University of Nottingham
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ISRCTN97695350

TRANEXAMIC ACID FOR INTRACEREBRAL HAEMORRHAGE: TICH-3 TRIAL

UPDATE MEETING

Professor Nikola Sprigg and Brittany Hare

On behalf TICH-3 Trial Team

Wednesday 17TH April 2024

Agenda

1. UK Recruitment update
2. Protocol amendment SA06 (pre-approval)
3. Out of hours recruitment
4. Electronic delegation logs
5. Enrolling Investigator Webinar
6. Contact details
7. How to enter missing data on eCRF
8. Co-enrolment with TICH-3
9. Upcoming events
10. Thank you
11. Questions?

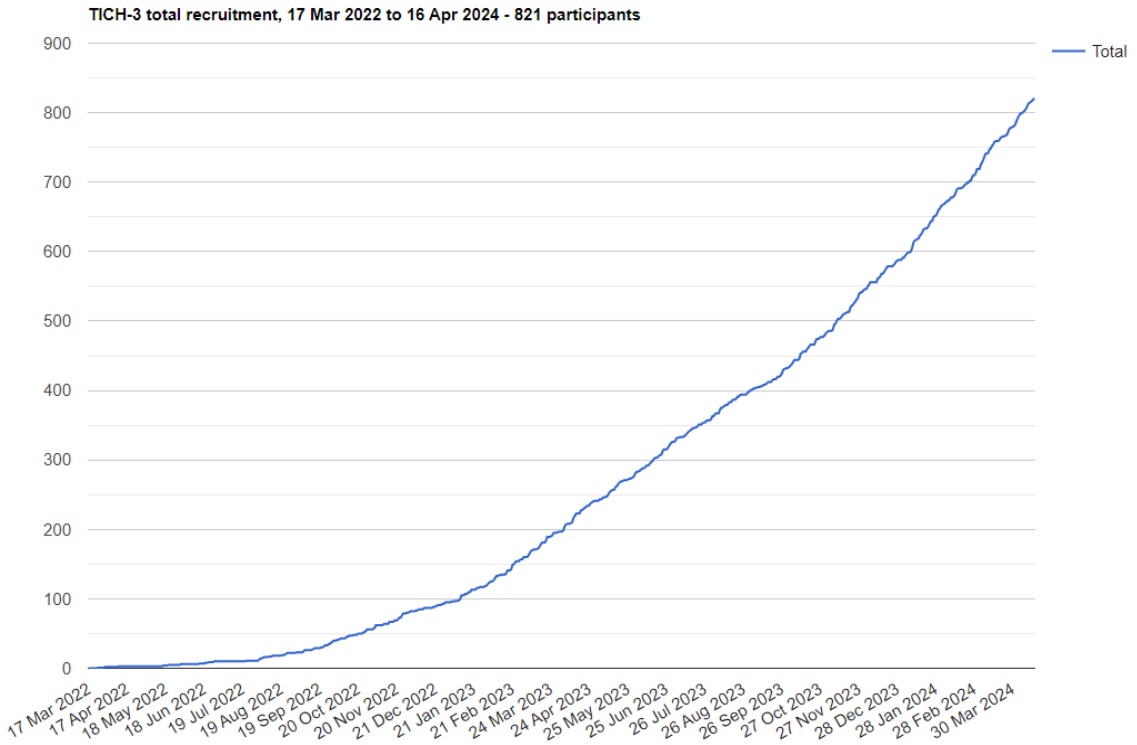
UK Recruitment Update

Site Status *(updated 16/04/2024)*	No.
Sites open to recruitment	70
Recruited *(528 participants in total)*	65
Not recruited	5
In set up	4
Initial feasibility assessments	6
Declined for now (capacity issues)	6
Withdrawn	9

Alternative text: map of UK with the UK sites active for recruitment plotted

International Recruitment Update

(updated 16/04/2024)	Sites open	Recruited
Malaysia	14/14	171
Finland	1/1	44
Georgia	3/4	33
Denmark	1/4	21
Italy	2/25	6
France	8/16	19
Ireland	1/6	1
Sweden	1/3	0
Totals	31/70	293



800!

