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ISRCTN97695350

TRANEXAMIC ACID FOR INTRACEREBRAL HAEMORRHAGE: TICH-3 TRIAL

INVESTIGATOR MEETING

Brittany Hare and Nikola Sprigg

On behalf TICH-3 Trial Team

22nd November 2023

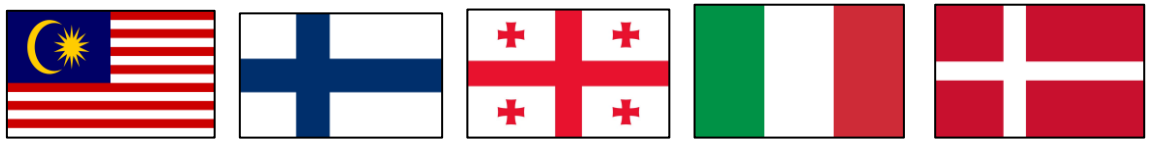
Agenda

1. Recruitment update
2. Out of hours recruitment – sharing best practice
3. Pilot progression review
4. Upcoming protocol amendment
5. TICH-3 Eligibility
6. ABC/2 Rule
7. FAQs
8. Standard of care for ICH
9. eCRF changes
10. Associate PI Scheme
11. Co-enrolment with TICH-3
12. Upcoming events
13. Thank you
14. Questions?

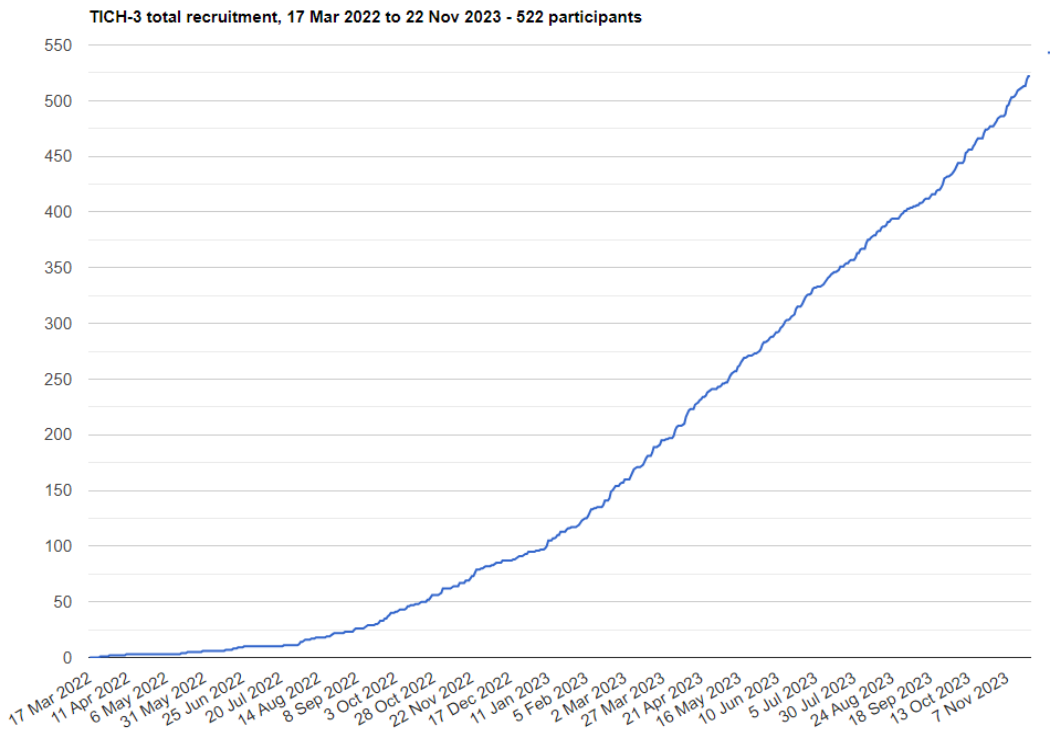
UK Recruitment Update

Site Status	No.
Sites open to recruitment	*60*
Recruited *(378 participants in total)*	*56*
Not recruited	*4*
In set up	10
Initial feasibility assessments	6
Declined for now (capacity issues)	8
Withdrawn	11

International Recruitment Update



	Sites open	Recruited
Malaysia	13/14	113
Finland	1/1	15
Georgia	3/4	13
Denmark	1/4	1
Italy	1/25	2
Totals	19	144



Combined total recruitment: 522

We have reached over 500 participants!

