV not greater than 60mls
2. Calculate HV manually using TICH-3 HV=ABC/2 calculator on the website[1] or alternatives e.g. mdcalc app[2] Dimensions can be obtained from neuroradiology or measured directly.
3. If ABC/2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

- ❖ Do not include IVH volume in calculation
- ❖ HV can be estimated by anyone trained to do so



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





https://www.mdcalc.com/abc2-formula-intracerebral-hemorrhage-volume

Decision to confirm eligibility rests with treating physician

CONSENT

Emergency Consent Process: ITALY

Rapid consent process, participants or relatives provide verbal consent

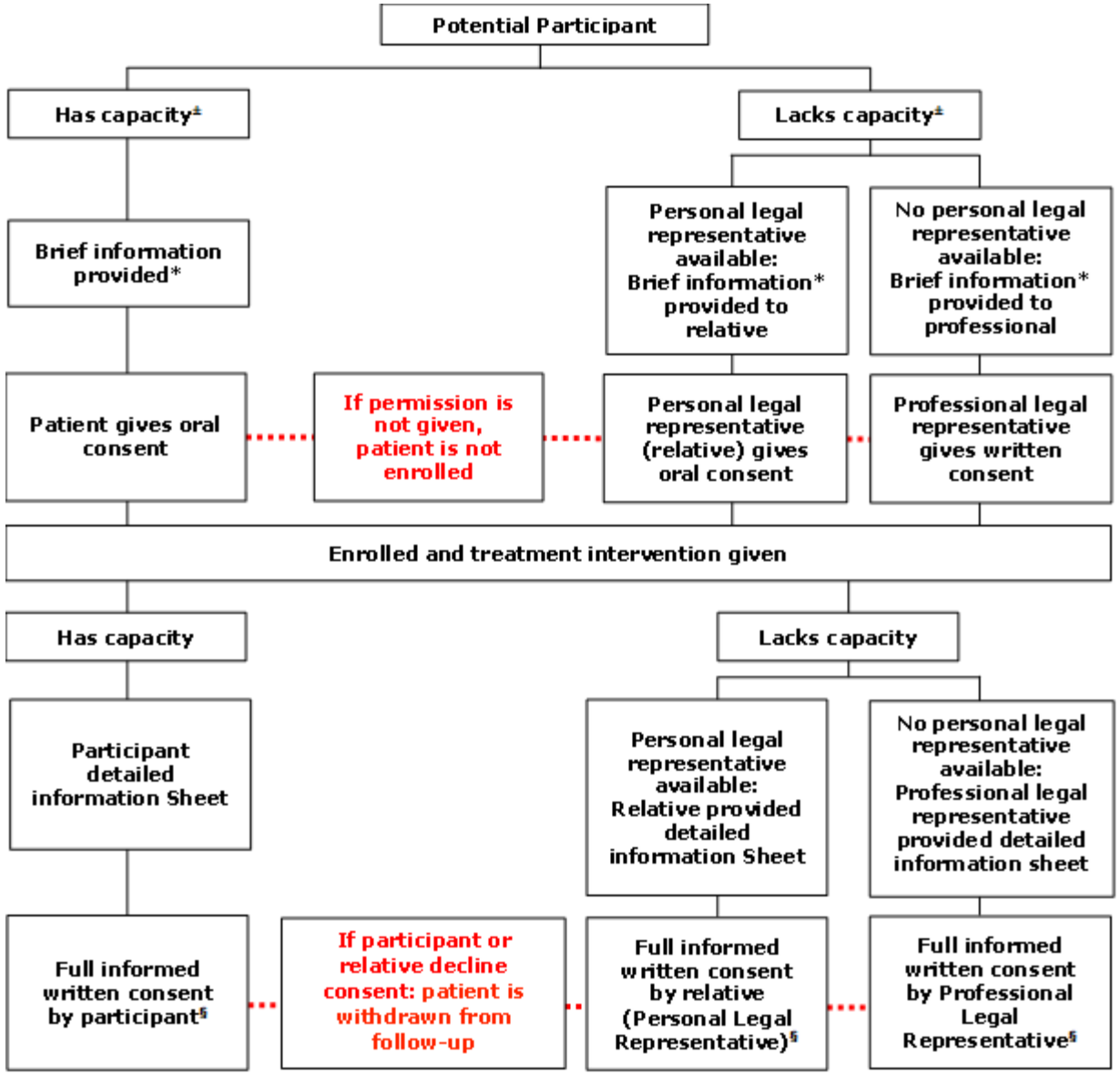
Full informed written consent to be obtained later after administration of IMP

<u>Hierarchy approach</u>

Patient has capacity – gives oral consent

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

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

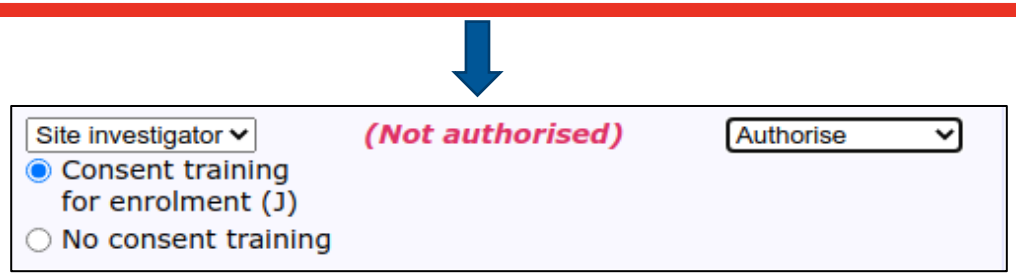


Delegated roles for consent: J and Z

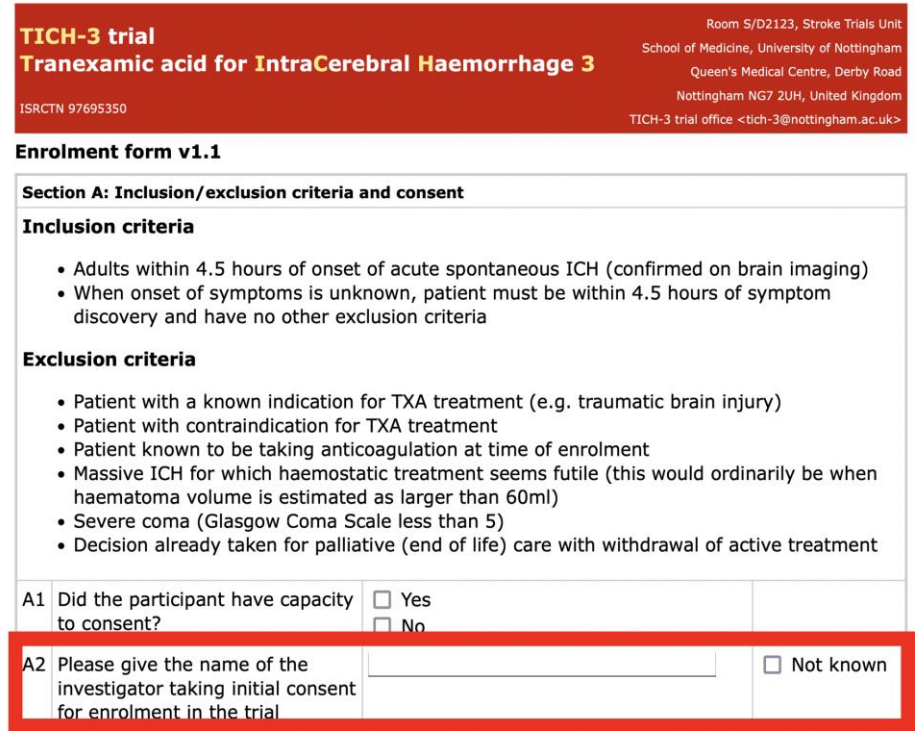
Person taking initial consent must be delegated role J

The PI must select whether code J should be applied as a delegated role.

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



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



Person taking written consent must be delegated role Z

Z assigned to those with relevant investigator roles (not pharmacists, radiology etc) and confirmed by PI.

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

Professional legal representative consent by an independent doctor

Enrolment consent by independent doctor

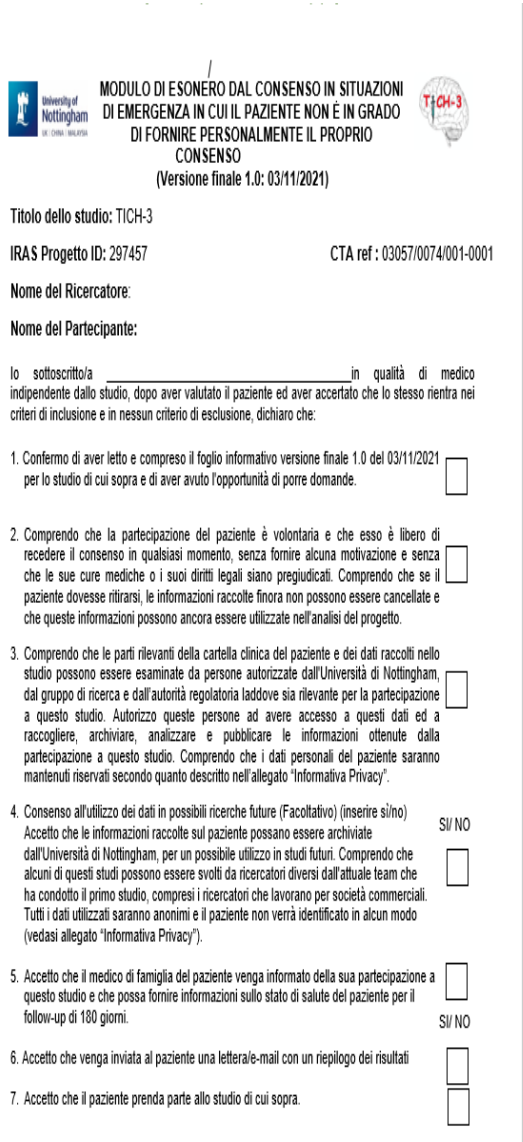
Short Information Sheet and Consent form should be used (pictured to the right). In this scenario this professional legal representative enrolment consent is handwritten and then a follow on written consent form is not required to be completed by the independent doctor. If the participant regains capacity or a relative becomes available they should complete the written follow on consent.

Follow on written consent by independent doctor

The follow on written consent form for professional legal representative should only be used if participant has capacity and consents for enrolment orally, then loses capacity and no relatives are contactable to provide the handwritten follow on consent. If the participant regains capacity or a relative becomes available they should complete the written follow on consent.