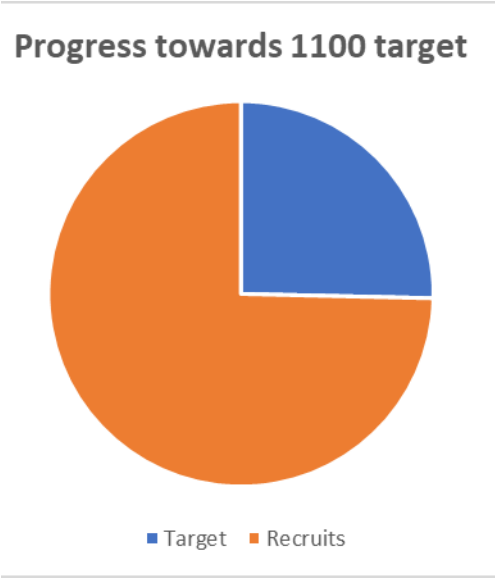
Combined total recruitment: 821

We have reached over 800 participants!

Thank you for all your recruitment into the TICH-3 trial, we couldn't do it without you!

Pilot progression review: updated targets

- Data to be reviewed again end of August 2024
- HTA 1,100 ppts and 120 sites (75 UK) by 31/08/2024



We are 74.64% towards the target participant recruitment

Project Month	Month	New Target	Actual No. sites
29	September-23	55	57
30	October-23	N/A	57
31	November 23	60	60
32	December 23	62	63
33	January 24	64	66
34	February 24	65	67
35	March 24	66	70
36	April 24	67	
37	May 24	68	
38	June 24	70	
39	July 24	73	
40	August 24	75	

Protocol amendment SA06 (PRE-APPOVAL)

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 out of hours
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.

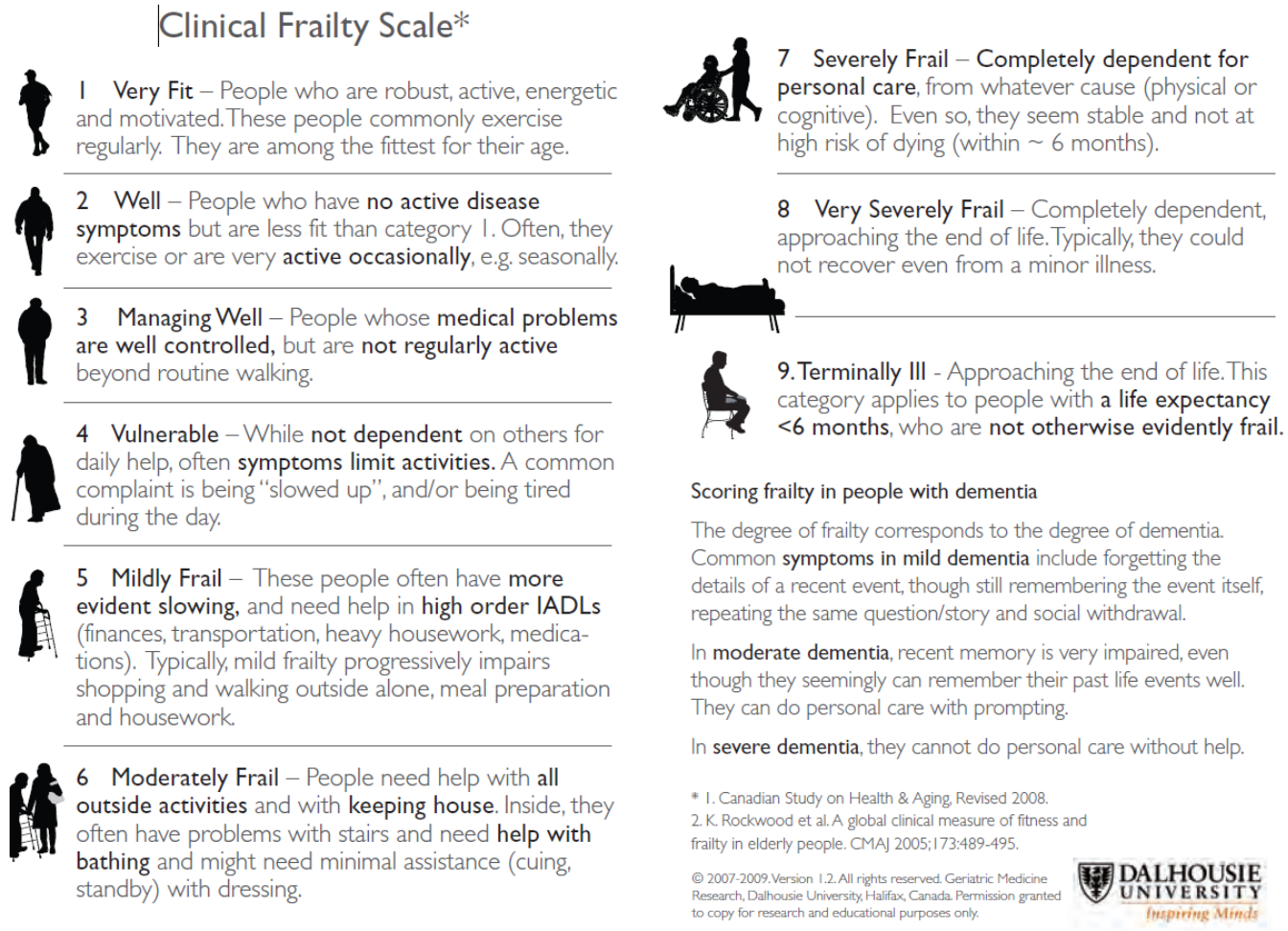
We have HRA and REC approval, pending MHRA approval.