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

Out of hours recruitment – sharing best practice

As of 13/11/2023 107/371 (29%) recruited out of hours

- QMC recruited 7/21
- University Hospital of North Durham 6/13 – Ami to share
- Charing Cross 8/17 – Vaishali or Tulsi to share
- Aberdeen 7/16 – Janice or Sandra to share
- Royal Derby 7/17
- St Georges 8/18 – Rita or Cai to share
- Royal Victoria Infirmary 10/13 – Vicky or one of the team to share
- Hull 8/8

The process is very simple for out of hours recruitment

1. **Confirm eligibility** – can be completed by any clinician they do not need to be on the TICH-3 delegation log
2. **Take initial oral enrolment consent** – consent process just needs to be documented in the medical record, we also allow remote recruitment over phone/telemedicine
   - Must be authorised on the TICH-3 deleagtion log with code J applied (enrolment consent for CTIMPs)
   - We have streamlined training for enrolling investigators https://stroke.nottingham.ac.uk/docs/TICH-3/UK_site_training/TICH-3%20Enrolling%20Investigator%20Training%20Final%20v2.1%2013.04.2023.pdf. Once training completed they then complete http://tich-3.ac.uk/?ZSelfRef to create the account for the TICH-3 website, the PI will then be notified by email to authorise the team member onto the delegation log after checking their GCP and CV.
3. **Complete QR code recruitment alert** – this is within each treatment pack and can be completed by anyone (do not need to be on delegation log, no logins required to complete the form to alert the team a recruitment has taken place)
4. **Prescribing and administration of the IMP** can be completed by anyone appropriately trained to do so, they do not need to be GCP trained or on the TICH-3 delegation log
5. **When the research team is next on site** you will see the recruitment alert in your emails to know a participant was recruited and then you would find the participant to take the follow-on written consent, add participant to website and begin data entry

Sharing best practice for out of hours recruitment

"We have good staff to support the trial and we have had good engagement. We have had direct to ward admissions. It is an easy trial and we have had good support from the trial team"

-Ami Wilkinson (University Hospital of North Durham.

"We have an Eligibility form that we leave with the drug box. We took part in TICH-2 and we are well versed with TICH-3. It is streamlined and we have the forms ready to make it easier".

-Sandra Williams (Aberdeen Royal Infirmary)

"We plan to start out of hours recruitment – what out of hours support is there?"

- Riham Muhammad (ULCH)

A: "We have 4 emergency contact numbers and mine is the first. These are available 24/7".
- Niki Sprigg

Feedback from Recruiting sites

"We have 6 A&E Nurses, 3 of which are familiar with TICH-3. The Research Nurses offer support from home and we take telephone calls. This is a work in progress and a long term study. We work 8am – 8pm 7 days a week and we attend a monthly research meeting".

-Rita Ghatala (St George's hospital)

Following a query from Addenbrooke's Hospital, Niki Sprigg added we are moving away from Physicians to have middle grades i.e Stroke Nurses and non-medics driving the trial locally.

Pilot Progression Review:

Received the go ahead to continue. A third of our recruitment has been out of hours which is fantastic. They would like more sites to be opened and they requested to review the data next August (2024). There is a trial in India and one in China but they will not answer the question on their own.

1/3 - Out of hours recruitment – Sharing best practice (Email submissions)

Queens Medical Centre – Amanda Buck (Senior Clinical Trial Researcher)

- The first patient was recruited by Niki out of hours, the other 6 have all involved a member of the research team, as we are a HSRC there is a consultant and research staff working until 18:00 weekdays and 16:00 most weekends. We have dedicated storage space in ED for storing IMP for our hyperacute trials. Pharmacy dispense a batch of kits and we store these locally, unused IMP is returned to pharmacy as is a copy of the accountability logs after each batch. Pharmacy preform a storge assessment and we temperature monitor the IMP storage cabinet. Access to drug 24/7 as we keep the key in the thrombolysis bag.

