Tranexamic acid for hyperacute spontaneous IntraCerebral Haemorrhage (TICH-3)

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Short title: **Tranexamic acid for IntraCerebral Haemorrhage**

Acronym: **TICH-3**

EudraCT number: **2021-001050-62**

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Statement: the clinical trial will be conducted in compliance with the protocol, with the Regulation and with the principles of good clinical practice.

TRIAL / STUDY PERSONNEL AND CONTACT DETAILS

Sponsor:
Contact name

University of Nottingham
Ms Angela Shone
Head of Research Governance
Research and Innovation
University of Nottingham
E Floor, Yang Fujia Building
Jubilee Campus
Triumph Road
Nottingham
NG8 1BB

Chief investigator:

Professor Nikola Sprigg
Professor of Stroke Medicine
University of Nottingham
Phone: 0115 8231765
Fax: 0115 8131767
Email: nikola.sprigg@nottingham.ac.uk

Co-investigators:
(Medical Expert)

Professor Philip Bath
Stroke Association Professor of Stroke Medicine
University of Nottingham
Phone: 0115 8231765
Fax: 0115 8131767
Email: philip.bath@nottingham.ac.uk

Dr Rob Dineen
Professor of Neuroimaging
University of Nottingham
Phone: 0115 82 31173
Fax: 0115 8231180
Email: rob.dineen@nottingham.ac.uk

Dr Michael Desborough
Academic Clinical Lecturer
Oxford University Hospitals
Phone: 01865 447900
Email: michael.desborough@ouh.nhs.uk

Professor Ian Roberts
Professor of Epidemiology & Public Health
London School of Hygiene & Tropical Medicine
Phone: 020 7299 4684
Email: ctu@lshtm.ac.uk

Professor Alan Montgomery
Professor of Medical Statistics and Clinical Trials
NCTU Director
Clinical Trials Unit
University of Nottingham
Phone: 0115 8231612
Email: alan.montgomery@nottingham.ac.uk

Professor Rustam Al-Shahi Salman
Professor of Clinical Neurology
University of Edinburgh
Phone: 0131 242 7014
Email: Rustam.al-shahi@ed.ac.uk

Professor Christine Roffe
Consultant Stroke Physician
University Hospitals of North Midlands NHS Trust
Phone: 01782 671655
Email: Christine.roffe@uhnm.nhs.uk

Professor David Werring
Professor of Clinical Neurology
UCL Institute of Neurology
Phone: 020 3108 7493
Email: d.werring@ucl.ac.uk

Associate Professor Timothy England
Clinical Associate Professor, Vascular Medicine
University of Nottingham
Phone: 01332 724668
Email: timothy.england@ottingham.ac.uk

Professor Timothy Coats
Professor of Emergency Medicine
University of Leicester
Phone: 0116 2585965
Email: tc61@le.ac.uk

Professor Marilyn James
Professor of Health Economics
University of Nottingham
Phone: 0115 8230245
Email: Marilyn.james@nottingham.ac.uk

	Associate Professor Caroline Rick Associate Professor of Methodology Nottingham Clinical Trials Unit University of Nottingham Phone: 0115 8231600 Email: caroline.rick@nottingham.ac.uk Professor Thompson G Robinson Professor of Stroke Medicine University of Leicester Phone: 0116 2522961 Email: tgr2@le.ac.uk
Trial / Study Statistician: (and co-applicant)	Trish Hepburn Phone: 0115 8231561 Fax: 0115 7484092 Email trish.hepburn@nottingham.ac.uk
Trial Pharmacist:	Maria Scott Phone: 0115 9691169 Fax: 0115 9709153 Email maria.scot@nuh.nhs.uk
Trial Coordinating Centre: **Centre:**	Stroke Trials Unit University of Nottingham Phone: 0115 8231782 Email: TICH-3@nottingham.ac.uk
Project / Trial Manager:	Tiffany Hamilton Phone: 0115 8231775 Fax: 0115 8231771 Email tiffany.hamilton@nottingham.ac.uk
Legal Representative in European Union:	Project Manager Katrina Tobin Director Prof Peter Kelly HRB Stroke Clinical Trials Network, Ireland UCD Clinical Research Centre Nelson Street, Dublin 7, Ireland Tel: +353 1 716 4576
Eudravigilance Legal Representative:	Thavarak OUK Centre Hospitalier Universitaire De Lille: 2 Avenue Oscar Lambret Cs 70001; Lille Cedex, 59037,France Phone: +33 (3) 20 44 57 17 Fax: +33 (3) 20 44 57 11 E-mail: thavarak.ouk@chru-lille.fr