We will notify all the sites directly once ethical approvals have been received and provide information of how to implement the amendment with the relevant documentation.

Protocol amendment – changes at sites

1. Collect pre-stroke baseline CFS

- This scale will be added to the enrolment eCRF
- You do not need to backfill data for existing participants but please collect for future participants once implemented



Clinical Frailty Scale*

1 **Very Fit** – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 **Well** – People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g. seasonally.

3 **Managing Well** – People whose **medical problems are well controlled,** but are **not regularly active** beyond routine walking.

4 **Vulnerable** – While **not dependent** on others for daily help, often **symptoms limit activities.** A common complaint is being "slowed up", and/or being tired during the day.

5 **Mildly Frail** – These people often have **more evident slowing,** and need help in **high order IADLs** (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 **Moderately Frail** – People need help with **all outside activities** and with **keeping house**. Inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.

7 **Severely Frail** – **Completely dependent for personal care**, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8 **Very Severely Frail** – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9. **Terminally Ill** - Approaching the end of life. This category applies to people with **a life expectancy <6 months**, who are **not otherwise evidently frail.**

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia**, they cannot do personal care without help.

* 1. Canadian Study on Health & Aging, Revised 2008.
2. K. Rockwood et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-495.

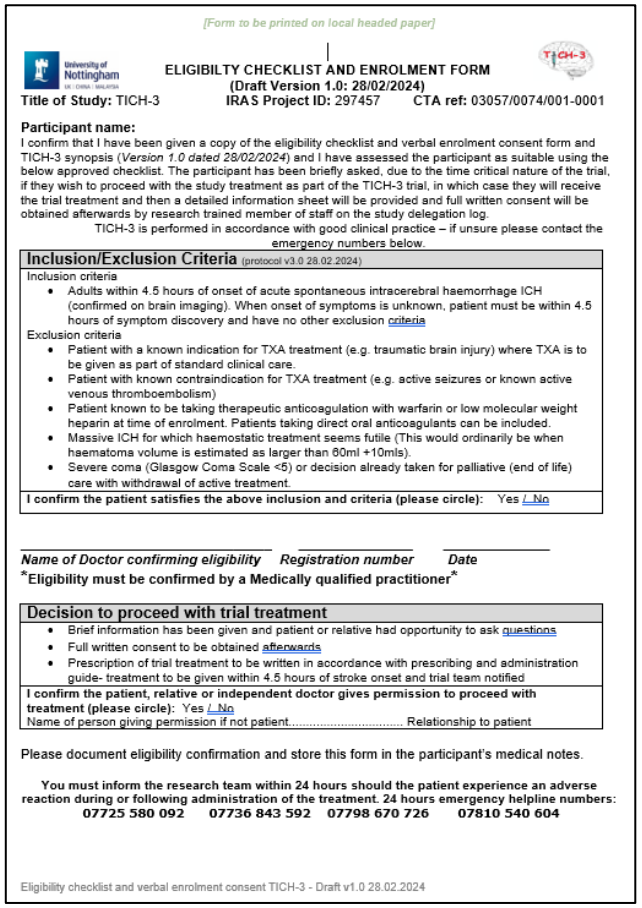
DALHOUSIE UNIVERSITY Inspiring Minds

Alternative text: validated CFS scale image of scoring values

Protocol amendment – changes at sites

2. Eligibility checklist