Informing relatives

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



MODULO DI ESONERO DAL CONSENSO IN SITUAZIONI DI EMERGENZA IN CUI IL PAZIENTE NON È IN GRADO DI FORNIRE PERSONALMENTE IL PROPRIO CONSENSO
(Versione finale 1.0: 03/11/2021)

Titolo dello studio: TICH-3

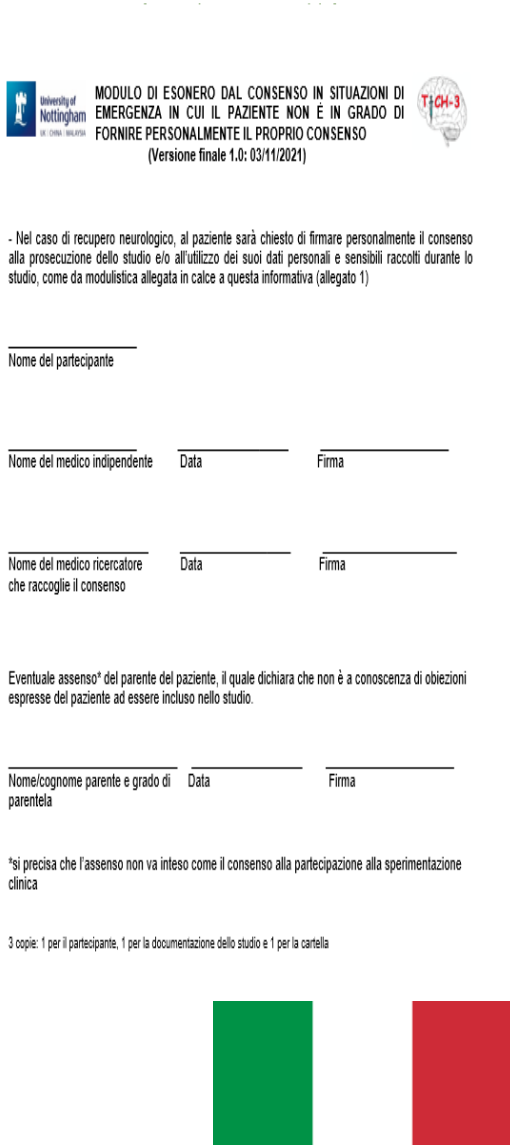
IRAS Progetto ID: 297457 **CTA ref :** 03057/0074/001-0001

Nome del Ricercatore:

Nome del Partecipante:

Io sottoscritto/a _____ in qualità di medico indipendente dallo studio, dopo aver valutato il paziente ed aver accertato che lo stesso rientra nei criteri di inclusione e in nessun criterio di esclusione, dichiaro che:

1. Confermo di aver letto e compreso il foglio informativo versione finale 1.0 del 03/11/2021 per lo studio di cui sopra e di aver avuto l'opportunità di porre domande. ☐
2. Comprendo che la partecipazione del paziente è volontaria e che esso è libero di recedere il consenso in qualsiasi momento, senza fornire alcuna motivazione e senza che le sue cure mediche o i suoi diritti legali siano pregiudicati. Comprendo che se il paziente dovesse ritirarsi, le informazioni raccolte finora non possono essere cancellate e che queste informazioni possono ancora essere utilizzate nell'analisi del progetto. ☐
3. Comprendo che le parti rilevanti della cartella clinica del paziente e dei dati raccolti nello studio possono essere esaminate da persone autorizzate dall'Università di Nottingham, dal gruppo di ricerca e dall'autorità regolatoria laddove sia rilevante per la partecipazione a questo studio. Autorizzo queste persone ad avere accesso a questi dati ed a raccogliere, archiviare, analizzare e pubblicare le informazioni ottenute dalla partecipazione a questo studio. Comprendo che i dati personali del paziente saranno mantenuti riservati secondo quanto descritto nell'allegato "Informativa Privacy". ☐
4. Consenso all'utilizzo dei dati in possibili ricerche future (Facoltativo) (inserire sì/no) SI/ NO
   Accetto che le informazioni raccolte sul paziente possano essere archiviate dall'Università di Nottingham, per un possibile utilizzo in studi futuri. Comprendo che alcuni di questi studi possono essere svolti da ricercatori diversi dall'attuale team che ha condotto il primo studio, compresi i ricercatori che lavorano per società commerciali. Tutti i dati utilizzati saranno anonimi e il paziente non verrà identificato in alcun modo (vedasi allegato "Informativa Privacy"). ☐
5. Accetto che il medico di famiglia del paziente venga informato della sua partecipazione a questo studio e che possa fornire informazioni sullo stato di salute del paziente per il follow-up di 180 giorni. SI/ NO ☐
6. Accetto che venga inviata al paziente una lettera/e-mail con un riepilogo dei risultati ☐
7. Accetto che il paziente prenda parte allo studio di cui sopra. ☐



MODULO DI ESONERO DAL CONSENSO IN SITUAZIONI DI EMERGENZA IN CUI IL PAZIENTE NON È IN GRADO DI FORNIRE PERSONALMENTE IL PROPRIO CONSENSO
(Versione finale 1.0: 03/11/2021)

- Nel caso di recupero neurologico, al paziente sarà chiesto di firmare personalmente il consenso alla prosecuzione dello studio e/o all'utilizzo dei suoi dati personali e sensibili raccolti durante lo studio, come da modulistica allegata in calce a questa informativa (allegato 1)

_____
Nome del partecipante

_____ _____ _____
Nome del medico indipendente Data Firma

_____ _____ _____
Nome del medico ricercatore che raccoglie il consenso Data Firma

Eventuale assenso* del parente del paziente, il quale dichiara che non è a conoscenza di obiezioni espresse del paziente ad essere incluso nello studio.

_____ _____ _____
Nome/cognome parente e grado di parentela Data Firma

*si precisa che l'assenso non va inteso come il consenso alla partecipazione alla sperimentazione clinica

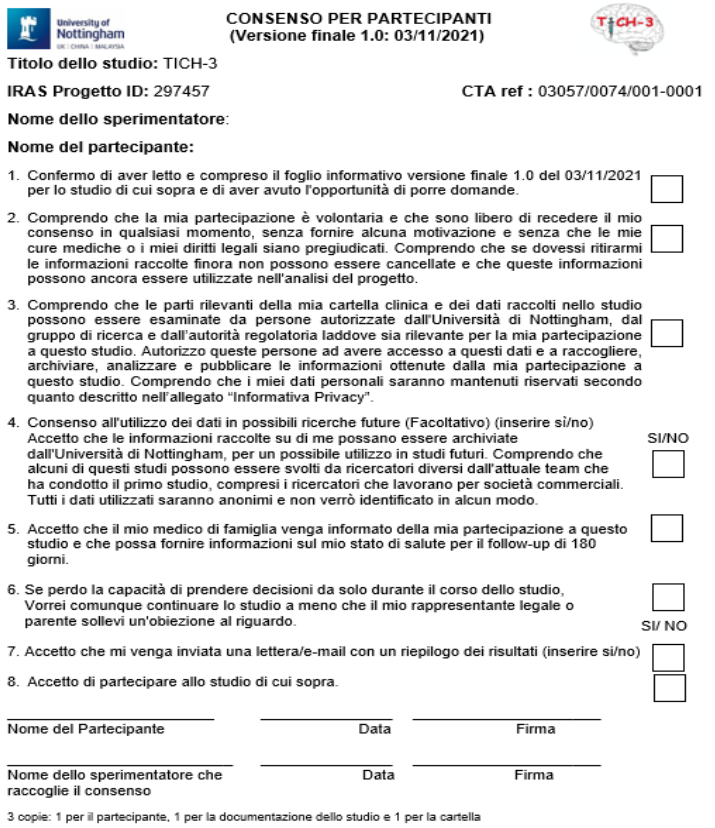
3 copie: 1 per il partecipante, 1 per la documentazione dello studio e 1 per la cartella

Written follow on consent

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

Full, written informed consent will be sought as soon as practicable, ideally within the next 24 hours. Written informed consent will be sought for access to medical notes and for participation in the trial follow up. The participant information sheet will be provided to the participant at this time if not already provided.

Please localise the consent forms and participant information sheets prior to printing, see WPD preparing trial documentation to help you with this https://stroke.nottingham.ac.uk/sif/docs/?sid=TICH-3



CONSENSO PER PARTECIPANTI
(Versione finale 1.0: 03/11/2021)

Titolo dello studio: TICH-3

IRAS Progetto ID: 297457 **CTA ref :** 03057/0074/001-0001

Nome dello sperimentatore:

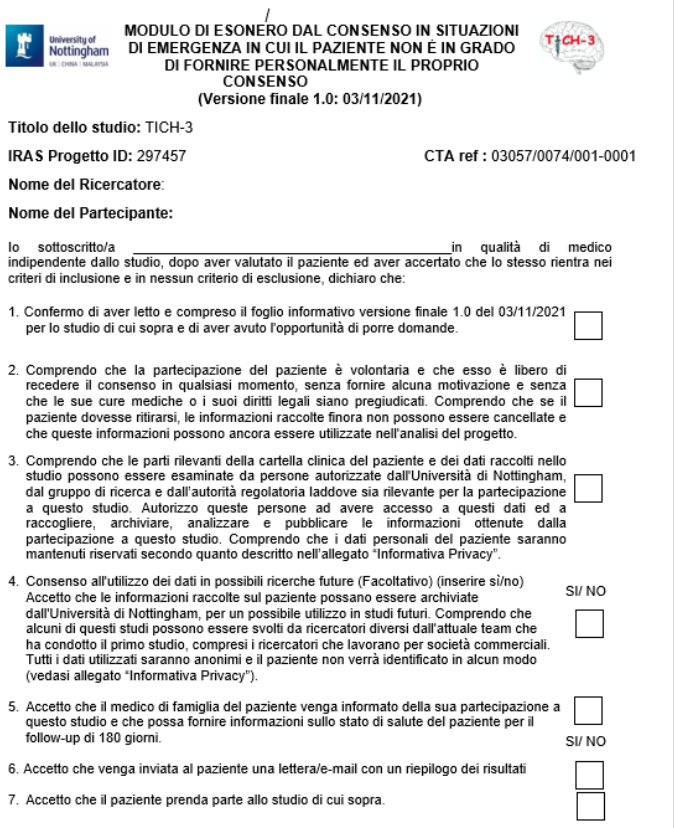
Nome del partecipante:

1. Confermo di aver letto e compreso il foglio informativo versione finale 1.0 del 03/11/2021 per lo studio di cui sopra e di aver avuto l'opportunità di porre domande. ☐
2. Comprendo che la mia partecipazione è volontaria e che sono libero di recedere il mio consenso in qualsiasi momento, senza fornire alcuna motivazione e senza che le mie cure mediche o i miei diritti legali siano pregiudicati. Comprendo che se dovessi ritirarmi le informazioni raccolte finora non possono essere cancellate e che queste informazioni possono ancora essere utilizzate nell'analisi del progetto. ☐
3. Comprendo che le parti rilevanti della mia cartella clinica e dei dati raccolti nello studio possono essere esaminate da persone autorizzate dall'Università di Nottingham, dal gruppo di ricerca e dall'autorità regolatoria laddove sia rilevante per la mia partecipazione a questo studio. Autorizzo queste persone ad avere accesso a questi dati e a raccogliere, archiviare, analizzare e pubblicare le informazioni ottenute dalla mia partecipazione a questo studio. Comprendo che i miei dati personali saranno mantenuti riservati secondo quanto descritto nell'allegato "Informativa Privacy". ☐
4. Consenso all'utilizzo dei dati in possibili ricerche future (Facoltativo) (inserire sì/no) SI/NO
   Accetto che le informazioni raccolte su di me possano essere archiviate dall'Università di Nottingham, per un possibile utilizzo in studi futuri. Comprendo che alcuni di questi studi possono essere svolti da ricercatori diversi dall'attuale team che ha condotto il primo studio, compresi i ricercatori che lavorano per società commerciali. Tutti i dati utilizzati saranno anonimi e non verrò identificato in alcun modo. ☐
5. Accetto che il mio medico di famiglia venga informato della mia partecipazione a questo studio e che possa fornire informazioni sul mio stato di salute per il follow-up di 180 giorni. ☐
6. Se perdo la capacità di prendere decisioni da solo durante il corso dello studio, Vorrei comunque continuare lo studio a meno che il mio rappresentante legale o parente sollevi un'obiezione al riguardo. SI/ NO ☐
7. Accetto che mi venga inviata una lettera/e-mail con un riepilogo dei risultati (inserire sì/no) ☐
8. Accetto di partecipare allo studio di cui sopra. ☐

Nome del Partecipante _____ Data _____ Firma _____

Nome dello sperimentatore che raccoglie il consenso _____ Data _____ Firma _____

3 copie: 1 per il partecipante, 1 per la documentazione dello studio e 1 per la cartella



MODULO DI ESONERO DAL CONSENSO IN SITUAZIONI DI EMERGENZA IN CUI IL PAZIENTE NON È IN GRADO DI FORNIRE PERSONALMENTE IL PROPRIO CONSENSO
(Versione finale 1.0: 03/11/2021)

Titolo dello studio: TICH-3

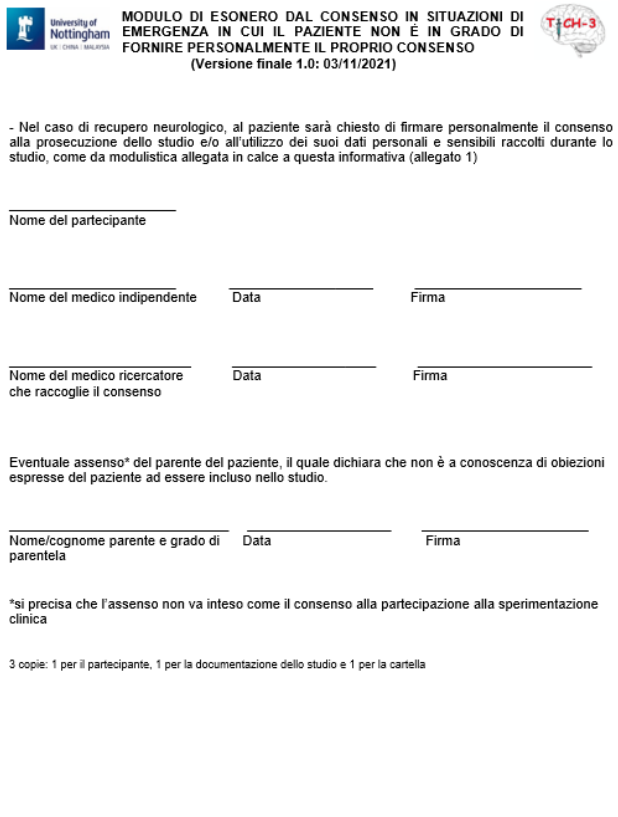
IRAS Progetto ID: 297457 **CTA ref :** 03057/0074/001-0001

Nome del Ricercatore:

Nome del Partecipante:

Io sottoscritto/a _____ in qualità di medico indipendente dallo studio, dopo aver valutato il paziente ed aver accertato che lo stesso rientra nei criteri di inclusione e in nessun criterio di esclusione, dichiaro che:

1. Confermo di aver letto e compreso il foglio informativo versione finale 1.0 del 03/11/2021 per lo studio di cui sopra e di aver avuto l'opportunità di porre domande. ☐
2. Comprendo che la partecipazione del paziente è volontaria e che esso è libero di recedere il consenso in qualsiasi momento, senza fornire alcuna motivazione e senza che le sue cure mediche o i suoi diritti legali siano pregiudicati. Comprendo che se il paziente dovesse ritirarsi, le informazioni raccolte finora non possono essere cancellate e che queste informazioni possono ancora essere utilizzate nell'analisi del progetto. ☐
3. Comprendo che le parti rilevanti della cartella clinica del paziente e dei dati raccolti nello studio possono essere esaminate da persone autorizzate dall'Università di Nottingham, dal gruppo di ricerca e dall'autorità regolatoria laddove sia rilevante per la partecipazione a questo studio. Autorizzo queste persone ad avere accesso a questi dati ed a raccogliere, archiviare, analizzare e pubblicare le informazioni ottenute dalla partecipazione a questo studio. Comprendo che i dati personali del paziente saranno mantenuti riservati secondo quanto descritto nell'allegato "Informativa Privacy". ☐
4. Consenso all'utilizzo dei dati in possibili ricerche future (Facoltativo) (inserire sì/no) SI/ NO
   Accetto che le informazioni raccolte sul paziente possano essere archiviate dall'Università di Nottingham, per un possibile utilizzo in studi futuri. Comprendo che alcuni di questi studi possono essere svolti da ricercatori diversi dall'attuale team che ha condotto il primo studio, compresi i ricercatori che lavorano per società commerciali. Tutti i dati utilizzati saranno anonimi e il paziente non verrà identificato in alcun modo (vedasi allegato "Informativa Privacy"). ☐
5. Accetto che il medico di famiglia del paziente venga informato della sua partecipazione a questo studio e che possa fornire informazioni sullo stato di salute del paziente per il follow-up di 180 giorni. SI/ NO ☐
6. Accetto che venga inviata al paziente una lettera/e-mail con un riepilogo dei risultati ☐
7. Accetto che il paziente prenda parte allo studio di cui sopra. ☐



MODULO DI ESONERO DAL CONSENSO IN SITUAZIONI DI EMERGENZA IN CUI IL PAZIENTE NON È IN GRADO DI FORNIRE PERSONALMENTE IL PROPRIO CONSENSO
(Versione finale 1.0: 03/11/2021)

- Nel caso di recupero neurologico, al paziente sarà chiesto di firmare personalmente il consenso alla prosecuzione dello studio e/o all'utilizzo dei suoi dati personali e sensibili raccolti durante lo studio, come da modulistica allegata in calce a questa informativa (allegato 1)

_____
Nome del partecipante

_____ _____ _____
Nome del medico indipendente Data Firma

_____ _____ _____
Nome del medico ricercatore che raccoglie il consenso Data Firma

Eventuale assenso* del parente del paziente, il quale dichiara che non è a conoscenza di obiezioni espresse del paziente ad essere incluso nello studio.

_____ _____ _____
Nome/cognome parente e grado di parentela Data Firma

*si precisa che l'assenso non va inteso come il consenso alla partecipazione alla sperimentazione clinica

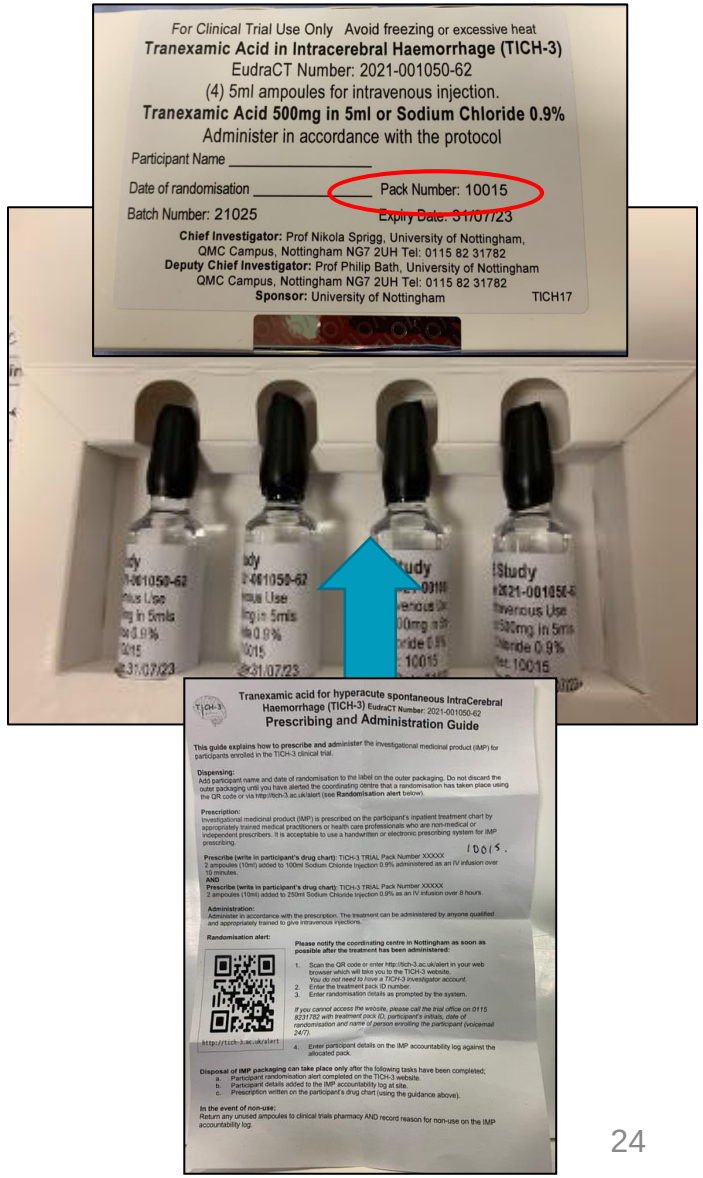
3 copie: 1 per il partecipante, 1 per la documentazione dello studio e 1 per la cartella

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

RANDOMISATION

Randomisation

- Blinded treatment packs will be randomly assigned to sites in blocks of 6 treatment packs
- TICH-3 will use simple randomisation
- After confirming eligibility and obtaining consent the investigator **randomises the patient by selecting and opening the treatment pack with the lowest pack number.**
- The prescribing and administration guide can be found inside each treatment pack.
- Due to emergency nature of trial randomisation is notified to the coordinating centre after the IMP has been administered by completing the randomisation alert (guidance for this is within the prescribing and administration guide).



Prescribing and Administering the IMP

Prescribing the IMP

Investigational medicinal product (IMP) is prescribed on the participant's inpatient treatment chart by appropriately trained medical practitioners or health care professionals who are non-medical or independent prescribers. It is acceptable to use a handwritten or electronic prescribing system for IMP prescribing.