SYNOPSIS

Title	Tranexamic acid for Hyperacute Spontaneous Intracerebral Haemorrhage (TICH-3)
Acronym	TICH-3
Short title	Tranexamic acid for Hyperacute Spontaneous Intracerebral Haemorrhage
Chief Investigator	Professor Nikola Sprigg
EU CTR Number	2022-500587-35-01
Objectives	To assess the clinical effectiveness of tranexamic acid (TXA) after ICH and determine whether TXA should be used in clinical practice. Primary objective: To assess the effect of TXA on early death (≤7days) Secondary objective: To assess the effect of TXA on dependency 6 months after ICH.
Trial Configuration	Pragmatic phase III prospective blinded randomised placebo-controlled trial.
Setting	Emergency departments, acute stroke services/units across the UK and worldwide.
Sample size estimate	2750 participants per group would allow detection of a difference of 2.57% in the proportion of deaths at day 7 between the placebo and TXA groups (7.74% deaths on TXA, OR of 0.73), at the 5% significance level (2-sided) with 90% power. As the primary outcome is death we anticipate there will be minimal loss to follow up.
Number of participants	At least 5500
Eligibility criteria	**Inclusion criteria:** i. Adults (≥ 18 years) ii. Presenting within 4.5 h of onset of acute spontaneous ICH iii. ICH confirmed on brain imaging iv. When onset of symptoms is unknown patient must be within 4.5 hours of symptom discovery and have no other exclusion criteria. v. Patients taking direct oral anticoagulants can be included vi. Informed consent according to Article 35 of (EU) No 536/2014 vii. Please see separate document for EU country specific Descriptors – see Appendix 2 and Part II document **Exclusion Criteria**: viii. Patient with a known recommended indication for TXA treatment (e.g. traumatic brain injury). ix. Patients with contraindication to TXA in view of treating physician should be excluded. I.e where the contraindication outweighs the risk of giving TXA to a patient as an emergency ICH treatment: a. Active seizures b. Current diagnosis of acute venous or arterial thrombosis c. Hypersensitivity to TXA or normal saline d. Patients with known underlying structural abnormality such as arteriovenous malformation, aneurysm, tumor. An underlying structural abnormality does not need to be excluded before enrolment, but where known, patients should not be recruited.

	x. Patient known to be taking therapeutic anticoagulation at time of enrolment, with the exception of direct oral anticoagulants (patients taking direct oral anticoagulants are not excluded). xi. Massive ICH for which haemostatic treatment seems futile (This would ordinarily be when haematoma volume is estimated as larger than 60ml) xii. Severe coma (Glasgow Coma Scale <5) xiii. Decision already taken for palliative (end of life) care with withdrawal of active treatment
Description of interventions	Intravenous TXA 2g: 1g loading dose given as 100 mls infusion over 10 minutes, followed by 1g in 250 mls infused over 8 hours. Comparator – matching placebo (normal saline 0.9%) administered by an identical regimen.
Duration of study	7.25 years project; approximately 5.25 years participant recruitment in the UK, 4.75 years in international sites, Start date 1 April 2022 Duration of study per participant: 6 months.
Randomisation and blinding	Randomisation will be to TXA vs. placebo in a 1:1 ratio. Due to the emergency situation, a straightforward randomisation process will be used, where sites will simply select the next available treatment pack, which will be a numbered box containing either TXA or placebo according to a computer-defined sequence. Boxes will be identical with the exception of the treatment pack number. Randomisation will be stratified by site with supply to each site balanced for TXA and placebo, using random permuted blocks of varying size. The IMP manufacturer will prepare blinded individual treatment packs containing four 5ml glass ampoules of TXA 500mg or sodium chloride 0.9% which will be very similar in appearance.
Outcome measures	**Primary outcome:** mortality at 7 days, Secondary functional outcome: modified Rankin Scale at (mRS) 180 days. Other secondary outcomes: Death at 2 days. Safety outcomes**:** Recorded in the first 7 days (or death if sooner): venous thromboembolism; arterial occlusive events (arterial thrombosis at any site, ischaemic stroke, transient ischaemic attack peripheral artery embolism, myocardial infarction, acute coronary syndrome); seizures. Quality of Life (EuroQol(Devlin et al., 2018), EQ-5D-5L, VAS), and cognition (AD-8)(Galvin et al., 2007) at day 180.
Resource and Cost Measures	Hospital resource and cost at discharge, to include: length of stay, days in ICU and treatments. Usual residence: Disposition at discharge and day 180. Patient level Health Resource Use Questionnaire at day 180.
Statistical methods	The analysis and presentation of the trial results will be in accordance with the CONSORT guidelines. The primary outcome will be compared analysing as randomised without imputation of missing data. Due emphasis will be placed on the confidence intervals for the between arm comparisons. A full Statistical Analysis Plan (SAP) based on the approved protocol will be published prior to database lock. The evaluation of the primary outcome will be performed using regression models for binary outcomes, with adjustment for key prognostic factors. The model will be fully specified in the SAP. Absolute and relative measures of effect and 95% confidence intervals will be presented. The primary outcome will also be investigated in pre-specified subgroups using appropriate interaction terms. The subgroups will be specified in the SAP and will, at a minimum include age, sex, systolic blood

	pressure, HV, GCS, the start of treatment (≤2 or >2 hours, ≤3 or >3 hours), antiplatelet (yes no), direct oral anticoagulation (DOAC) (yes, no) and intraventricular haemorrhage (yes, no).
Health Economic Analysis	Cost effectiveness of TXA versus usual care. Incremental cost effectiveness ratios (ICERs), net monetary benefit and cost effectiveness of usual care versus TXA
Simplicity of Trial Procedures	To reflect the time critical emergency nature of ICH, and to facilitate rapid enrolment in emergency departments, even in hospitals affected by the pandemic, patient enrolment (simple randomisation) and all other trial procedures are greatly streamlined. Informed consent is simple and data entry is minimal. Randomisation via taking the next treatment pack is simple and quick. Follow-up information is recorded at a single timepoint and may be ascertained by contacting participants, by post, phone or electronically, or by review of medical records and databases.
Ethical Considerations	ICH is a medical emergency and there are no approved medications for halting heamatoma expansion. The safety profile for TXA is well established from is frequent use clinically, and in large clinical trials. The process for obtaining participant informed consent will be in accordance with the regulatory requirements, and Good Clinical Practice (GCP) and reflect the emergency situation and time critical nature of the intervention, in accordance with Article 35 of (EU) No 536/2014 Vulnerable groups in this trial include incapacitated persons, pregnant or breastfeeding women. This will be in accordance with regulatory guidance.

