University of Nottingham
UK | CHINA | MALAYSIA

ISRCTN97695350

TRANEXAMIC ACID FOR INTRACEREBRAL HAEMORRHAGE: TICH-3 TRIAL

INVESTIGATOR MEETING

Professor Nikola Sprigg

On behalf TICH-3 Trial Team

12th October 2022

Agenda

1. Recruitment update
2. Eligibility FAQs
3. Trial delivery reminders
4. What to do in the event of a protocol violation
5. Delegation log
6. ICTMC 2022 Conference
7. Upcoming events
8. Thank you
9. Questions?

Recruitment Update

Site Status	Number
Sites open to recruitment	33
Recruited *(43 participants in total)*	18
Not – recruited	15
In set up	21
Initial feasibility assessments	10
Declined for now (capacity issues)	12
Withdrawn	7

Eligibility FAQs

- Is there a minimum cut off for haematoma volume measurement?

No, there is no lower limit.

- If the participant has had a previous ICH can they be enrolled?

Yes, recurrent bleeds are common, if the spontaneous ICH is classed as a new event then they can be enrolled. E.g. if discharged from hospital and then readmitted.

- Can a patient be enrolled if they are taking/have taken a DOAC recently?

Yes, patient can be enrolled as long as the last dose of DOAC was given more than 48 hours before recruitment.

- Does the IMP have to be given within the 4.5 hours timeframe?

Yes, the IMP must have started within 4.5 from symptom onset. Due to simple randomisation process and emergency consent procedure of oral consent the IMP can be administered ASAP when the patient is assessed to be eligible.

Trial delivery reminders

- Written consent after initial consent given by independent doctor

If it is not possible to obtain written consent i.e. relatives not contactable, patient lacks capacity, the patient will remain in the trial unless they/relative subsequently express a wish to withdraw from the trial. Contact details, documents and CRF data should be completed in the absence of a written consent form as permission for this was granted in the initial consent.

- Add participant to TICH-3 database

Participant should be added to the database as soon as possible after the IMP administration has begun (if over weekend or evening as soon as possible when research team on site) and consent form uploaded as soon as possible as well as contact details.

- Participant dies prior to discharge

Please complete SAE as soon as possible and also complete the discharge/death eCRF.

- Only prespecified safety events need to be reported as SAEs

Please see WPD 010 SAE reporting on the TICH-3 documents page https://stroke.nottingham.ac.uk/tich-3/docs/ which will guide you on what does need reporting as an SAE.

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.

Sponsors SOPS on the document page; see TA016 Serious GCP Breach Reporting

We have had a protocol violation where a TICH-3 treatment pack was given to a non-trial participant. The site actioned this very quickly on being made aware the violation had taken place and reported this to the coordinating centre and steps have been put into place at the site to ensure this does not happen again.

Delegation log

New team members

New member of the team can be added to the delegation log at any point as long as the training has been completed.

Enrolling investigators

It would be worth encouraging more team members to join the TICH-3 trial team who can take enrolment consent. There is a streamlined version of the 'Enrolling Investigator Training' for team members whose only role will be to take enrolment consent.

https://stroke.nottingham.ac.uk/docs/TICH-3/UK_site_training/TICH-3%20Enrolling%20Investigator%20Training%20Final%20v1.7%2028.07.2022.pdf

- Once the training is complete please return this to the co-ordinating centre TICH-3@nottingham.ac.uk

Deputy PI

Each site can nominate one deputy PI, which is advisable, this team member will have the role to approve the delegation log in the absence of the PI.