Do not need to be on delegation log to prescribe

Prescribe (write in participants drug chart):

TICH-3 - TRIAL Pack Number XXXXX

TRANEXAMIC ACID OR PLACEBO

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

AND

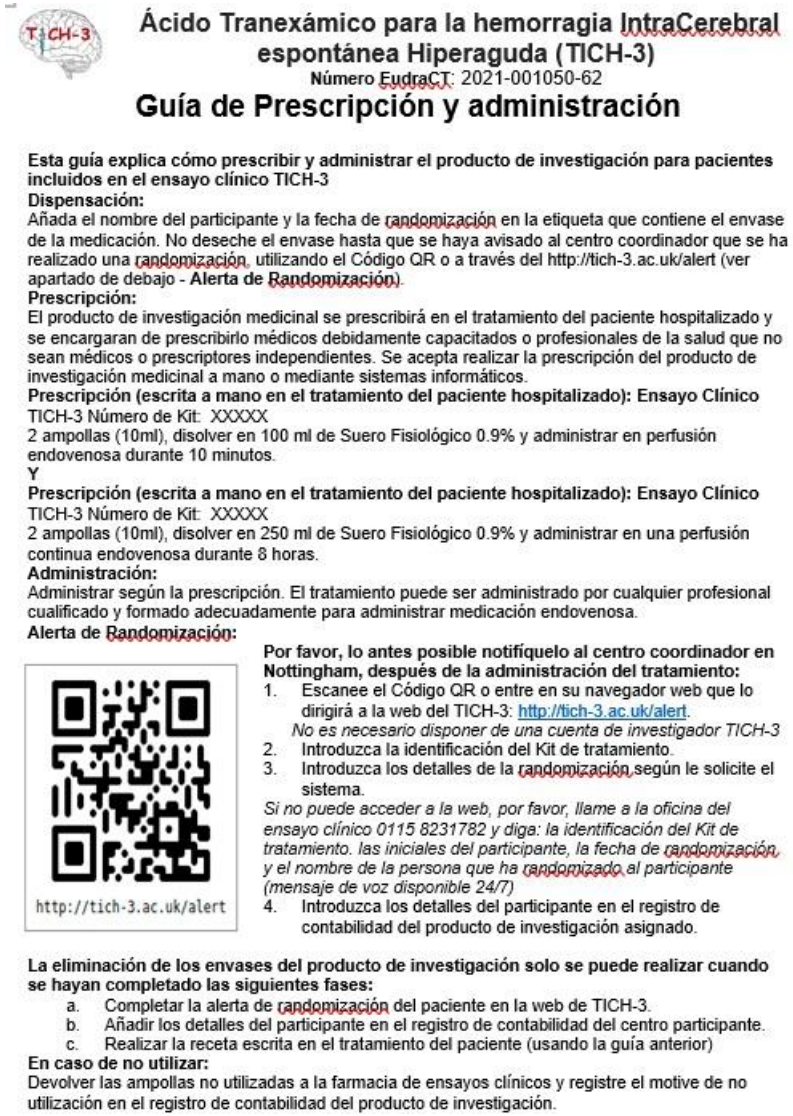
TICH-3 TRIAL Pack Number XXXXX

TRANEXAMIC ACID OR PLACEBO

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

Administering the IMP

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



Ácido Tranexámico para la hemorragia IntraCerebral espontánea Hiperaguda (TICH-3)

Número EudraCT: 2021-001050-62

Guía de Prescripción y administración

Esta guía explica cómo prescribir y administrar el producto de investigación para pacientes incluidos en el ensayo clínico TICH-3

Dispensación:

Añada el nombre del participante y la fecha de randomización en la etiqueta que contiene el envase de la medicación. No deseche el envase hasta que se haya avisado al centro coordinador que se ha realizado una randomización, utilizando el Código QR o a través del http://tich-3.ac.uk/alert (ver apartado de debajo - **Alerta de Randomización**).

Prescripción:

El producto de investigación medicinal se prescribirá en el tratamiento del paciente hospitalizado y se encargaran de prescribirlo médicos debidamente capacitados o profesionales de la salud que no sean médicos o prescriptores independientes. Se acepta realizar la prescripción del producto de investigación medicinal a mano o mediante sistemas informáticos.

Prescripción (escrita a mano en el tratamiento del paciente hospitalizado): Ensayo Clínico

TICH-3 Número de Kit: XXXXX

2 ampollas (10ml), disolver en 100 ml de Suero Fisiológico 0.9% y administrar en perfusión endovenosa durante 10 minutos.

Y

Prescripción (escrita a mano en el tratamiento del paciente hospitalizado): Ensayo Clínico

TICH-3 Número de Kit: XXXXX

2 ampollas (10ml), disolver en 250 ml de Suero Fisiológico 0.9% y administrar en una perfusión continua endovenosa durante 8 horas.

Administración:

Administrar según la prescripción. El tratamiento puede ser administrado por cualquier profesional cualificado y formado adecuadamente para administrar medicación endovenosa.

Alerta de Randomización:

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

Por favor, lo antes posible notifíquelo al centro coordinador en Nottingham, después de la administración del tratamiento:

1. Escanee el Código QR o entre en su navegador web que lo dirigirá a la web del TICH-3: http://tich-3.ac.uk/alert.
   No es necesario disponer de una cuenta de investigador TICH-3
2. Introduzca la identificación del Kit de tratamiento.
3. Introduzca los detalles de la randomización según le solicite el sistema.

Si no puede acceder a la web, por favor, llame a la oficina del ensayo clínico 0115 8231782 y diga: la identificación del Kit de tratamiento. las iniciales del participante, la fecha de randomización, y el nombre de la persona que ha randomizado al participante (mensaje de voz disponible 24/7)

4. Introduzca los detalles del participante en el registro de contabilidad del producto de investigación asignado.

La eliminación de los envases del producto de investigación solo se puede realizar cuando se hayan completado las siguientes fases:

a. Completar la alerta de randomización del paciente en la web de TICH-3.
b. Añadir los detalles del participante en el registro de contabilidad del centro participante.
c. Realizar la receta escrita en el tratamiento del paciente (usando la guía anterior)

En caso de no utilizar:

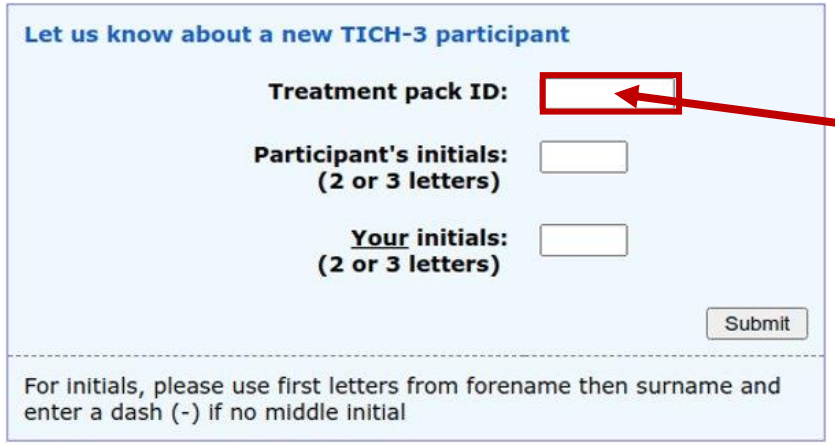
Devolver las ampollas no utilizadas a la farmacia de ensayos clínicos y registre el motive de no utilización en el registro de contabilidad del producto de investigación.

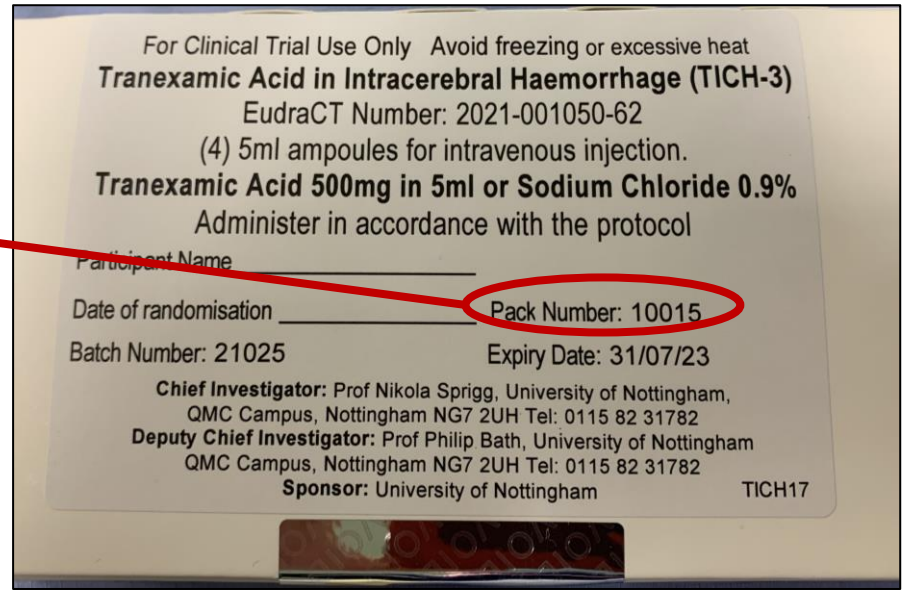
Randomisation Alert

1. Investigator will enter the treatment pack ID (pack number), participant initials and their own initials to alert the coordinating centre to a new randomisation.