Aberdeen Royal Infirmary – Janice Irvine (Stroke Research Nurse)

- All of our investigators were part of TICH-2 so are pretty confident speaking about the trial and trial procedures. We have a folder in ED that has a workflow to aid the process, the information sheets etc and an Eligibility checklist. The trial drugs are in a locked box in the ED clean area. The combination is only shared with the stroke doctors that are involved with the trial. There is a Stroke consultant on call 24hrs so if there is an ICH within 4.5hrs then they, where possible try to attend. I am always happy to be called if they have any issues.

2/3 - Out of hours recruitment – Sharing best practice (Email submissions)

- **Royal Derby Hospital – Catherine Addleton (Lead Clinical Trials Nurse)**
  The main reason it works is that we have our stroke specialist nurses on the delegation log (all GCP trained). When a suitable patient comes into our ED, they notify our stroke consultants. Once the stroke doctors have confirmed eligibility and consented (verbally), the stroke nurses randomise the patients, prescribe and start the infusion. We then follow up on the ward next day to get the written consent for follow up. In terms of the IMP, it is kept in a restricted access, locked cupboard in our ED, it is checked on a monthly basis by our trials pharmacy team. This means that the stroke nurses can access it whenever they need to for the study as they have a key, even if its out of hours.

- **University Hospital of North Durham – Ami Wilkinson (Clinical Research Nurse)**
  Thanks for the feedback. Ultimately there is no magic formula. We are lucky to have proactive consultants, specialist nurses and incredible nursing staff who facilitate out of hours recruitment. As research delivery staff we are always flexible with remote out of hours support – but now that we are familiar with the recruitment process this is rarely needed. The trial drug packs are kept in a secure cupboard in the clean utility on the ward so there is always easy access for the staff out of hours. We have to give credit to the pragmatic trial design and support from you guys too- such a pleasure to work on this trial. Hope to add to our figures soon.

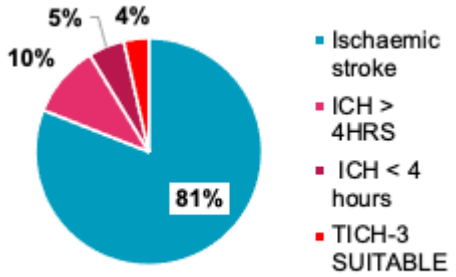
3/3 - Out of hours recruitment – Sharing best practice (Email submissions)

Charing Cross Hospital - Vaishali Dave (research nurse)

- Our first recruitment was out of hours, so that was a good start. We also had a thrombectomy simulation fellow who was interested in research. Our strategy generally is to leverage anyone interested in research, get them trained and delegated. This happened here. The bonus is that he was doing his simulation work out of hours and could recruit to TICH-3 when a patient came in. I always made sure that he had the research team contact, so he could obtain high-quality advice from one of us when required. This speaks to the flexibility of the team and providing remote expertise. The research team also cover out of hours as part of being a HSRC, which meant that we had that on the ground too. The take-home message is broad awareness and expansive delegation of co-Is. We have always tried to make the culture that everyone can play a part in research. So if you can get PI and senior consultant support on this message it makes it a lot easier. Also, making double-sure that the consent form is kept safe and that consent is adequately documented on our electronic records. It is a privilege to lead on TICH-3 at our site and I am so proud to be part of offering ICH patients a study to go into - there aren't many studies that do.

Pilot progression review

- 'Recruit at pace'
- Open more sites
- Recruitment out of hours
- Some idea of proportion of ICH patients that are eligible?



12% of all stroke patients 11,600 last year
SSNAP data: range 16 – 200 pts/site/year median
50% of patients arrive at hospital > 4 hours 5,800
SSNAP data: range from 8 – 100 pts/site/year
Majority of patients present out of traditional working hours: 1400
Most hospitals recruit in working hours (24%/ week)
SSNAP data: range from 2 – 25 pts /site/year
1000 –TICH-3 included 300 UK pts last 12 months from 55 sites

- Data to be reviewed again end of August 2024

Upcoming protocol amendment:

- Is there anything that would be helpful to clarify/change/highlight?
- Anything on the forms that is difficult/confusing?

Any suggestions from sites/investigators?

Updates from Niki Sprigg

Protocol Amendments:

The Doctor confirming eligibility and taking permission for the drug to be administered does not need to be on the delegation log. We are trying to streamline in the next protocol amendment and we are hoping to submit this next month.