- Please inform the co-ordinating centre of who you would like to nominate as deputy PI

ICTMC 2022 Conference

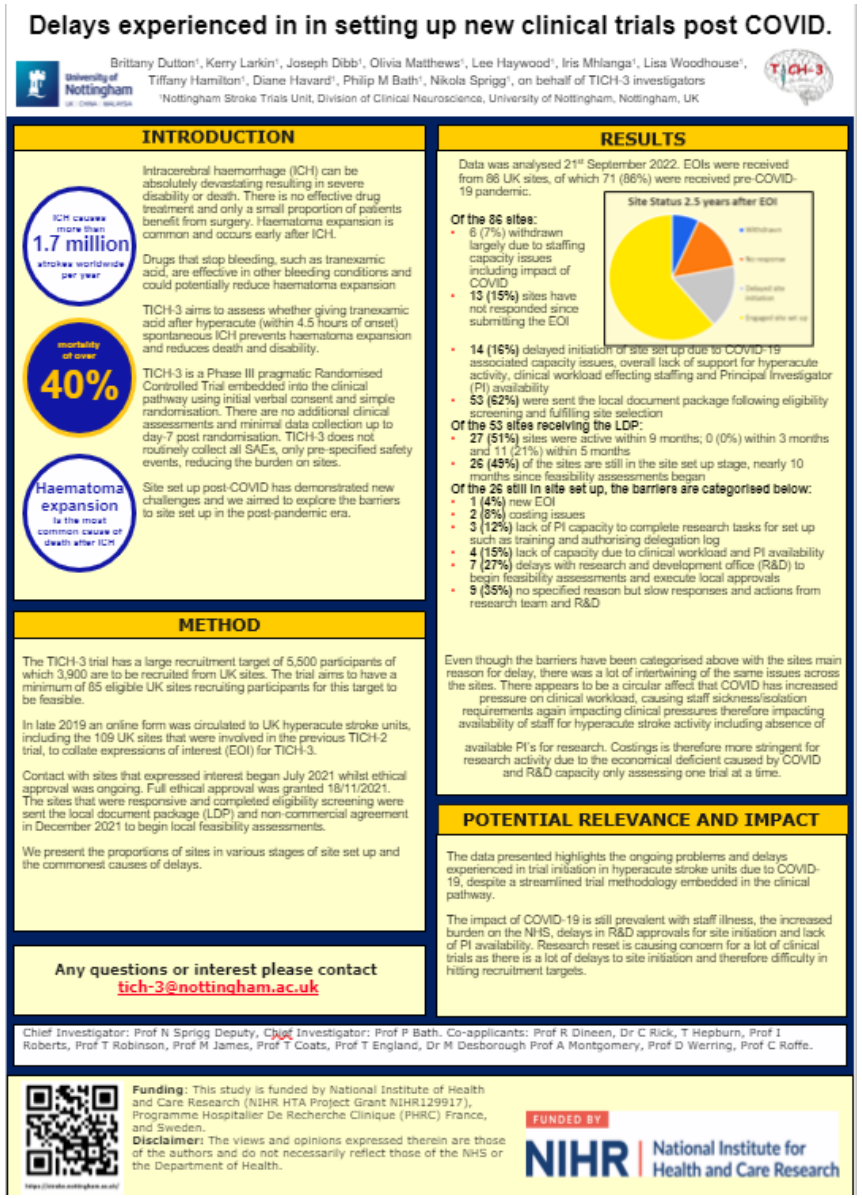
Members from TICH-3 trial team attended International Clinical Trials Methodology Conference 2022

- Poster: Delays experienced in in setting up new clinical trials post COVID

➢ View the poster on the TICH-3 documents page https://stroke.nottingham.ac.uk/sif/docs/?sid=TICH-3

- Oral presentation: Effectiveness of a simple recruitment animation for increasing rates of recruitment and retention of ethnic minority participants in a large multicentre stroke trial: A SWAT

➢ Positive feedback SWAT and trial design



Delays experienced in in setting up new clinical trials post COVID.

Brittany Dutton[1], Kerry Larkin[1], Joseph Dibb[1], Olivia Matthews[1], Lee Haywood[1], Iris Mhlanga[1], Lisa Woodhouse[1], Tiffany Hamilton[1], Diane Havard[1], Philip M Bath[1], Nikola Sprigg[1], on behalf of TICH-3 investigators
[1]Nottingham Stroke Trials Unit, Division of Clinical Neuroscience, University of Nottingham, Nottingham, UK

INTRODUCTION

ICH causes more than 1.7 million strokes worldwide per year

mortality of over 40%

Haematoma expansion is the most common cause of death after ICH

Intracerebral haemorrhage (ICH) can be absolutely devastating resulting in severe disability or death. There is no effective drug treatment and only a small proportion of patients benefit from surgery. Haematoma expansion is common and occurs early after ICH.