SCAN
QR CODE

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





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

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'.

x Do not open another treatment pack

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

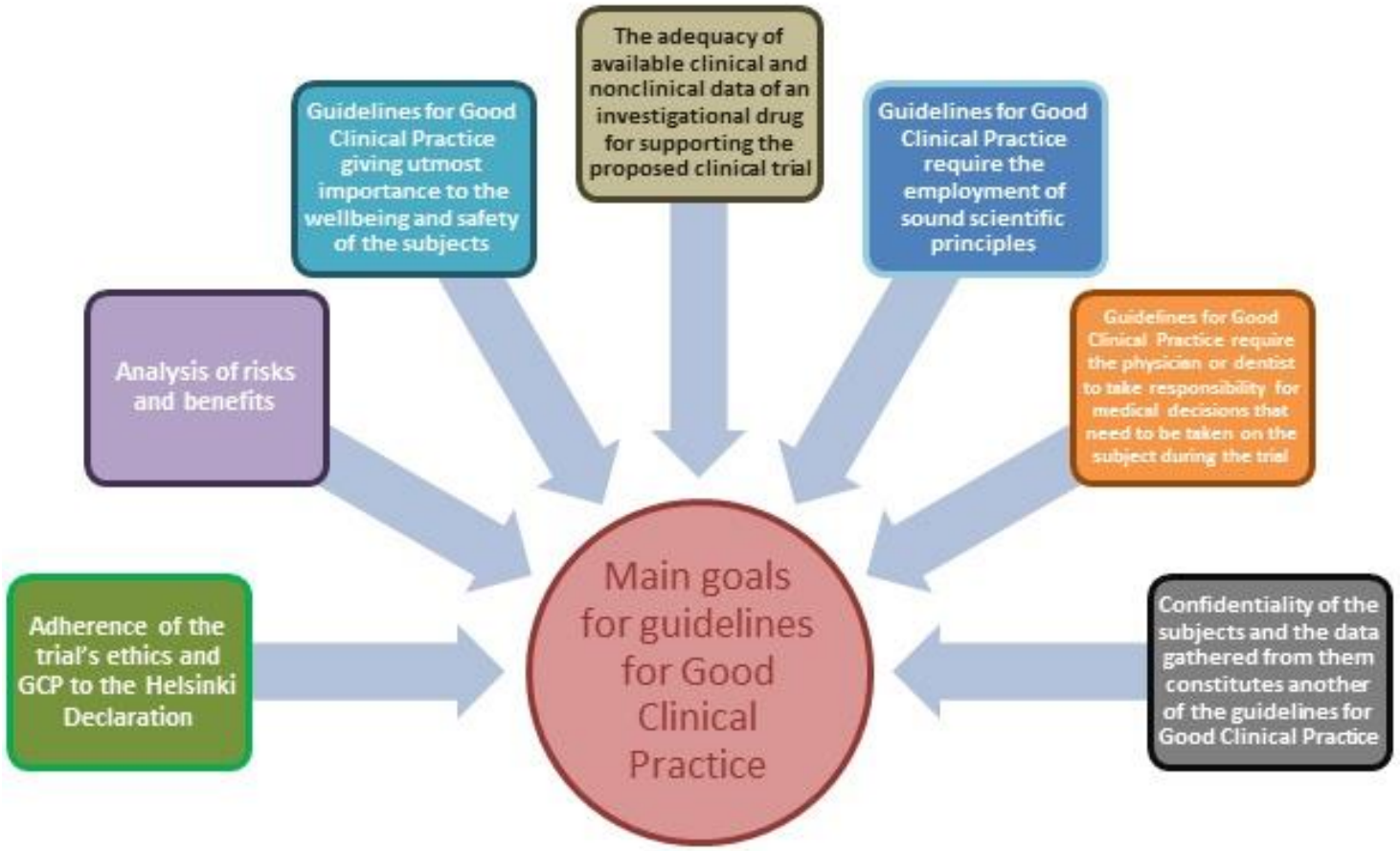
SAFETY MONITORING

Safety outcomes
Serious adverse reaction (SAR)
Suspected Unexpected Serious Adverse Reaction (SUSAR)
Serious adverse event (SAE)

Good Clinical Practice (GCP) : Principles

- 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 Spainish

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 **Note: Death is an end result, not an independent event**	
A5a	Event sub-categorisation *Please only enter a code/description from the SAE sub-category list*	

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

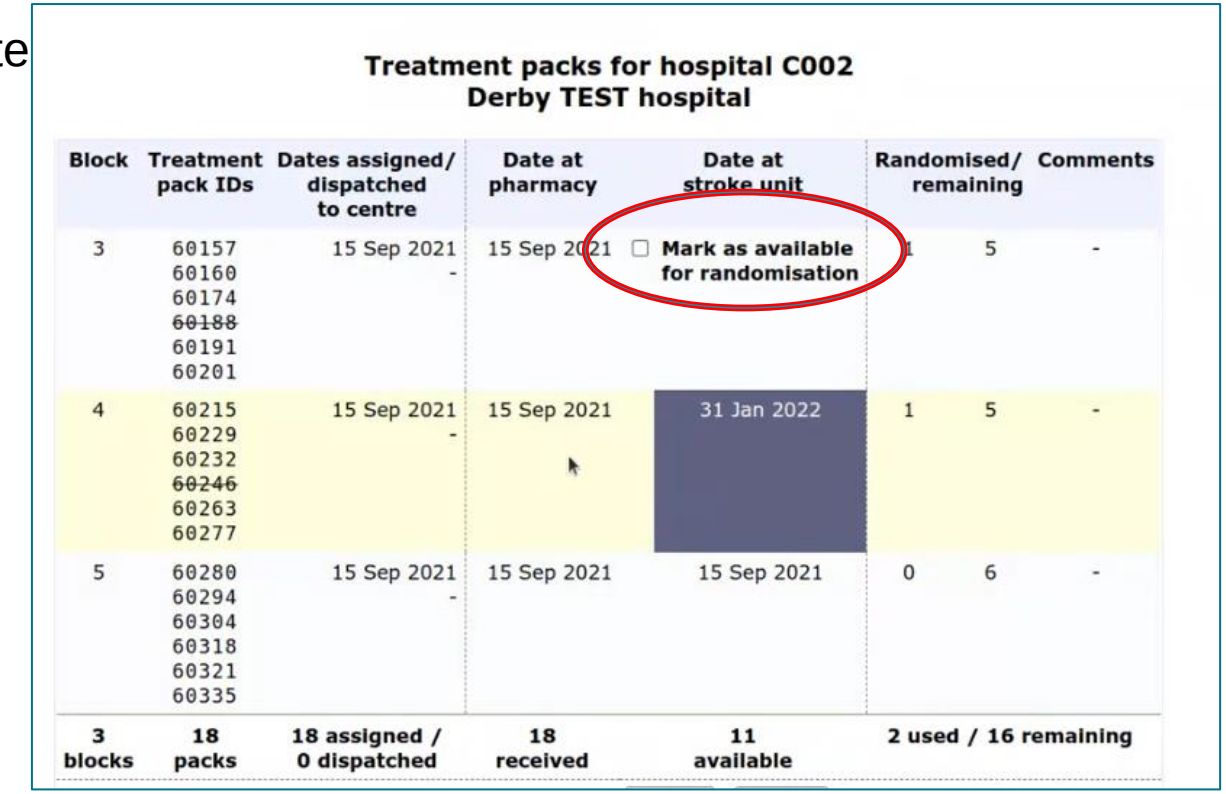
- Coordinating centre will order drug for dispatch once site is nearly ready to commence recruitment
- Blinded treatment packs will be randomly assigned to sites in blocks of 6 treatment packs

- 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	☐ 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

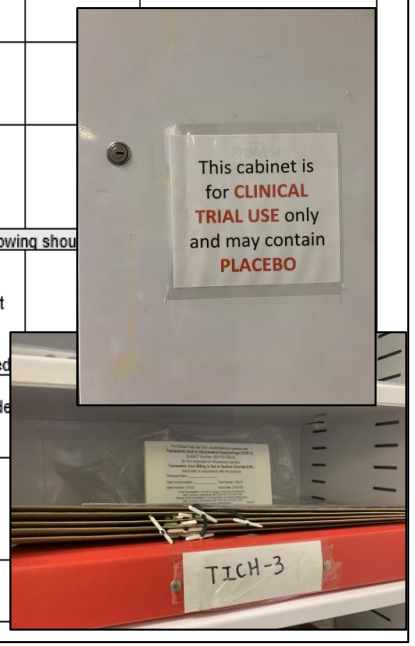
IMP Paperwork (1): Set up, IMP receipt

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.