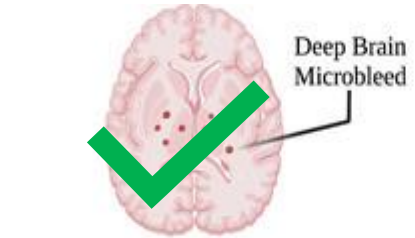
Haematoma Volume:

ABC/2 rule is an estimation. Naveem Gadapa (Queens Hospital, Romford) added that they use A1 for haematoma volume estimation. TICH-3 Trial Medic Chaamanti Menon has done slides on HV and is happy to provide training.

TICH-3 Eligibility: Spontaneous ICH

Inclusions

Small vessel disease and hypertension and cerebral amyloid angiopathy are causes for spontaneous ICH that can be included.



Hypertension Microangiopathy

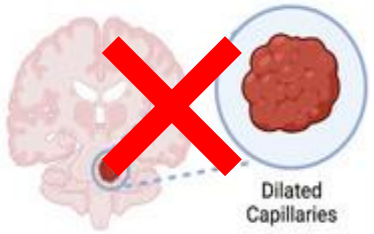
Cerebral Amyloid Angiopathy

Exclusions

AVM, aneurysm, cavernous angioma are structural abnormality that causes secondary ICH.

You **do not need to exclude these abnormalities** before enrolment (e.g. with CTA) BUT if these abnormalities are known about at the time of enrolment the participants should be excluded from TICH-3.

Arteriovenous Malformation

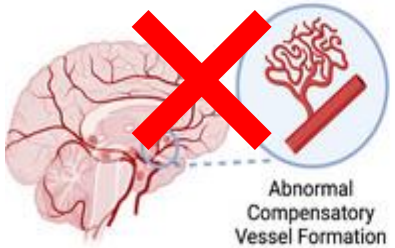


Cavernous Angioma

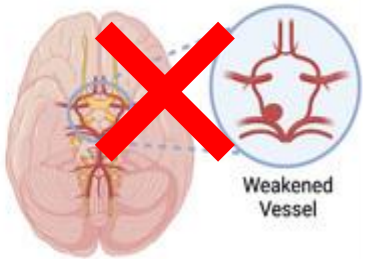
Central Venous Sinus Thrombosis

Venous clots in the brain can also cause venous bleeds and infarcts, it is vital to identify these patients early as the treatment for their bleed is with anticoagulation.