Drugs that stop bleeding, such as tranexamic acid, are effective in other bleeding conditions and could potentially reduce haematoma expansion

TICH-3 aims to assess whether giving tranexamic acid after hyperacute (within 4.5 hours of onset) spontaneous ICH prevents haematoma expansion and reduces death and disability.

TICH-3 is a Phase III pragmatic Randomised Controlled Trial embedded into the clinical pathway using initial verbal consent and simple randomisation. There are no additional clinical assessments and minimal data collection up to day-7 post randomisation. TICH-3 does not routinely collect all SAEs, only pre-specified safety events, reducing the burden on sites.

Site set up post-COVID has demonstrated new challenges and we aimed to explore the barriers to site set up in the post-pandemic era.

METHOD

The TICH-3 trial has a large recruitment target of 5,500 participants of which 3,900 are to be recruited from UK sites. The trial aims to have a minimum of 85 eligible UK sites recruiting participants for this target to be feasible.

In late 2019 an online form was circulated to UK hyperacute stroke units, including the 109 UK sites that were involved in the previous TICH-2 trial, to collate expressions of interest (EOI) for TICH-3.

Contact with sites that expressed interest began July 2021 whilst ethical approval was ongoing. Full ethical approval was granted 18/11/2021. The sites that were responsive and completed eligibility screening were sent the local document package (LDP) and non-commercial agreement in December 2021 to begin local feasibility assessments.

We present the proportions of sites in various stages of site set up and the commonest causes of delays.

Any questions or interest please contact tich-3@nottingham.ac.uk

RESULTS

Data was analysed 21st September 2022. EOIs were received from 86 UK sites, of which 71 (86%) were received pre-COVID-19 pandemic.

Site Status 2.5 years after EOI

Of the 86 sites:
- 6 (7%) withdrawn largely due to staffing capacity issues including impact of COVID
- 13 (15%) sites have not responded since submitting the EOI
- 14 (16%) delayed initiation of site set up due to COVID-19 associated capacity issues, overall lack of support for hyperacute activity, clinical workload effecting staffing and Principal Investigator (PI) availability
- 53 (62%) were sent the local document package following eligibility screening and fulfilling site selection

Of the 53 sites receiving the LDP:
- 27 (51%) sites were active within 9 months; 0 (0%) within 3 months and 11 (21%) within 5 months
- 26 (49%) of the sites are still in the site set up stage, nearly 10 months since feasibility assessments began

Of the 26 still in site set up, the barriers are categorised below:
- 1 (4%) new EOI
- 2 (8%) costing issues
- 3 (12%) lack of PI capacity to complete research tasks for set up such as training and authorising delegation log
- 4 (15%) lack of capacity due to clinical workload and PI availability
- 7 (27%) delays with research and development office (R&D) to begin feasibility assessments and execute local approvals
- 9 (35%) no specified reason but slow responses and actions from research team and R&D

Even though the barriers have been categorised above with the sites main reason for delay, there was a lot of intertwining of the same issues across the sites. There appears to be a circular affect that COVID has increased pressure on clinical workload, causing staff sickness/isolation requirements again impacting clinical pressures therefore impacting availability of staff for hyperacute stroke activity including absence of available PI's for research. Costings is therefore more stringent for research activity due to the economical deficient caused by COVID and R&D capacity only assessing one trial at a time.

POTENTIAL RELEVANCE AND IMPACT

The data presented highlights the ongoing problems and delays experienced in trial initiation in hyperacute stroke units due to COVID-19, despite a streamlined trial methodology embedded in the clinical pathway.

The impact of COVID-19 is still prevalent with staff illness, the increased burden on the NHS, delays in R&D approvals for site initiation and lack of PI availability. Research reset is causing concern for a lot of clinical trials as there is a lot of delays to site initiation and therefore difficulty in hitting recruitment targets.

