PROTOCOL AMEDMENT SUMMARY

Final version 3.1 25/04/2024

Protocol amendment SA_06_24 and MA_24_24

- SA_06_24 approved 22/04/2024 and MA_24_24 approved 26/04/2024

Please note SA_06_24 was approved for Protocol Final v3.0 28/02/2024 and then a minor amendment was submitted straight away under MHRA guidance to correct a few typographical errors. MA_24_24 was approved for Protocol Final v3.1 25/04/2024.

The protocol that sites must adhere by is now TICH-3 Protocol Final v3.1 25/04/2024.

Summary of changes

The aim of this protocol amendment is fivefold

1. To capture participant co-morbidity using the Clinical Frailty Score (CFS)
2. To measure post stroke fatigue using Fatigue Severity Scale (FSS-7)
3. To streamline the health economics/resource use form to improve data completion for patients
4. To add an eligibility checklist to facilitate enrolment when no one on delegation log available
5. Took this opportunity to make some minor text changes to the protocol, including updating the literature review and adding points of clarity to assist investigators

Enrolment consent when research team are not available

- We have received ethical approval to implement the eligibility checklist and enrolment form (SA_06_24 and MA_24_24)
- This form allow medics at the local site that are not on the TICH-3 delegation log and may not be GCP trained to be fully informed of the TICH-3 trial by reading the synopsis on the eligibility checklist and enrolment form and then using the checklist to assess their eligibility. If eligible the clinician will discuss with the potential participant and if consent is taken, they will be enrolled into the trial and will receive the trial treatment.
- All study materials, including protocol and related documents, will be available online and there will be a 24-hour telephone service, supported by medical consultant staff and trained coordinating centre research staff.
- Within each treatment pack is a prescribing and administration guide, the team member on site completes a recruitment alert (the team member does not need to be on the delegation log or have a log in for the TICH-3 website to complete) which emails all team members on the sites delegation log and the coordinating centre that a recruitment has taken place so that when the delegated research team are next on site they can follow up the participant as normal and obtain the follow on written consent.
- This approach is to ensure participants do not miss out on the opportunity to participate in the trial because they present when the research team are not present, particularly in smaller hospitals or outside working hours. This approach has the support of our stroke survivor group, and will be monitored closely, and any protocol violations reported to sponsor and the trial steering committee.
- We have worked very closely with our PPI group to develop and co-design this approach which we believe is proportional to risk benefit; tranexamic acid is a relatively low risk intervention, with an established safety profile, in the setting of a time critical medical emergency, ICH is a devastating condition with no effective drug treatment available.

Eligibility checklist and enrolment form FAQs (SA_06_24 and MA_24_24)

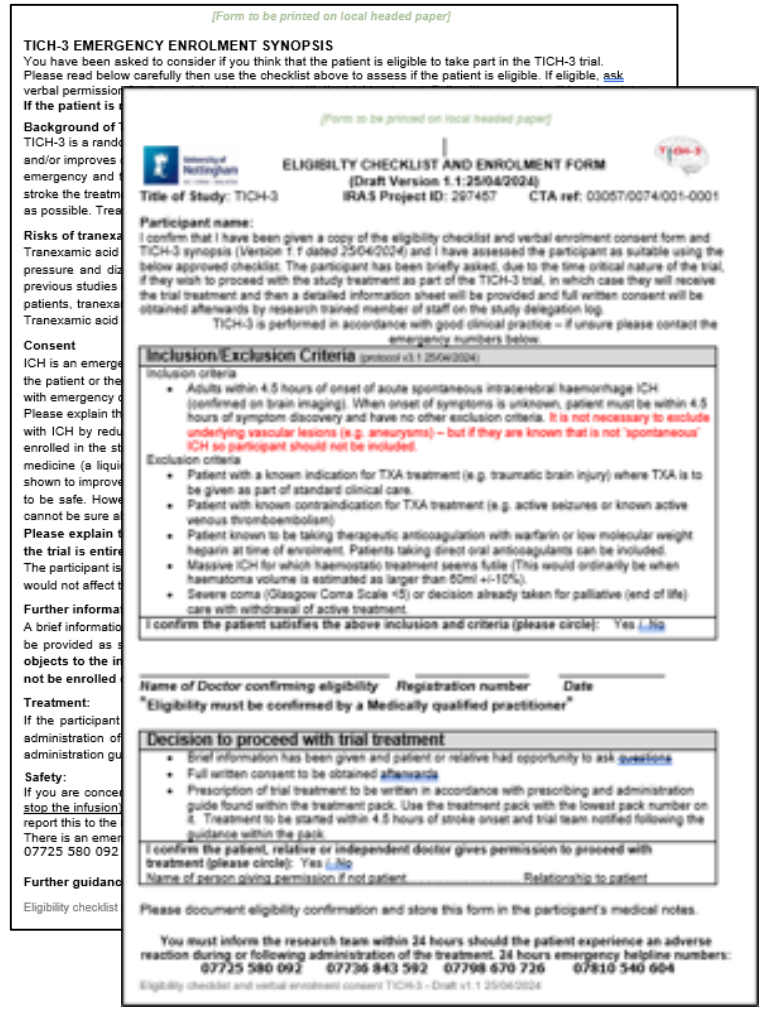
When can this method of consent be used? This is ONLY to be used when the delegated research team are not available to consent participants into TICH-3.

Who can take consent via this method? Site PI may delegate enrolment and administration of the IMP to appropriately trained members of the treating clinical team (not on TICH-3 delegation log, does not need to be GCP trained or have CV on file). There is no minimum grade doctor. Eligibility must be assessed by a medically qualified practitioner under the clinical trial regulations.