Risk factors: young, women, pregnancy, present with headache



Moyamoya Disease

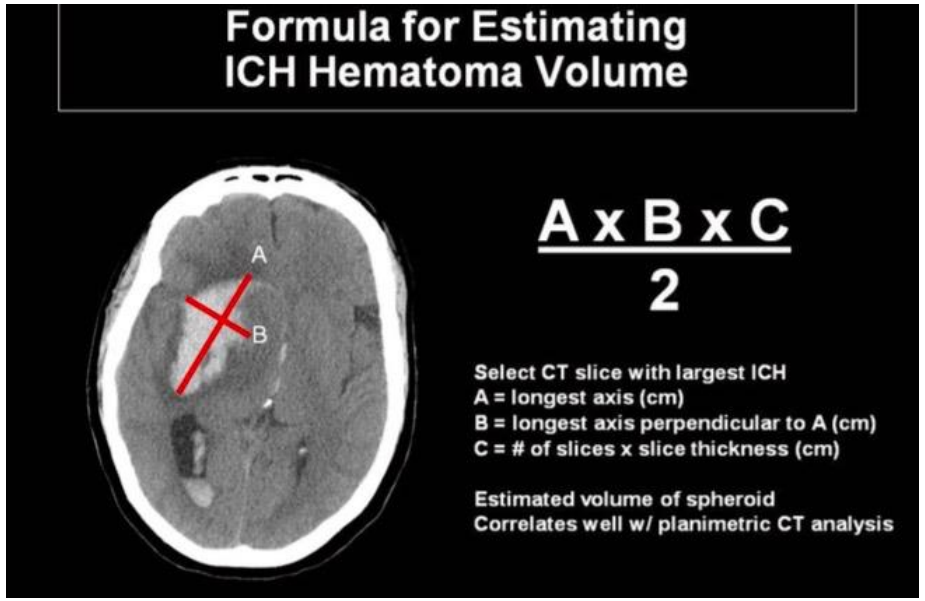


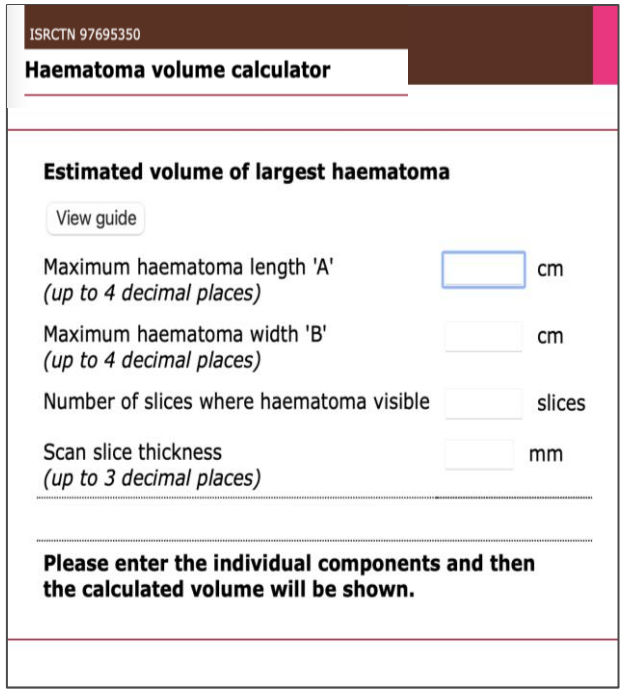
Aneurysm

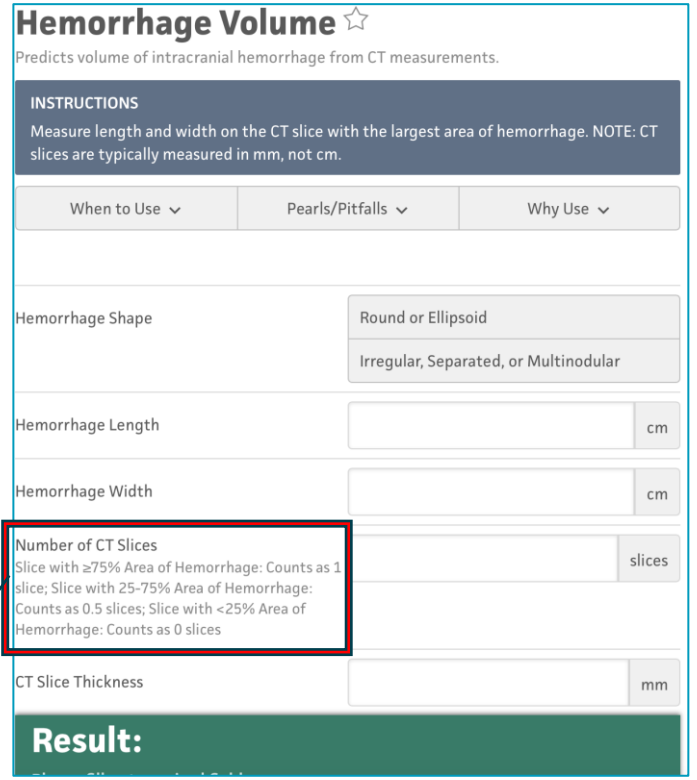
ABC/2 Rule

1. Calculate HV manually using TICH-3 HV=ABC/2 calculator on the website or alternatives e.g. mdcalc app Dimensions can be obtained from neuroradiology or measured directly.
2. If ABC/2 not possible: measure the maximum length of the hematoma. Exclude - if max length A > 5cm

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







Reference to 25-75% of hemorrhage size can be ignored

FAQs from Sites

1. I understood from previous correspondence that if the patient has two bleeds, the total volume of both together shouldn't exceed 60mL. What about when writing the location on the eCRF? And when writing the measurement? Which one do we write?

- It is very unlikely that there will be two bleeds in to two separate locations and it will need assessment per case which the coordinating centre will be able to help with.

2. If a recruited patient lacked capacity at the time of recruitment (and NOK consented), but regained it afterwards, do we reconsent? Or it wouldn't make a difference because they already received the IMP?