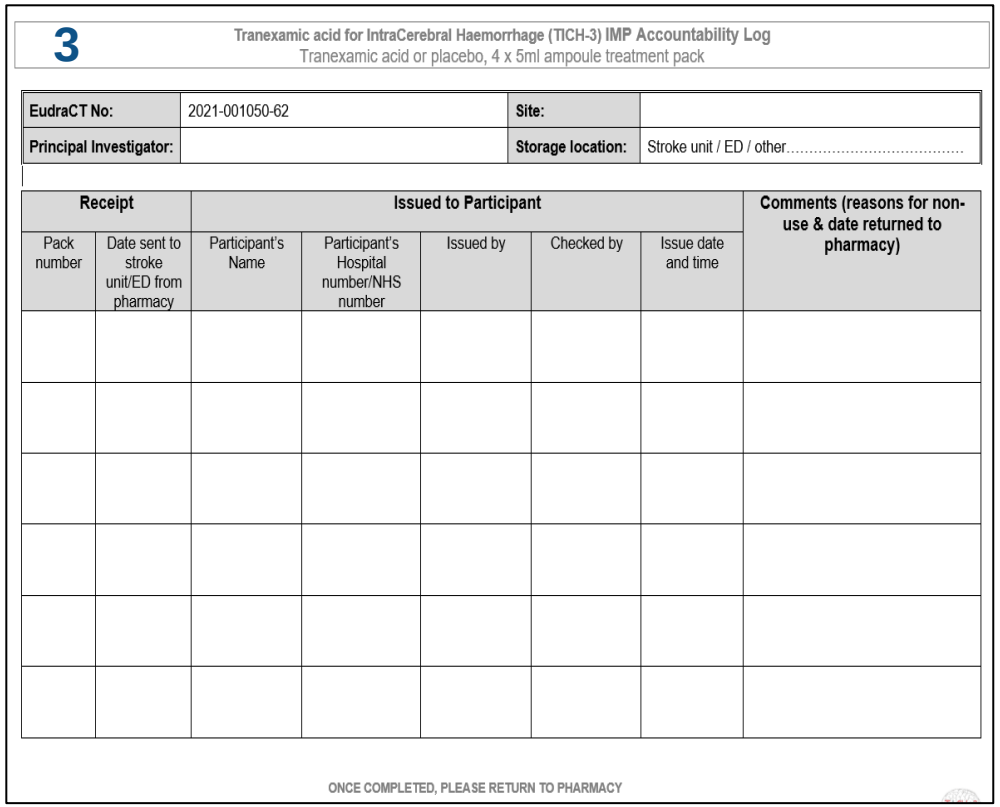
2

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	

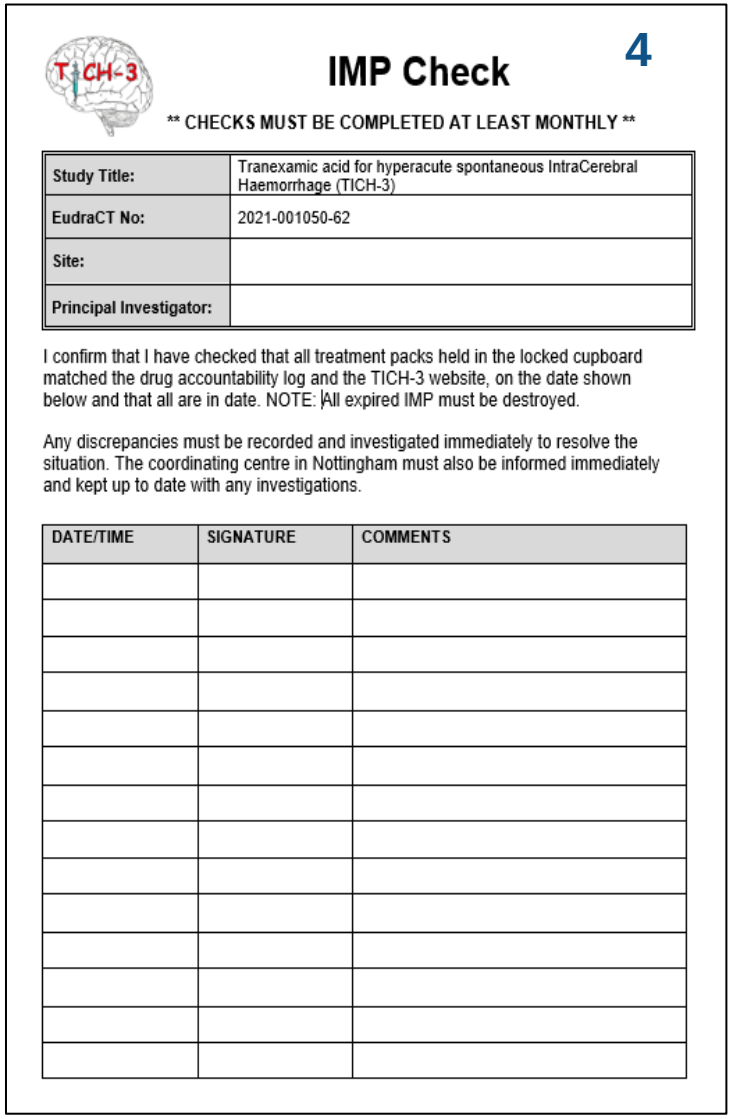
ONCE COMPLETED, PLEASE RETURN TO PHARMACY

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

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.



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.

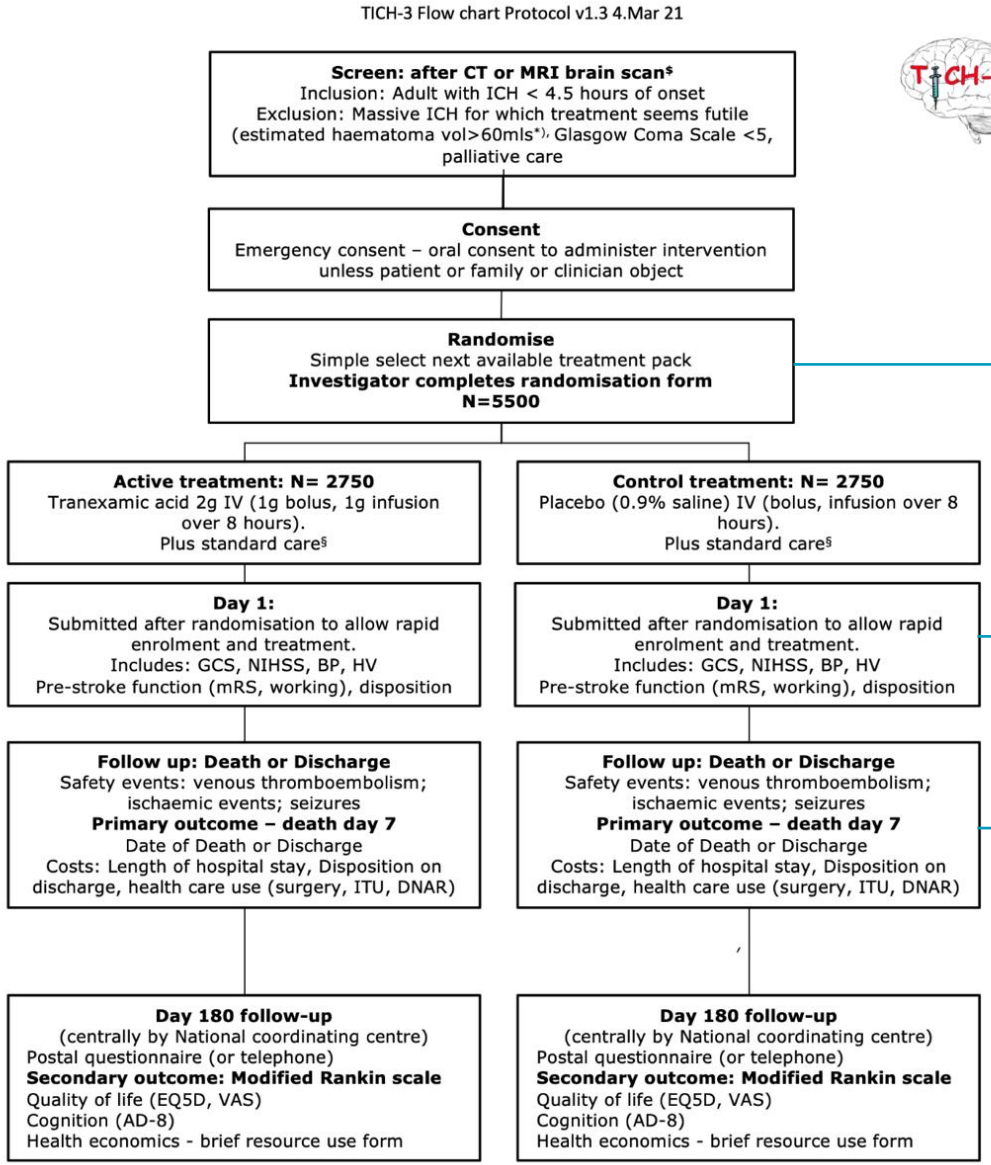
Any discrepancies must be recorded and investigated immediately to resolve the situation. The coordinating centre in Nottingham must also be informed immediately and kept up to date with any investigations.

DATE/TIME	SIGNATURE	COMMENTS

The 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.

DATA COLLECTION

Trial Flow Chart:

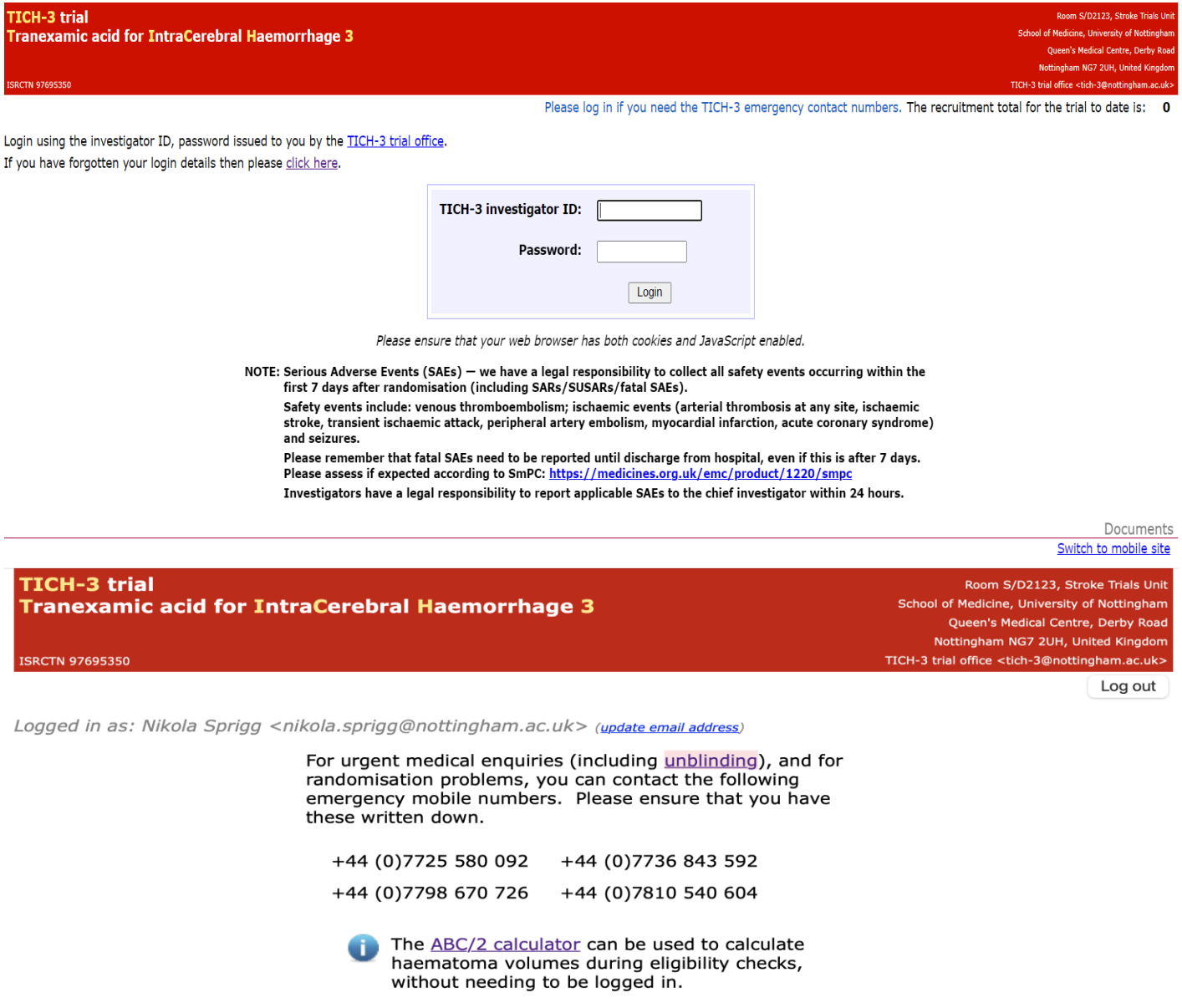


Electronic Case Report Forms (eCRFs) to be completed by local site

- Randomisation alert
- Enrolment form
- Contact details form
- Day 7 follow-up AND Discharge/death

(See separate guidance for completion of these eCRFs)