ABBREVIATIONS

ACS	Acute coronary syndrome
ADR	Adverse Drug Reaction
AD-8™	Cognition measure
AE	Adverse Event
BP	Blood pressure
CF	Informed Consent Form
CI	Chief Investigator overall
CEA	Cost Effectiveness Analysis
CUA	Cost Utility Analysis
ICER	Incremental Cost Effectiveness Ratio
CEAC	Cost Effectiveness Acceptability Curves
NMB	Net Monetary Benefit
CRF	Case Report Form
CT	Computed tomogram
CTA	Computed tomogram angiogram
DAP	Data Analysis Plan
DMC	Data Monitoring Committee
DOAC	Direct Oral Anticoagulation
DNACPR	Do not attempt cardiopulmonary resuscitation
DVT	Deep vein thrombosis
EOT	End of Trial
EQ-5D™	EuroQol 5-Dimension 5-Level quality of life assessment tool
GCP	Good Clinical Practice
HG	Haematoma growth
HEE	Health economic evaluation
HV	Haematoma volume
ICH	Intracerebral haemorrhage
IS	Ischaemic stroke
NIHR	National Institute for Health Research
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Myocardial infarction
NHS	National Health Service
mRS	modified Rankin Scale
NIHSS	National Institutes for Health Stroke Scale
PE	Pulmonary embolism
PI	Principal Investigator at a local centre
PIS	Participant Information Sheet
REC	Research Ethics Committee
R&D	Research and Development department
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction

SWAT	Study within a trial
TBI	Traumatic brain injury
TMG	Trial Management Group
TSC	Trial Steering Committee
TXA	Tranexamic acid
VAS	Visual analogue scale
VTE	Venous thromboembolism

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TRIAL / STUDY BACKGROUND INFORMATION AND RATIONALE

ICH is a medical emergency and causes more than 1.7 million strokes worldwide per year(Feigin et al., 2009; O'Donnell M.; Venketasubramanian N.; Baker-Collo S.; Lawes CMM.; Wang W.; Shinohara Y.; Witt E.; Ezzati M.; Murray C., 2013) with a mortality of over 40%.(Flaherty et al., 2006) More than 10,000 people suffered an ICH last year in England. There is no effective drug treatment for ICH, and only a small proportion of patients benefit from surgery. Haematoma growth is common, occurs early,(Brott et al., 1997; Davis et al., 2006) and is the most common cause of death after ICH. It can potentially be prevented by haemostatic therapies, which are effective in other bleeding conditions.(Collaborators, 2010; WOMAN Trial Collaborators, 2017) Time from symptom onset, baseline haematoma growth and anti-thrombotic therapy use are all independent predictors of haematoma growth.(Al-Shahi Salman et al., 2018) The Computed Tomography (CT) spot sign can also improve the prediction model but has not been successful in previous trials(Gladstone et al., 2019) and is not routinely performed in clinical practice.

ICH related disability causes massive burdens to the affected individual, their family and society. ICH was identified as a priority research area by The Stroke Association, with interventions to stop bleeding as a treatment target.(*https://www.stroke.org.uk/news/haemorrhagic-stroke-workshop-priority-setting*, 2014) The incidence of ICH is increasing due to high blood pressure and the ageing population, with ICH-related death and disability set to rise.(Feigin V et al., 2013; Kleindorfer et al., 2010) Recent improvements in stroke pathways have led to rapid imaging, with early diagnosis providing an opportunity to rapidly administer treatments. Implementation of an effective haemostatic therapy such as TXA is therefore possible in ICH.
The proposed study will build on experience from the NIHR HTA funded TICH-2 trial,(Sprigg et al., 2018) streamline trial methods and enable rapid enrolment of those most likely to benefit. If the haemostatic effect demonstrated in TICH-2 (with reduction in early death) is confirmed in TICH-3, this could change clinical practice globally. By enrolling participants earlier and excluding those with established large HVs, TICH-3 targets patients with the greatest potential to benefit.

Review of existing evidence: TXA in other bleeding conditions
TXA is an antifibrinolytic agent licensed for perioperative use. It reduces mortality after trauma and childbirth and is most effective when given rapidly after the onset of bleeding.(Gayet-Ageron et al., 2018)
The CRASH 3 RCT("Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial," 2019) of TXA in traumatic brain injury has been published since submission of stage 1 application: TXA was safe in 12737 participants with traumatic brain injury. Overall, there was a reduction in day 30 head injury related mortality (Risk reduction RR 0.94; 95%CI 0.86-1.02), in a pre-specified sensitivity analysis excluding very severe head injury (RR 0.89; 95%CI 0.80-1.0), and benefit in mild-moderate head injury deaths (RR 0.78; 95%CI 0.64-0.95). The effect size was greater when early death (< 24 hours) was the outcome RR 0.81 (95% CI 0.69–0. 95) within 24 h. When patients with a GCS score of 3 and those with bilateral unreactive pupils at baseline were excluded, the RR was 0.72 (0.56–0.92).

Rapid treatment was the most effective in mild-moderate head injury, with some benefit up to 4.5 hours. There was no benefit in patients with severe coma score, irrelevant of time.

Summary of TXA data in non-ICH patients: TXA is effective at reducing mortality due to bleeding after trauma, post-partum haemorrhage and traumatic brain injury. Treatment is most effective when given early and the effect is greatest on early mortality. A number of differences in patient population, pathophysiology and natural history mean these results cannot simply be translated to ICH patients.