- This is only to be used when the delegated research team are not available to consent patient into TICH-3.
- 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).
- This would be facilitated and documented by the use of an approved study synopsis, eligibility checklist and enrolment form (see form pictured).
- 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.



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University of Nottingham

ELIGIBILTY CHECKLIST AND ENROLMENT FORM
(Draft Version 1.0: 28/02/2024)

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 1.0 dated 28/02/2024*) 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 v3.0 28.02.2024)

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

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 +10mls).
- 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- treatment to be given within 4.5 hours of stroke onset and trial team notified

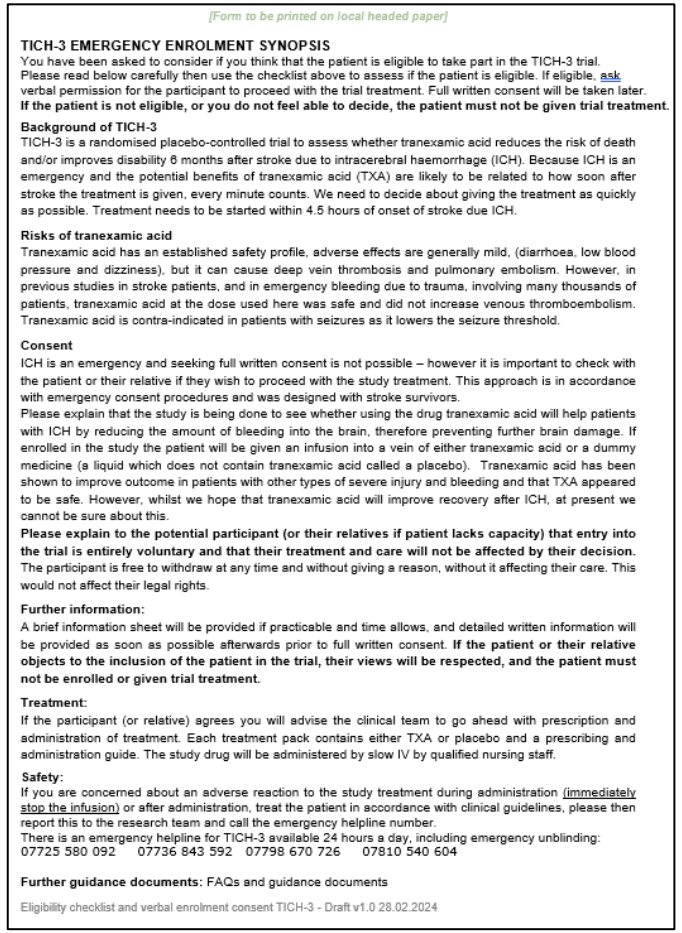
I confirm the patient, relative or independent doctor gives permission to proceed with treatment (please circle): Yes / No
Name of person giving permission if not patient..... Relationship to patient

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 v1.0 28.02.2024

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 for the participant to proceed with the trial treatment. Full written consent will be taken later. **If the patient is not eligible, or you do not feel able to decide, the patient must not be given trial treatment.**

Background of TICH-3

TICH-3 is a randomised placebo-controlled trial to assess whether tranexamic acid reduces the risk of death and/or improves disability 6 months after stroke due to intracerebral haemorrhage (ICH). Because ICH is an emergency and the potential benefits of tranexamic acid (TXA) are likely to be related to how soon after stroke the treatment is given, every minute counts. We need to decide about giving the treatment as quickly as possible. Treatment needs to be started within 4.5 hours of onset of stroke due ICH.