Logging onto TICH-3 website

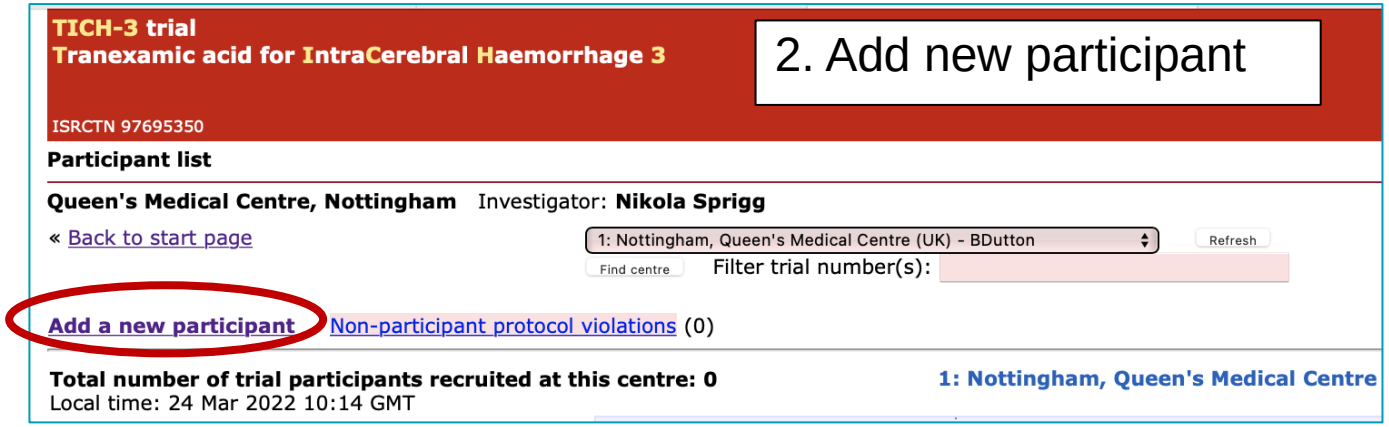


- Coordinating centre will set up an account for investigators – we need the completed attendance at investigator training log completed (electronic signatures are accepted) and returned to us via email to know who needs logins for the TICH-3 website and subsequently added to the delegation log
- Additional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

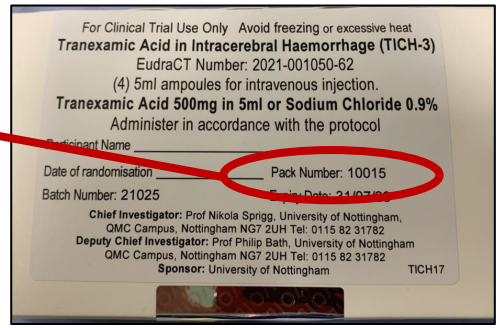
Adding a new participant to the database

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

1. Complete randomisation alert

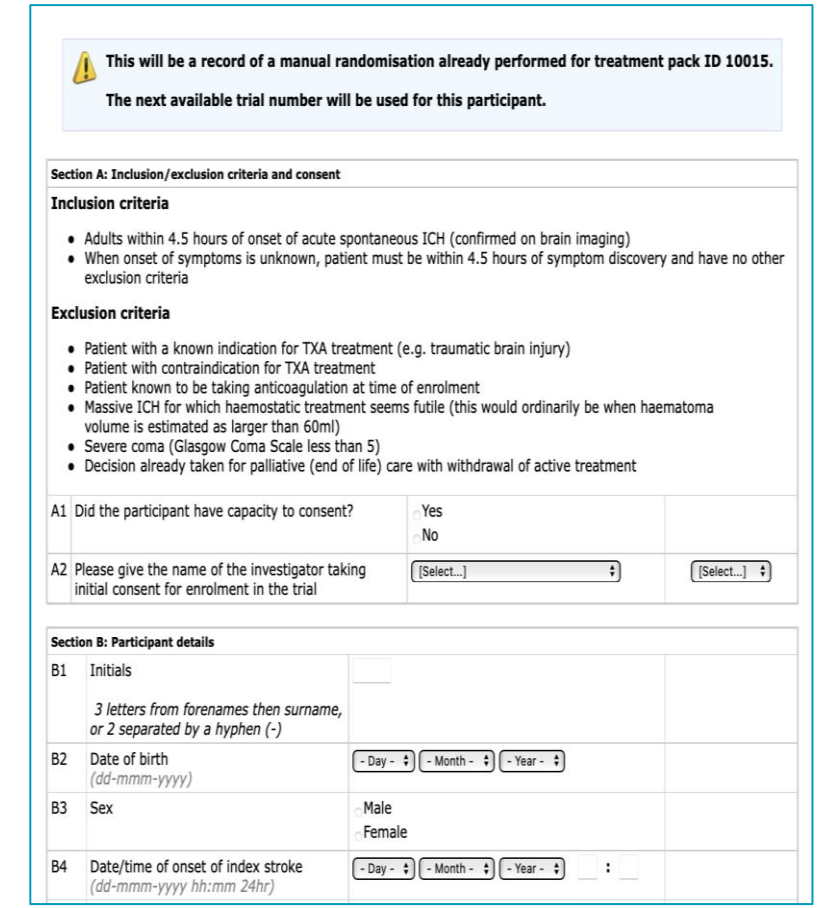


3. Need treatment pack ID number

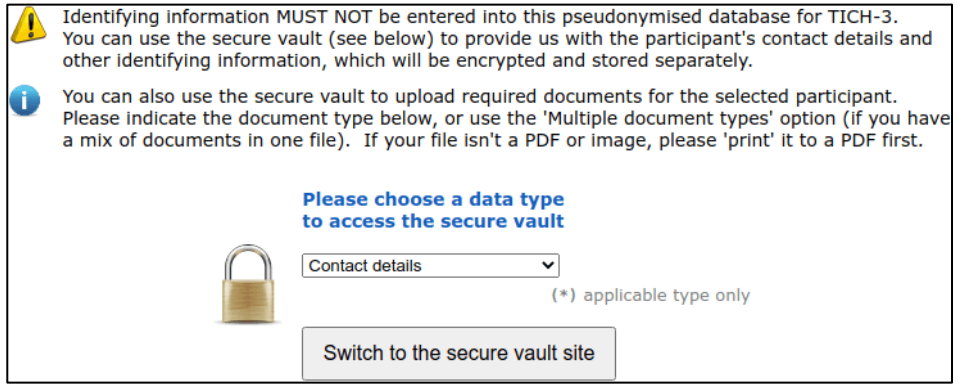


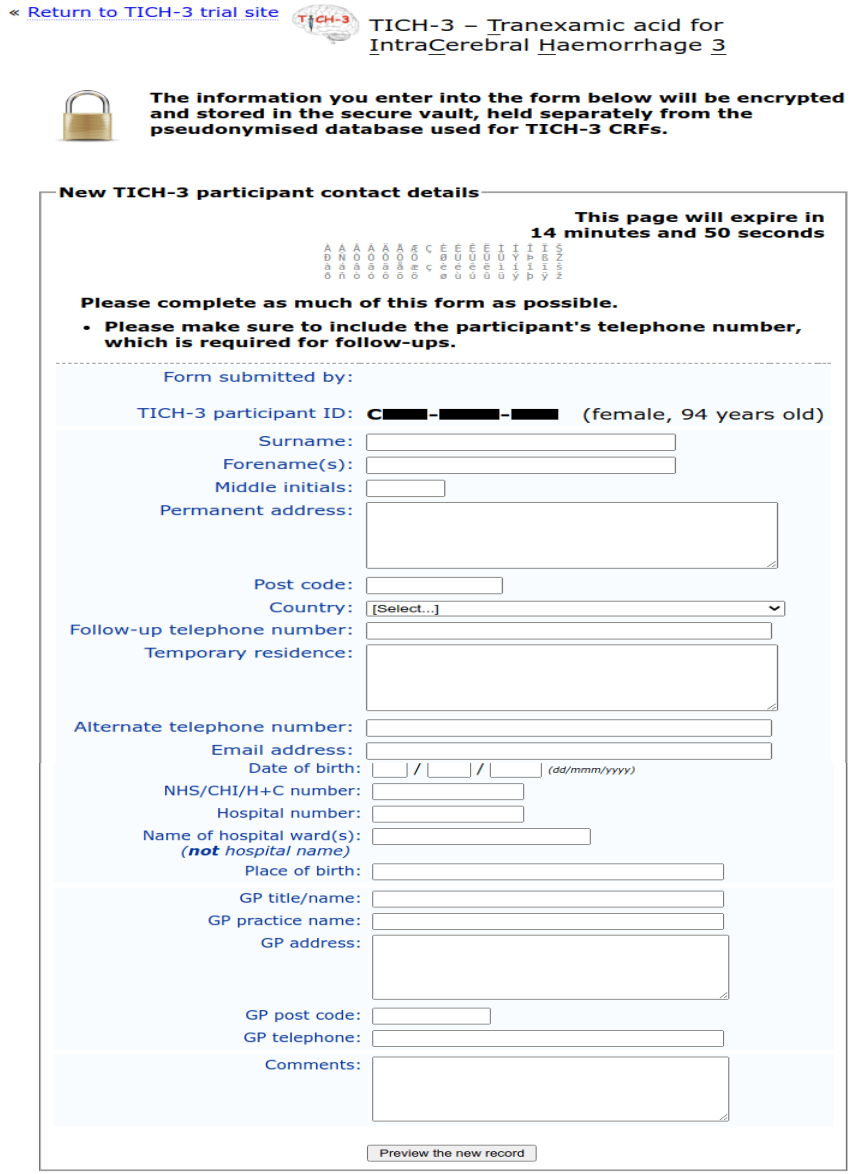
4. Confirm randomisation site

5. Complete enrollment form



Contact Details Form





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.

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

Enrolment eCRF

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

Room S/D2123, Stroke Trials Unit
School of Medicine, University of Nottingham
Queen's Medical Centre, Derby Road
Nottingham NG7 2UH, United Kingdom
TICH-3 trial office <tich-3@nottingham.ac.uk>

Enrolment form v1.1

Section A: Inclusion/exclusion criteria and consent

Inclusion criteria

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

Exclusion criteria

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

A1	Did the participant have capacity to consent?	☐ 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)* *If unknown, please use date/time of first dose*	D ____ / M _____ / Y _____ H _____ : M _____	
B6	Allocated treatment pack ID		

Day 7 follow-up eCRF

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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?	☐ 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)	☐ Not applicable ☐ Not known

Discharge/death eCRF

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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 ☐ 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	☐ Not known
A2b	Did the participant return to their original place of residence? *If died, please select 'No'*	☐ Yes ☐ No	☐ Not known
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 ☐ Intracerebral haemorrhage with underlying cause ☐ Ischaemic stroke with haemorrhagic transformation ☐ Ischaemic stroke without haemorrhagic transformation ☐ Non-stroke/other	☐ Not known

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

- The following eCRFs need to be completed in order on the TICH-3 website http://tich-3.ac.uk/live/

1. Enrolment form
2. Day 7 follow-up
3. Discharge or death in hospital

Total number of trial participants recruited at this centre: 2
Local time: 6 Apr 2022 13:13 BST

✔ **There are no active data queries**

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

Participant ID/age at randomisation	Event date	Treatment pack ID	Randomised	Contacts/ documents	Day 7 follow-up	Discharge/ death	SAEs
C001-0001-F-G 93	23 Mar 2022	10015	23 Mar 2022	Y NNN	29 Mar 2022	27 Mar 2022	‡ Select 1
C001-0002-F-0 65	29 Mar 2022	10029	29 Mar 2022	Y NNN	4 Apr 2022	–	Select

- Trial team members on the delegation log will have received an investigator ID and password to securely log in to the TICH-3 website
- You will need to enter the patients date of birth when entering data to confirm correct participant
- The forms can be completed early if the participant dies or is discharged before day 7 e.g. If participant dies at day 2 you still need to complete day 7 form and discharge/death form
- If repatriated before day 7 please complete forms early and then check if patient still alive at day 7 and enter data

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

Uploading Consent forms

The coordinating centre will complete ongoing monitoring of the eCRF data and consent forms.