How is this consent process documented? This would be facilitated and documented by the use of an approved study synopsis, eligibility checklist and enrolment form which then would be stored in the participant's medical record.

What happens after this consent? Participant will be enrolled, and treatment administered by appropriate trained team members at the site. Full written consent would then be obtained as soon as practicable by a member of the local research team who is GCP trained and delegated the responsibility on the study delegation log.

Alternative text: screenshot of the eligibility checklist and enrolment form



[Form to be printed on local headed paper]

TICH-3 EMERGENCY ENROLMENT SYNOPSIS

You have been asked to consider if you think that the patient is eligible to take part in the TICH-3 trial. Please read below carefully then use the checklist above to assess if the patient is eligible. If eligible, ask verbal permission

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Further guidanc

Eligibility checklist

[Form to be printed on local headed paper]

University of Nottingham

ELIGIBILTY CHECKLIST AND ENROLMENT FORM

(Draft Version 1.1 25/04/2024)

Title of Study: TICH-3 IRAS Project ID: 297457 CTA ref: 03057/0074/001-0001

Participant name:

I confirm that I have been given a copy of the eligibility checklist and verbal enrolment consent form and TICH-3 synopsis (Version 1.1 dated 25/04/2024) and I have assessed the participant as suitable using the below approved checklist. The participant has been briefly asked, due to the time critical nature of the trial, if they wish to proceed with the study treatment as part of the TICH-3 trial, in which case they will receive the trial treatment and then a detailed information sheet will be provided and full written consent will be obtained afterwards by research trained member of staff on the study delegation log.

TICH-3 is performed in accordance with good clinical practice – if unsure please contact the emergency numbers below

Inclusion/Exclusion Criteria (protocol v3.1 25/04/2024)

Inclusion criteria

- Adults within 4.5 hours of onset of acute spontaneous intracerebral haemorrhage 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. It is not necessary to exclude underlying vascular lesions (e.g. aneurysms) – but if they are known that is not 'spontaneous' ICH so participant should not be included.

Exclusion criteria

- Patient with a known indication for TXA treatment (e.g. traumatic brain injury) where TXA is to be given as part of standard clinical care.
- Patient with known contraindication for TXA treatment (e.g. active seizures or known active venous thromboembolism)
- 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.
- Massive ICH for which haemostatic treatment seems futile (This would ordinarily be when haematoma volume is estimated as larger than 60ml +/-10%).
- Severe coma (Glasgow Coma Scale <5) or decision already taken for palliative (end of life) care with withdrawal of active treatment.

I confirm the patient satisfies the above inclusion and criteria (please circle): Yes / No

Name of Doctor confirming eligibility | Registration number | Date

Eligibility must be confirmed by a Medically qualified practitioner

Decision to proceed with trial treatment

- Brief information has been given and patient or relative had opportunity to ask questions
- Full written consent to be obtained afterwards
- Prescription of trial treatment to be written in accordance with prescribing and administration guide found within the treatment pack. Use the treatment pack with the lowest pack number on it. Treatment to be started within 4.5 hours of stroke onset and trial team notified following the guidance within the pack.

I confirm the patient, relative or independent doctor gives permission to proceed with treatment (please circle): Yes / No

Name of person giving permission if not patient | Relationship to patient

Please document eligibility confirmation and store this form in the participant's medical notes.

You must inform the research team within 24 hours should the patient experience an adverse reaction during or following administration of the treatment. 24 hours emergency helpline numbers: 07725 580 092 07736 843 592 07798 670 726 07810 540 604

Eligibility checklist and verbal enrolment consent TICH-3 - Draft v1.1 25/04/2024

Consent process flowchart

Trained staff on TICH-3 delegation log available

Verbal consent obtained by trained staff on TICH-3 delegation log (code J)

No trained staff on delegation log available

Clinical team use eligibility checklist and enrolment form

Open next lowest numbered treatment pack to randomise.

Prescribe and administer trial treatment.

QR code recruitment alert.

Document in medical notes eligibility and consent process.

When research team next on site

Follow on written consent obtained by trained staff on TICH-3 delegation log (code Z)

Add participant to TICH-3

Add a new participant

Upload consent form to secure vault.

Collect contact details and add to secure vault.

Begin eCRF data collection.

Enrolment form eCRF changes SA_06_24

1. Collect VAS score

You do not need to backfill data for existing participants, please collect for participants recruited after implementation of SA_06_24.

I7a	Imaginable health state points score *Best imaginable=100 / worst imaginable=0*		☐ Not done ☐ Not known
I7b	Who answered the question?	☐ Participant ☐ Carer	☐ Not applicable ☐ Not known

2. Collect pre-stroke baseline CFS

You do not need to backfill data for existing participants, please collect for participants recruited after implementation of SA_06_24.

Section J: Clinical frailty scale

Pre-morbid clinical frailty scale, judged on their ability approx. 2 weeks prior to admission

Scoring guide: https://stroke.nottingham.ac.uk/tich-3/links/CFS

J1	Clinical frailty scale	☐ 1 - Very fit ☐ 2 - Well ☐ 3 - Managing well ☐ 4 - Vulnerable ☐ 5 - Mildly frail ☐ 6 - Moderately frail ☐ 7 - Severely frail ☐ 8 - Very severely frail ☐ 9 - Terminally ill	☐ Not done ☐ Not known

3. If eligibility and enrolment form used please state this on question A2

A2	Please give the name of the investigator taking initial consent for enrolment in the trial	*Where a medic (non-investigator) took consent out of hours, please write 'Consent by eligibility check list'.*	☐ Not known