TXA after intracerebral haemorrhage (ICH):

Observational studies: 2 small observational studies of TXA after ICH have been reported. Sorimachi et al. reported a retrospective observational before–after study comparing the efficacy of rapid infusion of TXA 2 g over 10 min to prolonged infusion of 1 g over 6 h in patients presenting within 24 h of ICH. The study recruited 156 patients (>80% presented within 3 h of onset) and showed that rapid infusion was associated with less haematoma enlargement of >20% than prolonged infusion (17.5% vs. 4.3%, $p = 0.011$).-The authors subsequently reported a study of additional 95 patients treated with rapid infusion of TXA with HE occurring in 4.2% of these patients. However, there was no control arm in either study.
Ojacastro et al. reported an observational study of 30 patients aged 40–70 years with hypertensive ICH who received either intravenous TXA 500 mg for three doses or standard care. The study is reported as an abstract only, with no data other than a general statement of HV reduction with TXA without effect on length of stay or in-hospital National Institute of Health Stroke Scale (NIHSS).

Randomised controlled trials of TXA after ICH:
A systematic review in 2018 was inconclusive about the safety and efficacy of antifibrinolytics after ICH as there were only 2 published randomised controlled trials (RCTs) with a total of 57 participants(Rustam Al-Shahi Salman et al., 2018). 3 other studies were on-going and one TICH-2 (lead by this group) reported in 2018.The results of the completed RCTs and summary of on-going trials are presented below. The majority of studies use the radiological endpoint haematoma expansion (HE) as a surrogate outcome measure, to demonstrate haemostasis. Dependency assessed by modified Rankin Scale is the most frequently used functional outcome.

Randomised controlled trials n=<100 participants:
The TXA in IntraCerebral Haemorrhage (TICH) trial(Sprigg et al., 2014) recruited 24 patients within 24 h of ICH to receive either 1 g TXA or placebo over 10 min followed by 1 g over 8 h. This trial was designed as a feasibility trial and not to investigate efficacy.

Arumugam et al.(Arumugam et al., 2015) conducted a single-centre, single-blind RCT that allocated 30 patients to receive within 8 h of ICH either intravenous TXA 1 g over 10 min followed by 1 g over 8 h or placebo. Participants in the control group experienced more haematoma expansion compared to the treatment group. The mean Glasgow Outcome Scale score was 3.6 in the control group and 4.4 in the treatment group, but no estimated between group difference was provided.

The Norwegian Intracerebral Haemorrhage Trial (NOR-ICH, EudraCT number 2012-005594-30) was a multicentre prospective randomised, open-label, blinded endpoint (PROBE) trial. The study has terminated early due to problems with recruitment and has not been published. Approximately 30 participants were enrolled.

Tranexamic acid for Hyperacute Spontaneous Intracerebral Haemorrhage-2: Most of the data on TXA in ICH come from TICH-2(Sprigg et al., 2018) (n=2325, treatment within 8 hours of ICH, delivered by the co-applicants) which showed that TXA was safe, led to reduction in HE (adjusted odds ratio (aOR) 0.80; 95%CI 0.66-0.98, p=0.03) and reduction in early day 7 deaths (aOR 0.73; 95%CI 0.53-0.99; p=0.04), but no difference in functional outcome of modified Rankin Scale at 3 months (aOR 0.88; 95%CI 0.76-1.08).(Sprigg et al., 2018) In keeping with data from CRASH-3 in TBI, the effect on early mortality was greater: day 2 OR (aOR 0.61 95% CI 0.38 - 0.98 p=0.04). In a UK sub-study, (n=1873) following patients up to one year, there was no difference in functional outcome using a shift analysis (aOR 95% 0.91 CI: 0.77-1.09; p=0.30) but there was difference in cumulative mortality (cox proportional hazard analysis) (aHR 0.77, 95% CI 0.64-0.94; p=0.0086). There was also a trend for participants in the TXA group to have better discharge disposition and less likely to be in an institution.

Interpretation of data from TICH-2: Inclusion of participants too late after ICH, when HE had already occurred and a more modest haemostatic effect than expected are likely to explain the neutral primary outcome of TICH-2.(Broderick, 2018).Treatment effect was possibly diluted by

inclusion of patients with large HV already pre-destined to a bad outcome. Hence TXA is still considered a viable treatment option (Cordonnier et al., 2018) and studies with a shorter time window are needed.(Donnan, 2019) Participants enrolled within 4.5 h in TICH-2 had a reduction in poor functional outcome (aOR 0.84; 95%CI 0.70-1.01). Furthermore an *ad hoc* analysis of 1377 participants with small haematomas (<60 ml) enrolled early (within 4.5 h) suggested possible reduction in early death by day 7 (aOR 0.70; 95%CI 0.43-1.15; p=0.15).

Evidence from other ICH studies:
Three RCT have recently completed and another is ongoing: Details are given below but these are all small studies with radiological measures as primary outcome and therefore unlikely to change practice, even as part of a planned prospective individual patient data meta-analysis.(Zhe Kang Law, 2017)

The Spot sign and TXA On Preventing ICH growth – AUStralasia Trial STOP-AUST (NCT01702636) was a phase-II multicentre randomised, double-blind, placebo-controlled trial exploring the efficacy of TXA in preventing HE in ICH patients, recruiting patients from Australia, Finland and Taiwan. The trial selected patients with a positive spot sign on CT angiography to receive either placebo or 1 g TXA over 10 min followed by 1 g over 8 h. The primary outcome measure was HE by 24 h, with mRS and thromboembolic complications at 90 days as secondary outcomes. They recruited a total of 100 participants The primary outcome was not different between the two groups: 26 (52%) patients in the placebo group and 22 (44%) in the TXA group had intracerebral haemorrhage growth (odds ratio [OR] 0·72 [95% CI 0·32-1·59], p=0·41). There was no evidence of a difference in the proportions of patients who died or had thromboembolic complications between the group.(Meretoja et al., 2020)