Risks of tranexamic acid

Tranexamic acid has an established safety profile, adverse effects are generally mild, (diarrhoea, low blood pressure and dizziness), but it can cause deep vein thrombosis and pulmonary embolism. However, in previous studies in stroke patients, and in emergency bleeding due to trauma, involving many thousands of patients, tranexamic acid at the dose used here was safe and did not increase venous thromboembolism. Tranexamic acid is contra-indicated in patients with seizures as it lowers the seizure threshold.

Consent

ICH is an emergency and seeking full written consent is not possible – however it is important to check with the patient or their relative if they wish to proceed with the study treatment. This approach is in accordance with emergency consent procedures and was designed with stroke survivors.

Please explain that the study is being done to see whether using the drug tranexamic acid will help patients with ICH by reducing the amount of bleeding into the brain, therefore preventing further brain damage. If enrolled in the study the patient will be given an infusion into a vein of either tranexamic acid or a dummy medicine (a liquid which does not contain tranexamic acid called a placebo). Tranexamic acid has been shown to improve outcome in patients with other types of severe injury and bleeding and that TXA appeared to be safe. However, whilst we hope that tranexamic acid will improve recovery after ICH, at present we cannot be sure about this.

Please explain to the potential participant (or their relatives if patient lacks capacity) that entry into the trial is entirely voluntary and that their treatment and care will not be affected by their decision. The participant is free to withdraw at any time and without giving a reason, without it affecting their care. This would not affect their legal rights.

Further information:

A brief information sheet will be provided if practicable and time allows, and detailed written information will be provided as soon as possible afterwards prior to full written consent. **If the patient or their relative objects to the inclusion of the patient in the trial, their views will be respected, and the patient must not be enrolled or given trial treatment.**

Treatment:

If the participant (or relative) agrees you will advise the clinical team to go ahead with prescription and administration of treatment. Each treatment pack contains either TXA or placebo and a prescribing and administration guide. The study drug will be administered by slow IV by qualified nursing staff.

Safety:

If you are concerned about an adverse reaction to the study treatment during administration (immediately stop the infusion) or after administration, treat the patient in accordance with clinical guidelines, please then report this to the research team and call the emergency helpline number.
There is an emergency helpline for TICH-3 available 24 hours a day, including emergency unblinding:
07725 580 092 07736 843 592 07798 670 726 07810 540 604

Further guidance documents: FAQs and guidance documents

Eligibility checklist and verbal enrolment consent TICH-3 - Draft v1.0 28.02.2024

Out of hours recruitment

Out of hours recruitment is key to the TICH-3 trial in an attempt to reach the large 3,900 UK recruitment target

29% (154/528) all UK recruitment is out of hours

- 89 Monday - Friday
- 65 Saturday – Sunday

Congratulations to the sites that recruited out of hours and over a bank holiday weekend!

- Southmead Hospital 1st recruit
- Kings Mill Hospital 2nd recruit
- UCLH
- Craigavon Area Hospital

We hope the eligibility checklist and enrolment form will maximise chances of recruitment and out of hours and give every participant opportunity to receive trail treatment.

Electronic delegation logs

- Can all PIs please complete reviews of your site's electronic delegation log
  a. Please check if there are any team members pending approval onto the delegation log and action as appropriate
  b. Please sign team members off the delegation log as role finished if they have left the team, you do this by selecting 'role finished' on the drop down box and then enter your password and click submit at the bottom of the page

  c. Please guide new team members (e.g. registrars) to complete training https://stroke.nottingham.ac.uk/sif/docs/?sid=TICH-3 and then complete the self-referral https://stroke.nottingham.ac.uk/sif/live/sif_training_self-referral.php?sid=TICH-3&redirected=on to go onto the delegation log

- It is good practice to nominate a deputy PI who will also be able to authorise the delegation log, please let us know which delegated team member you would like to nominate as deputy PI

Enrolling Investigator Webinar

- We have some upcoming Enrolling Investigator Webinars that will serve as a refresher to the existing team members on the delegation log and also can be attended by new team members to get onto your sites TICH-3 electronic delegation log e.g. new registrars, ED doctors. The more enrolling investigators there are on the delegation log maximises the chances of participant recruitment.