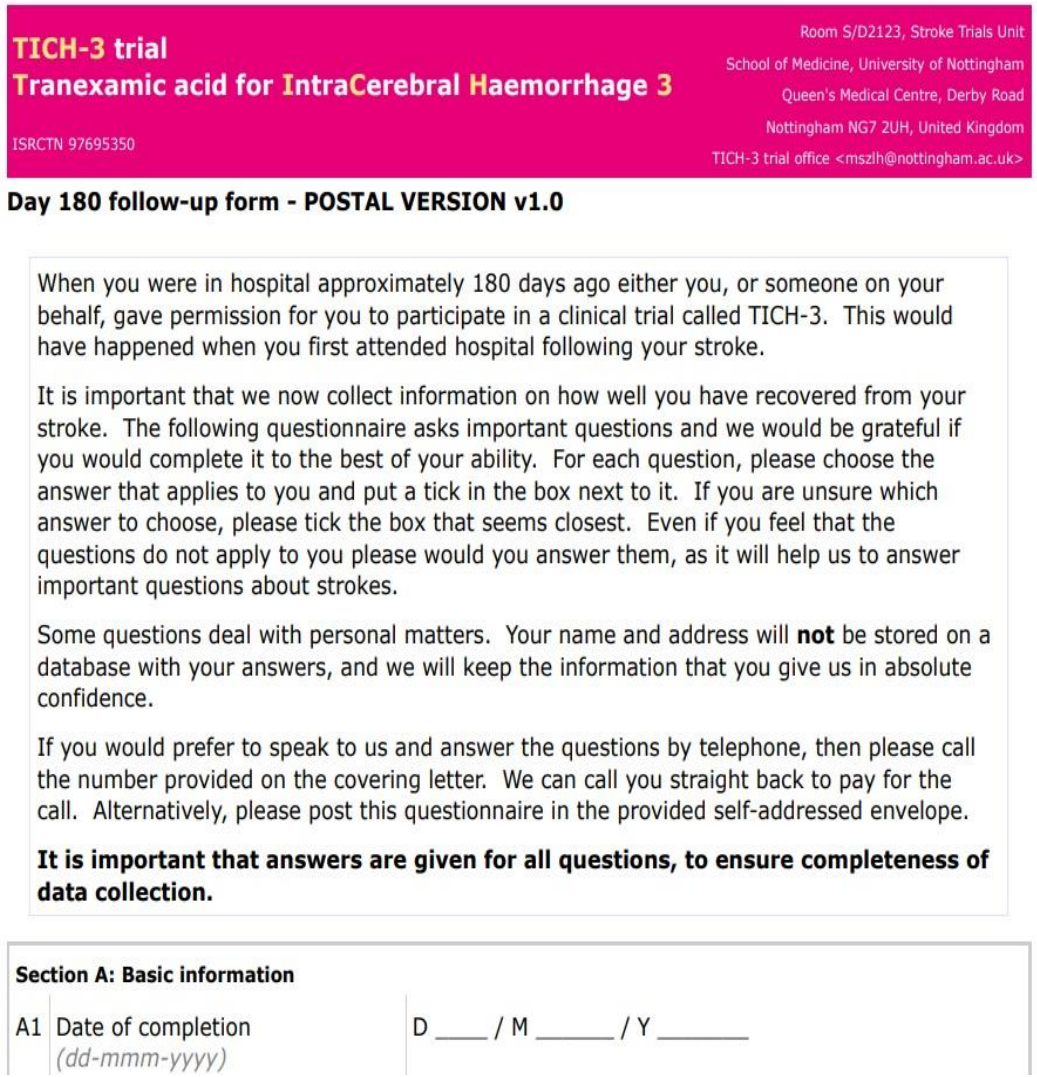
Consent forms

Please upload consent forms to the secure vault site via the TICH-3 website as soon as possible after enrolment. Please do not anonymise consent forms as we need to see who gave and received consent.

Day 180 Follow up in ITALY

180 day follow up done via telephone call

Co-ordinating site to decide on Follow up co-Ordinator



TICH-3 trial
Tranexamic acid for IntraCerebral Haemorrhage 3

ISRCTN 97695350

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

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

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

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

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

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

Section A: Basic information

A1	Date of completion *(dd-mmm-yyyy)*	D ____ / M _____ / Y _____

LOCAL SITE FILE

Local Site File Contents

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

TICH-3 trial – Tranexamic acid for IntraCerebral Haemorrhage 3

Trial documents

Emergency contacts

This page does not provide the emergency mobile numbers.

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

Approved protocol

- Protocol Final v1.0 03.11.2021 fully signed.pdf

Expression of interest

- Online expression of interest form

Trial documents

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

UK site training

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

Information sheets and consent forms

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

Pharmacy documents

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

Electronic delegation Log

Only people appropriately trained and delegated responsibility on the delegation log can take consent.

Anyone who is involved in the trial needs to be on the delegation log; nurses, admin entering data onto online platform, doctors, pharmacist handling the IMP. Can have as many people on the delegation log as required.

The training and roles delegated should be appropriate to the respective job role.

Completing training log will generate an email to the PI asking them to sign you on to the log

Requirements for the local team member to be able to go on the TICH-3 delegation log;

- **Up to date investigator CV**
- **Evidence of GCP training**
- **Completion of TICH-3 training relevant to role in trial**

It is the local PI's responsibility to check local teams investigator CV and GCP before they can be signed off on the delegation log

New members to the team need adding to the delegation log (meeting the requirements above) before they can start working on the TICH-3 trial.

If staff leave the team the PI is required to sign and date 'role finished' against their name.

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

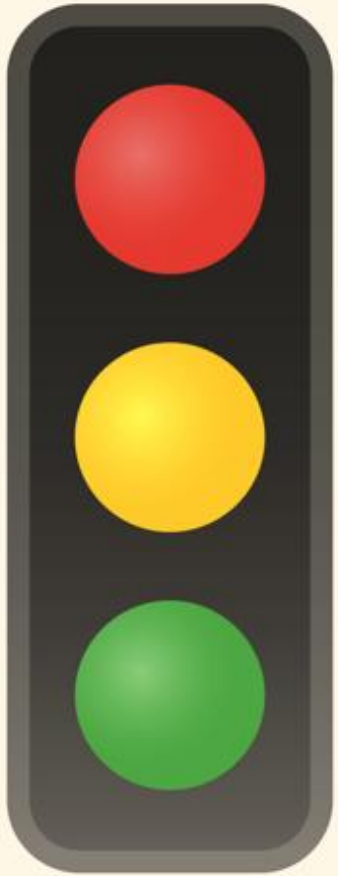
Log ID	Investigator name/ID	Certificate/ date trained	Roles and responsibilities*	Delegation log status
1	**Kailash Krishnan** *Consultant Physician* (KKrishnan)	G9L3P7 2 Feb 2022	**Principal investigator** ABCDEFGHIJKLMNOPQRSTUVWXY	7 Mar 2022 08:23 **Authorised** *Kailash Krishnan*
2	**Nikola Sprigg**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

SUMMARY

TICH-3 Key Points

- Pragmatic design and methods
- Inclusion criteria – ICH < 4.5 hours,
  Exclusion - massive ICH (low GCS < 5, HV < 60mls), contraindication to tranexamic acid (e.g. seizures)
- Emergency consent – initially oral followed by written consent
- Simple randomisation – use the lowest available treatment pack number
- QR code randomisation alert – inform trial office of enrolment
- Safety monitoring – safety events for 7 days, SAR and SUSAR
  Venous and arterial occlusive events and seizures
- Central postal/telephone follow up at 6 months

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
- Signed contracts between sites/national coordinators and the University of Nottingham

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

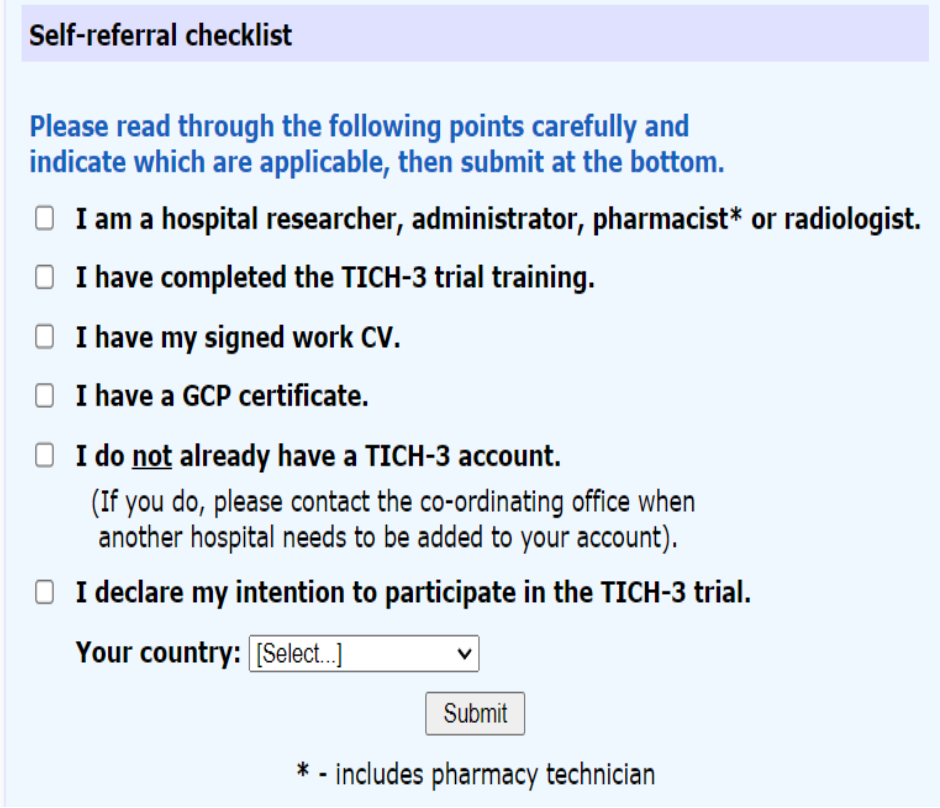
We will advise once everything has been checked and confirm that the site can open to TICH-3 by sending the regulatory green light email from the University of Nottingham sponsor.

- 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



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

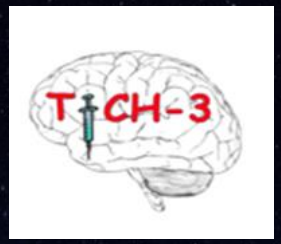
Trial Coordinating Centre contact information:

+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



Grazie
Qualsiasi domanda?