TXA for Acute ICH Growth prEdicted by Spot Sign TRAIGE (NCT02625948) is a multicentre phase-II randomised, double blind, placebo-controlled trial recruiting patients from China who have a positive spot sign on CT angiography and can be treated within 8 h from onset. The trial compared the efficacy of intravenous TXA followed by intravenous TXA 1 g infusion over 8 h versus placebo. The primary outcome measure is HE by 24 h, with mRS and thromboembolic complications at 90 days as secondary outcomes. The trial recently completed recruitment of 171 participants and results did not differ significantly between the two groups: 36 (40.4%) patients in the TXA group and 34 (41.5%) patients in the placebo group had intracranial haemorrhage growth (OR 0.96, 95% CI 0.52 to 1.77, p=0.89). Although in the secondary outcome analysis the TXA group had lower 90 day mortality compared to placebo (8.1% vs 10.0%, p=0.71), all of the secondary outcomes were statistically insignificant.(Liu et al., 2021)

Recently completed trial:TXA for IntraCerebral Haemorrhage secondary to Novel Oral AntiCoagulants TICH-NOAC (NCT02866838) was a multicentre international double-blind placebo-controlled trial, investigating the safety and efficacy of TXA in ICH related to non–vitamin K (direct) oral anticoagulants (NOAC).[34] The time window for recruitment is up to 12 h after the onset of ICH. Patients are randomised to receive TXA 1 g bolus followed by 1 g infusion over 8 h or placebo. All patients receive standard treatment including specific antidote where available. TICH-NOAC aims to demonstrate that treatment with TXA reduces rate of HE as measured at 24 h compared to the best medical treatment. The trial randomized 63 patients within 12 hours of symptom onset and treated them with TXA or placebo within 30 minutes of randomization. there was no evidence that TXA (1g bolus then 1g infusion) prevents hematoma expansion, with rates of almost 50% in both arms. Rates of severe disability and death were also comparable in the treatment and placebo arms. Prespecified subgroup analyses identified several factors associated with the effect of TXA on hematoma expansion, including time-to-treatment and blood pressure. These data will inform future investigations of the role of TXA in NOAC-associated ICH. The study was presented at European Stroke Conference May 2022. The study was presented at European Stroke Conference May 2022.(Lyrer Philippe, 2022)

On-going trials:
Stopping Haemorrhage With TXA for Hyperacute Onset Presentation Including Mobile Stroke Units STOP-MSU **(**NCT03385928) will include patients from Australia with acute spontaneous ICH, who are ≥18 years of age and are eligible for treatment within 2 hours of stroke onset. The study will test the hypothesis that intracranial haemorrhage patients treated with intravenous TXA within 2 hours of symptom onset will have lower rates of HE as compared to placebo. The study is ongoing. (Yassi et al., 2022).
Conclusion: More high-quality data from large RCTs in ICH are urgently needed, particularly in patients soon after ICH onset, when the risk of haematoma a growth is highest and the potential benefit from TXA greatest. Evidence of benefit on clinical outcomes (rather than radiological surrogate measures such as HE) in ICH is necessary to change practice in stroke services in the UK and worldwide.

Literature regarding the safety and side effects of TXA in ICH:
In TICH -2, the largest TXA trial done in ICH patients to date, participants in the tranexamic acid group had fewer predefined safety outcomes and serious adverse events than those in the placebo group at day 2 (379 [33%] patients vs 417 [36%] patients, p=0·0272), day 7 (456 [39%] vs 497 [43%], p=0·0200), and 90 days (521 [45%] vs 556 [48%], p=0·0393; appendix). There was no increase in venous thromboembolic events (39 [3%] patients in the tranexamic acid group vs 37 [3%] in the placebo group; p=0·98) or arterial occlusions (myocardial infarction, acute coronary syndrome, or peripheral arterial occlusion) in the tranexamic acid group compared with the placebo group. Seizure was the most common safety outcome (77 [7%] patients in the tranexamic acid group vs 85 [7%] in the placebo group) and nervous system disorders were the most common serious adverse events (149 [13%] vs 163 [14%]), followed by infections (98 [8%] vs 116 [10%]) (Sprigg et al., 2018).

In TRAIGE, there were a total of 171 participants and only Two patients had major thromboembolic events (acute cerebral infarction), one in each group (Liu et al., 2021).

In STOP AUST trial out of 100 patients enrolled in the study there were two (4%) thromboembolic complications in the placebo group and one (2%) in the tranexamic acid group (Meretoja et al., 2020).

In the CRASH 3 trial, a trauma ICH study also using 2g of TXA, TXA was safe in 12737 participants with traumatic brain injury. The risk of vascular occlusive events was similar in the tranexamic acid and placebo groups (RR 0·98 (0·74–1·28). The risk of seizures was also similar between groups (1·09 [95% CI 0·90–1·33])("Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial," 2019).

In a recent metanalysis looking at a total of 234 studies with 102,681 patients found that in bleeding patients, there was no evidence that TXA increased the risk of thrombotic events (RR = 1.00 [95% CI 0.93–1.08]), seizures (1.18 [0.91–1.53]), venous thromboembolism (1.04 [0.92–1.17]), acute coronary syndrome (0.88 [0.78–1.00]) or stroke (1.12 [0.98–1.27]). In a dose-by-dose sensitivity analysis, seizures were increased in patients receiving more than 2 g/day of TXA (3.05 [1.01–9.20]). However when looking individually at thrombotic events in spontaneous ICH subgroup the risk of thrombotic events appeared higher in the TXA group than in the control group (1.33 [1.09–1.63]) but in a dose-by-dose sensitivity analysis, thrombotic events were not increased in patients receiving 2 g/day of TXA or less (≤ 2 g/day: 0.94 [0.84–1.05]) (S. et al., 2021)

Three recent meta-analyses evaluating the effect of TXA in patient with ICH concluded that TXA could reduce haematoma expansion and it was safe with no increase of thromboembolic events. (Mf et al., 2021; S. et al., 2021; W. et al., 2019).