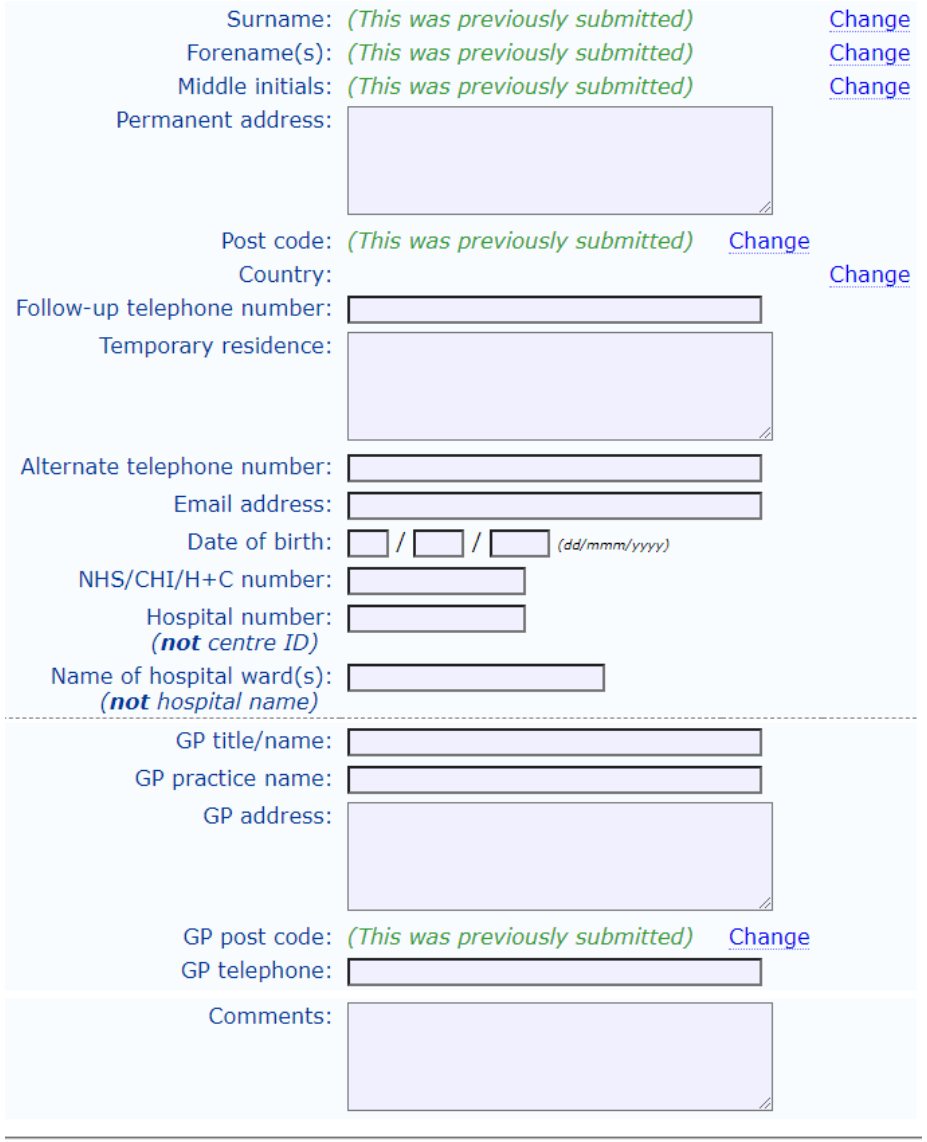
- These 30 minute training webinars are intended for team members whose role will be to confirm eligibility for potential participants and to then take consent for enrolment into the TICH-3 trial. These training webinars will be a presentation for around 15 minutes and then 15 minutes for any questions.

- **Could you please let us know your email address or the email addresses of the team members at your site and which webinar you/they would like to attend and we will add you/them to the invite list. Please ask them to block the time in the calendar and we will send the direct teams invite to their calendars a few days before the meeting.**

- Wednesday 15th May 12.30 – 1pm Click here to join the meeting

- For new team members, once training has been completed (by attending one of the above webinars) please use the self-referral link https://stroke.nottingham.ac.uk/tich-3/?ZSelfRef to create your account for the TICH-3 website, the PI will then be notified by email to authorise you onto the online delegation log.