- Yes the participant should always be re consented for the follow on written consent if they regain capacity whilst in hospital. The follow on written consent is for the coordinating centre to complete the follow up on day 180. Oral enrolment consent is for the treatment to be administered.

Hierarchy approach in UK

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

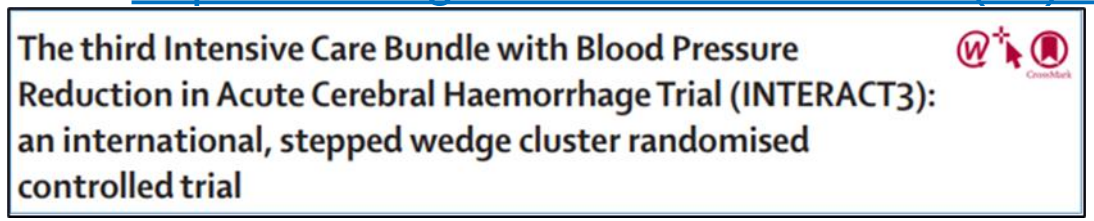
Standard of care for ICH

- All participants should receive standard care for ICH as per the local clinical pathway and guidelines. This is likely to include:

✓ Referral to stroke unit

✓ **Blood pressure lowering as per clinical guidelines[1] target**
For patients with BP 150-220mmHg aim for BP 130-140mmg
x Do not use the same cannula for study drug infusion and blood pressure lowering infusions– need separate IV access line

aiming for a target of BP< 140mmHg as per clinical guidelines, supported by the recent INTERACT -3 Results https://doi.org/10.1016/S0140-6736(23)00806-1


The third Intensive Care Bundle with Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT3): an international, stepped wedge cluster randomised controlled trial

✓ Consideration of referral to neurosurgery or critical care if appropriate

✓ Prophylaxis of venous thromboembolism with intermittent compression stockings

Please note tranexamic acid is not standard of care for spontaneous ICH

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

eCRF changes and retrospective data collection

- Enrolment eCRF

We will be adding question E2b ‘Intraventricular haemorrhage (IVH) present on scan?’

- Day 7 eCRF

We will be adding questions

- A3a: Was tranexamic acid given open-label as part of clinical care?
- A3b: If yes, please provide explanation.

These are really important questions and therefore we may have to ask for the site's assistance is answering these questions retrospectively for the participants already recruited.

Associate PI Scheme

Are you a new researcher looking for training in research studies?

TICH-3 is registered for the Associate PI scheme, this is a great opportunity for doctors, nurses and other healthcare professionals to gain knowledge of what it means to deliver an NIHR portfolio trial.

Key points

- A 6 month in-work training opportunity providing practical experience for healthcare professionals starting their research career.
- Receive a certificate endorsed by NIHR and Royal Colleges
- Ideally you will apply to form the scheme 1 month before the site is ready to open and begin recruitment
- Engage with the TICH-3 coordinating centre during the 6 month scheme (we will sign off part of your checklist

You can find more information here: NIHR Associate PI Scheme Website.

You can register here: NIHR Associate PI Scheme Applicant Registration Form.

We recommend sites consider appointing an associate PI – please discuss if any questions.

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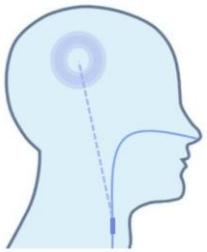
Co-enrolment with TICH-3

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 (co-enrol 48 hours post recruitment to TICH-3)



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, please let us know so your site (PI and R&I) can document they agree to co-enrolment at your site.

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

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

Upcoming events

- UKSF ICC Birmingham, 4 to 6 December 2023

- Investigator meeting **Tuesday 5th December 8 – 8.50am in hall 7**

- The Stroke Trials Unit, Nottingham will be located at stand C10

The Chief Investigator Professor Nikola Sprigg will be at the meeting and the stand and would love to meet you all in person!

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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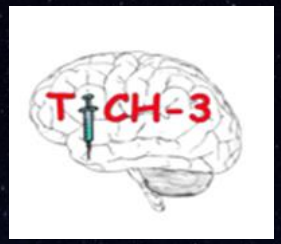

Any questions?