This trial will be a standard interventional clinical trial, in keeping with CT regulations 536/2914 Chapter 1 Article 2 Definition 2 There is sufficient data to support the safety of TXA use however TICH 3 will follow up pre-specified safety outcomes i.e seizures and thromboembolic events for the first 7 days. TICH 3 will focus on efficacy of TXA use in ICH.

Scientific advice has not been sought from any competent Agency, Member State or third country.

DETAILS OF INVESTIGATIONAL MEDICINAL PRODUCT(S)

There are no investigational medical devices to be used in this trial.

Description and Manufacture

Intravenous tranexamic acid or matched placebo of intravenous Sodium Chloride 0.9% 5ml ampoules.

The IMP or placebo are both chemical and are not narcotics, psychotrophic or radiopharmaceuticals and neither consist of genetically modified organsims.
Neither the IMP or placebo are orphan drugs and the medical condition under investigation is not an orphan condition.

Tranexamic acid 100mg/ml 5ml ampoules are a licensed product and an example summary of the product characteristics is available for investigators.

The use of tranexamic acid in this study is in accordance with Article 2 (2) of Regulation 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (hereafter Reg 536/2014) and as such this trial is classed as a clinical trial of an investigational medicinal product.

Packaging and labelling

Sharp Clinical Services Ltd located in Rhymney Wales UK NP22 5RL will prepare blinded individual treatment packs containing four 5ml glass ampoules of tranexamic acid 500mg or sodium chloride 0.9% which will be very similar in appearance by the addition of a heat shrink sleeving. Ampoules and the secondary carton will be labelled in accordance with ANNEX VI LABELLING OF INVESTIGATIONAL MEDICINAL PRODUCTS AND AUXILIARY MEDICINAL PRODUCTS from the Official Journal of the European Union assuming that the primary and secondary packaging remain together throughout the trial. To facilitate identification the carton and the ampoules contained within it will be labelled with the same unique pack number.

Where manufacture and labelling of the ampoules and secondary carton was performed before issue of the EU CT number, sites and investigators will be advised that the EuDRACT number has been superseded by the EU CT number 2022-500587-35. All subsequent labelling will contain the EU CT number.

Detailed prescribing and administration instructions will be provided in the treatment pack.

Sharp Clinical will export the treatment packs to Manufacturing Packaging Farmaca (MPF) B.V Neptunus 12, 8448 CN Heerenven, The Netherlands for QP release and distribution to European sites with the exception of Sweden whereby Sharp will distribute to the central pharmacy in Uppsala which will then distribute to sites as mandated by Swedish law.

The final product will be QP released by the designated person at Sharp Clinical Services to provide blinded trial treatment packs for this trial.

Storage, dispensing and return

Sharp Clinical Services Ltd EU address named as Manufacturing Packaging Farmaca (MPF) B.V. Neptunus 12, 8448 CN Heerenveen, The Netherlands will store the treatment packs and distribute to pharmacies within trial sites using a web-based system control. Pharmacy at each participating site will take receipt of numbered supplies from Sharp Clinical Services.

The web-based system operates as follows. Participating centres will be allocated a batch of trial treatment. The container numbers for these batches are tracked by the web-based system to the participating site and once receipt has been confirmed they are released for use in the trial. When the supplies at the participating centre reach a pre-determined level then a re-order is triggered, and a further supply of trial treatment is sent to the corresponding participating site.

The packs will be stored at room temperature (not above 25 degrees) and must not be refridgerated or frozen, in a restricted access area. the SmPC recommends storage temperature to not exceed 25°C .and treatment packs will be labelled accordingly. Where manufacture and labelling of secondary carton was performed before EU regulatory review investigators will be reminded they must not store above 25°C and must not refrigerate or freeze. All subsequent labelling will contain the instructions Do not store above 25°C. Do not refrigerate or freeze.

The IMP will be clearly labelled for clinical trial use only. Each pack will be a numbered box containing either TXA or placebo according to a computer-defined sequence.

The local site investigator is responsible for ensuring trial treatment accountability, including reconciliation of trial treatment and maintenance of trial treatment records, throughout the course of the study in accordance with Clinical Trials Regulatory requirements. Responsibility can be delegated to the site pharmacy clinical trials staff in accordance with local process.

Following enrolment personnel at sites will simply select the next available treatment pack, which will be a numbered box containing either TXA or placebo according to a computer-defined sequence. Boxes will be identical with the exception of the treatment pack number.
The participant will subsequently be allocated a participant trial number based on the treatment pack number when the treatment pack number is entered to the electronic case report form.

Prescription: The treatment will be prescribed by appropriately trained medical practitioners or health care professionals who are non-medical supplementary or independent prescribers. *It is acceptable to use handwritten or electronic prescribing system for IMPs prescribing.*

Dispensing will be recorded on the appropriate trial specific accountability forms. Trial treatment must not be used for any other purpose than the present study. Returned trial treatment that has been dispensed to a participant must not be re-dispensed to a different participant. Any unused drug will be returned to pharmacy.

Placebo

The placebo will be supplied, packaged, labelled, QP released and distributed as for the active IMP.