Contact details


Surname: (This was previously submitted) Change
Forename(s): (This was previously submitted) Change
Middle initials: (This was previously submitted) Change
Permanent address:
Post code: (This was previously submitted) Change
Country: Change
Follow-up telephone number:
Temporary residence:
Alternate telephone number:
Email address:
Date of birth: / / (dd/mmm/yyyy)
NHS/CHI/H+C number:
Hospital number: (**not** centre ID)
Name of hospital ward(s): (**not** hospital name)
GP title/name:
GP practice name:
GP address:
GP post code: (This was previously submitted) Change
GP telephone:
Comments:

- Please obtain as much information as possible for the participant contact details to give as many options as possible to contact for day 180 follow up
- Next of kin details are really important as a lot of these participants unfortunately do not have capacity

Alternative text: screenshot of the eCRF where contact details are entered

How to enter missing data on eCRF

Guidance for completing eCRF data entry and missing data

Click here for a link to the help guide to completing electronic case report forms and missing data

Guidance for completing data corrections

Click here for a link to the document for completing data corrections

Co-enrolment with TICH-3

Co-enrolment is permitted, and sponsor approved for the following University of Nottingham sponsored trials (contract with site not required)

- MAPS-2 (IC now up-to 24 hours to enrol)
- PhEAST (IC now 2 – 31 days)

Co-enrolment has been agreed with the following non-University of Nottingham sponsored CTIMPs (contract with site REQUIRED before co-enrolment is permitted)

- TRIDENT
- ENRICH-AF (MASTER CONTRACT NOW AGREED)

If you are taking part in either trial above, please let us know so your site (PI and R&I) can document they agree to co-enrolment at your site.

NEW CO-ENROLMENT AGREEMENT IMPLEMENTED FOR NEW TRIALS, does not need localising at each site, the master agreement signed by the 2 trials CIs – please get in touch to discuss any co-enrolment.

Please let us know if there are any other trials you may wish to co-enrol with so that we can begin the contracts/agreement process.

CO-ENROLMENT MUST NOT TAKE PLACE UNLESS THERE IS AN AGREEMENT IN PLACE

There is a co-enrolment log on the TICH-3 documents page https://stroke.nottingham.ac.uk/sif/docs/?sid=TICH-3

Upcoming events

- European Stoke Organisation Conference (ESOC) 15-17 May 2024, Switzerland
- International Clinical Trials Methodology Conference (ICTMC), Edinburgh, September 2024
- World Stroke Congress (WSC) – 26 Oct 2024, Abu Dabi
- UK Stroke Forum (UKSF) December 2024, Liverpool

Acknowledgements

TICH-3 would not be possible without:

All our participants and their families – we thank them for agreeing to take part and help us try to find better treatments for stroke due to intracerebral haemorrhage.

Thank you also to:

- TICH-3 Investigators
- TICH-3 staff Nottingham Stroke Trials Unit, Nottingham Clinical Trials Unit
- TICH-3 co-applicants
- Collaborators including Andrew Willis
- Nottingham Stroke Research Partnership Group - PPIE
- TICH-3 trial steering committee, data monitoring committee
- Funders – NIHR HTA

The Centre for Ethnic Health Research
national centre for tackling health inequalities

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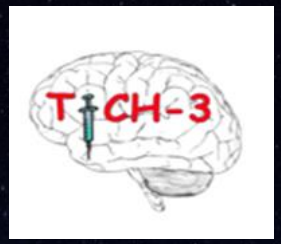

Any questions?

Q & A (part 2)

Question: Is SWAT to be shown to participant or family?

Answer: NS response, can use it for both participant or relative and at both timepoints, initial verbal enrolment consent or follow-on written consent. Feedback from site: We do not tend to use it before verbal consent as the video is 4 minutes long”

Question: Can we obtain written consent at enrolment?

Answer: Yes but this may delay treatment and therefore this is why we have ethically approved process for verbal enrolment consent in the first instance.

Question: Was their PPI input with regards to the protocol amendment?

Answer: Niki is part of research partner group which meets every month and yes the PPI group felt very strongly that every person should have equal opportunity to patriciate in research and therefore the protocol amendment allows for clinic team to enrol participants when the research team are not available.

Question: Good to hear about protocol amendment. Is there any need for CV/GCP?

Answer: The member of clinical team does not need to have GCP or CV on file.