Chief Investigator: Prof N Sprigg Deputy, Chief Investigator: Prof P Bath. Co-applicants: Prof R Dineen, Dr C Rick, T Hepburn, Prof I Roberts, Prof T Robinson, Prof M James, Prof T Coats, Prof T England, Dr M Desborough Prof A Montgomery, Prof D Werring, Prof C Roffe.

Funding: This study is funded by National Institute of Health and Care Research (NIHR HTA Project Grant NIHR129917), Programme Hospitalier De Recherche Clinique (PHRC) France, and Sweden.
Disclaimer: The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NHS or the Department of Health.

FUNDED BY NIHR | National Institute for Health and Care Research

Upcoming events

UK Stroke Forum 2022, ACC Liverpool

Join our CIs face to face at the UK Stroke Forum for the Nottingham Stroke Trials Unit Investigator Meetings:

- TICH-3: Thursday 1st December 10:35 - 11.05 GMT, Room 12

Baseline CT Scan upload training

Our trial medic Chaamanti will provide some training for uploading baseline CT scans to the TICH-3 website at the next investigator meeting.

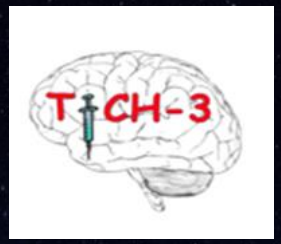
Next TICH-3 Investigator meeting

- Have you found these sessions beneficial?
- Are monthly sessions useful?

Thank You

The TICH-3 trial would not be possible without the support of our investigators, thank you very much to everyone that has joined us thus far!

University of Nottingham
UK | CHINA | MALAYSIA



Any questions?

Co-enrolment update

- **MAPS-2** – Professor Christine Roffe and Professor Nikola Sprigg supported co-enrolment for TICH-3 and MAPS-2 and co-enrolment can occur. No explicit contract is needed.

- **TRIDENT** – Open to co-enrol – please contact us if you wish to co-enrol as there will need to be a contract signed before co-enrolment can take place.

- **ENRICH AF** – close to obtaining permission to co-enrol

Q&A during session

Q: Is the 4.5 hours for randomisation from wake up?
A: From symptom discovery

Q: Can a patient be enrolled if on Warfarin?
A: To be excluded needs to be treatment dose anticoagulation

Q: Can a Research Nurse be Deputy PI?
A: Yes, if they've has appropriate training and has some clinical role and dependent on how senior the Research Nurse is. Please discuss with us on ad hoc basis if unsure

Q: Can a Stroke Research Nurse with non- medical prescribing qualification be able to prescribe the study drug?
A: Yes, anyone appropriate trained can prescribe the IMP

Q&A during session

Q: How far to push for relative's consent after initial enrolment consent been given by an independent doctor?

A: If you think the prognosis is poor, might not be appropriate to seek relative's consent. Must make as much reasonable attempt as possible and document this. Further input from Alan in Edinburgh; if we have independent doctor consent, we are covered legally that do not need to have consent from relative. It is stated in protocol that independent doctor consent means participant remains in the trial unless there is objection.

Q: Many HSRCs struggle to create/maintain PPI groups

A: Nottingham set theirs up 15 years ago and there is a core group and virtual group. There is a monthly virtual meet, requires coordination but extremely rewarding. NIHR provides funding for PPI and this is worth exploring.

Feedback on investigator meetings

We asked for feedback on

- Have you found these sessions beneficial?
- Are monthly sessions useful? Would a session in November be beneficial?

Responses

November/December, I think November good, Beginning of December May be good, November's good for us too, 2monthly ?, yes or beginning of December, November would be good for those not able to attend UKSF, Monthly is good. If it is every month then if someone misses one month they can dial into the next monthly one, Having one in Nov would be nice, November would be useful, These sessions are really helpful, thank you! November would be great!, These sessions are very useful, Thank you. Very useful meeting, very informative session, Thank you so much. Really helpful update.

The general consensus was that monthly session would be useful so will plan the next one for November. Invite to follow.