Known Side Effects

Gastrointestinal disorders (nausea, vomiting, diarrhoea) may occur. Hypotension has occasionally been reported after rapid intravenous infusion. Rare instances of colour vision disturbances have been reported following long-term use. Rare cases of thromboembolic events have been reported. Rare cases of allergic skin reactions have also been reported.

TXA will counteract the thrombolytic effect of fibrinolytic preparations, but these would be contra-indicated in patients with haemorrhagic stroke.

Reference Safety Information:

Example Tranexamic Acid SmPC (ADVANZ Pharma): https://stroke.nottingham.ac.uk/docs/TICH-3/MHRA_documents/TICH-3 Focus Tranexamic Acid 100mg ml Solution for Injection Summary of Product Characteristics %28SmPC%29 20210202 REVISION.pdf

Section 4.8 of the SmPC, Section 10: date of last revision 02 February 2021, will act as the reference safety information for Tranexamic acid

Example Sodium Chloride SmPC: https://stroke.nottingham.ac.uk/docs/TICH-3/MHRA_documents/TICH-3%20Sodium%20Chloride%20Injection%20BP%200.9%20percent%20w%20v%20Summary%20of%20Product%20Characteristics%20%28SmPC%29.pdf

Section 4.8 of the SmPC Section 10: date of last revision 01 April 2020, will act as the reference safety information for sodium chloride

SmPCs will be reviewed annually and any significant changes with respect to the safety information will be considered and sites will be updated accordingly following regulatory approvals as required

Drug accountability

Intracerebral haemorrhage is a medical emergency. The trial has been designed to embed within the clinical pathway for hyperacute stroke, such that hyperacute stroke patients are assessed immediately on arrival to hospital and urgent brain imaging performed to exclude haemorrhage, to allow thrombolysis to be given to patients with ischaemic stroke. Patients who have ICH confirmed on brain imaging will be offered participation in TICH-3. Unless they disagree to participate the IMP will be administered, and written consent taken later. As such the IMP needs to be available for immediate administration once the diagnosis of ICH has been confirmed. If the IMP has been opened and no diagnosis of ICH has been confirmed, the IMP will be destroyed according to local procedures. Hence it will be necessary to take the IMP with the patient to the scanner, as is done with thrombolysis drugs, often as part of a ‘thrombolysis kit or grab bag’. The IMP is clearly labelled for clinical trial use only. The remainder of the drug supplies will be kept in a secure, limited access storage area.

The investigator and the local site pharmacist shall maintain records of the study drug’s delivery to the pharmacy, an inventory at the site, the distribution to each participant, and the return to the pharmacy or alternative disposition of unused study drugs. These records will include dates, quantities received, batch / serial numbers, expiration dates, and the unique code numbers (patient trial number) assigned to the trial participant. Investigators and /or the local site pharmacists will maintain records that document adequately that the participants were provided with the correct study medication. These records will be part of each patient’s Case Report Form (CRF). All study medication packs received by the pharmacy shall be accounted for.

Interaction with other medicinal products and other forms of interaction

TXA will be given as a single use treatment in this trial therefore there will be no prohibited concomitant therapy use. Subjects using therapeutic anticoagulation other than DOACs at enrolment are excluded from the study.

TRIAL / STUDY OBJECTIVES AND PURPOSE

PURPOSE

To assess the clinical effectiveness of TXA after ICH. The results will determine whether TXA should be used in clinical practice to treat ICH.
Hypothesis: TXA improves outcome after ICH by stopping haematoma expansion, preventing early death and improving functional status in survivors.

PRIMARY OBJECTIVE

To assess the effect of TXA versus usual care on early death ⩽7days after ICH.

SECONDARY OBJECTIVES

To assess the effect of TXA versus usual care on dependency (modified Rankin Scale) at day 180 after ICH.
To assess the cost effectiveness and cost utility (based on discharge and destination) of TXA versus usual care at day 180 after ICH.

TRIAL / STUDY DESIGN

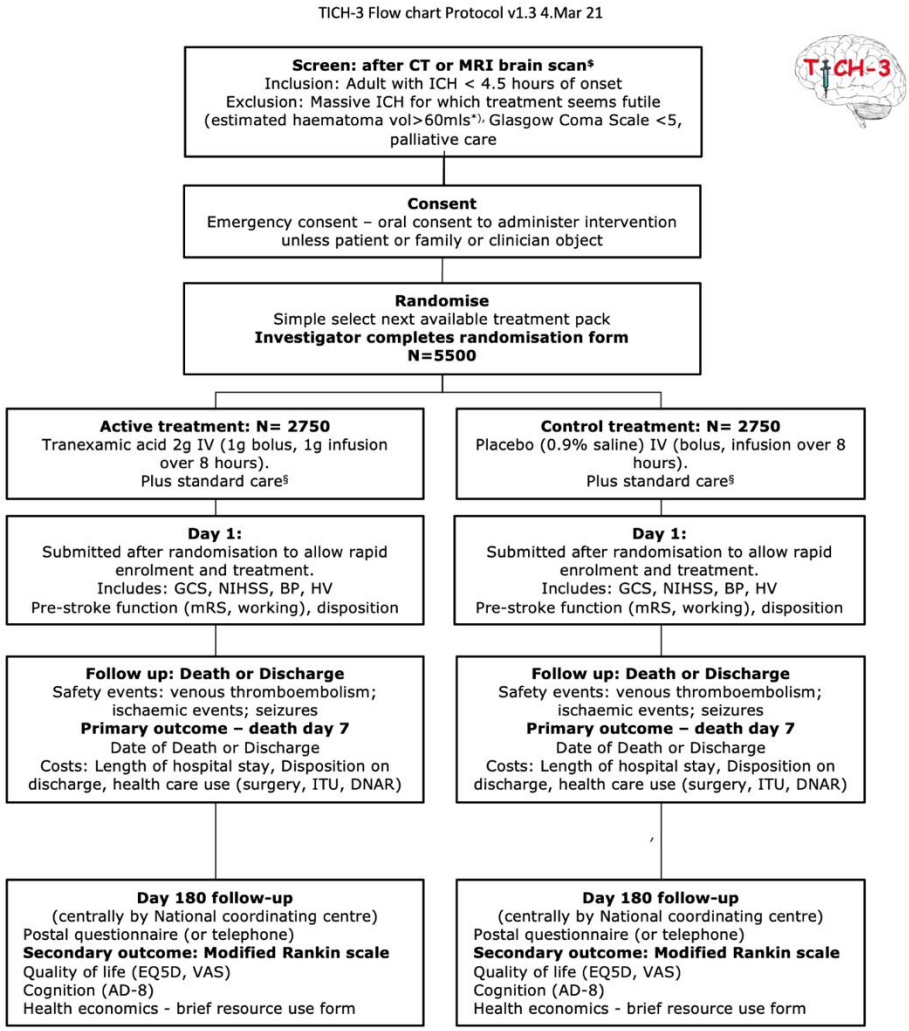
TRIAL / STUDY CONFIGURATION

Pragmatic phase III prospective blinded randomised placebo-controlled trial performed in two phases: a 30-month internal pilot phase with pre-specified progression criteria then main phase (approximately 145 centres, recruit to a total of 5500 participants).
There will be no break in recruitment as the trial proceeds from the start-up phase to the main phase unless the pre-specified stopping criteria are met.

Figure 1 below shows a schematic diagram of trial design, procedures and stages, randomisation, baseline & intermediate visits, final visit, and long-term follow-up.

TRIAL FLOW CHART

Figure 1



§ standard imaging on arrival to hospital for all suspected acute stroke patients; *estimated haematoma volume
§ standard care for ICH including blood pressure lowering and admission to stroke unit as indicated
National coordinating centre is Nottingham in the UK
International follow-up will be coordinated and delivered by the countries National Coordinator
Abbreviations: ICH Intracerebral haemorrhage, IV intravenous, NIHSS National Institute Health Stroke Scale, HV haematoma volume, DNAR do not attempt resuscitation; GCS Glasgow coma scale, Blood Pressure, ITU intensive care unit, EQ5D EuroQuol 5 Domain, VAS visual analogue scale, AD-8 The Washington University Dementia Screening Test

Simplicity of Trial Procedures

To reflect the time critical emergency nature of ICH, and to facilitate rapid enrolment in emergency departments, even in hospitals affected by the pandemic, patient enrolment (simple randomisation) and all other trial procedures are greatly streamlined. Informed consent is simple and data entry is minimal. Randomisation via taking the next treatment pack is simple and quick. Follow-up information is recorded at a single timepoint and may be ascertained by contacting participants, by post, phone, electronically, or by review of medical records and databases.

Primary Endpoint

Primary outcome:

Early death up to and including day 7 after ICH onset.

Justification of primary outcome: Functional outcome using the mRS at 90 days is the recommended outcome measure after stroke. However, our hypothesis is that TXA improves

outcome by stopping HE. HE is the most common cause of early death after ICH, TXA is a haemostatic therapy, therefore we believe early mortality ≤7 days is the most appropriate outcome for TICH-3.

Secondary endpoint

Pre-specified secondary endpoint of importance: functional outcome: Dependency assessed by modified Rankin Scale (Sulter et al., 1999) at 180 days

Other secondary outcomes:

Safety endpoints

Recorded in the first 7 days (or death if sooner): venous thromboembolism; arterial occlusive events (arterial thrombosis at any site, ischaemic stroke, transient ischaemic attack, peripheral artery embolism, myocardial infarction, acute coronary syndrome) and seizures.

Secondary outcomes at 2 days

1. Death up to and including Day 2 after ICH onset

Secondary outcomes at 180 days

1. Functional status (mRS) which includes death and dependency
2. Quality of life (EQ-5D™)
3. Home time (no of days spent at home rather than in hospital or an institution)
4. Cognition (AD-8)(Galvin et al., 2007)

Health economic Data at Discharge

These will include the following to full evaluate all costs and outcomes associated with the inpatient stay

1. Antihypertensive therapy
2. Do not attempt resuscitation orders (DNAR),
3. Admission to intensive care unit,
4. Neurosurgical intervention,
5. Hospital length of stay,
6. Discharge disposition.
7. Eq5d

Health economic Data at 6 months

1. Readmissions,
2. Institutionalization
3. Days at home
4. Health and social use using brief patient data proforma (particularly in community, social care and primary care use)
5. Eq5d

Stopping rules and discontinuation

Participants may withdraw consent for treatment or follow up at any time. Study medication may be stopped at any time by the investigator or treating physician if deemed advisable, however the study medication is only administered for the first 8 hours of the trial.
In the event that clinical evidence of a safety event (thrombosis or seizure) occurs or is brought to the investigator or treating physician's attention during the infusion of the IMP, the infusion must be stopped. This will be recorded as part of the trial documentation and safety monitoring.

An independent Data Monitoring Committee will monitor safety of participants and will report to the Trial Steering Committee. The study may be stopped by the sponsor at any time for safety reasons. The standard Sponsor DMC contract and Charter will be prepared containing details of membership, terms and conditions and full details of stopping guidelines. The DMC will report their recommendation to the independent chair of the TSC.

RANDOMISATION AND BLINDING

Randomisation will be to TXA or placebo in a 1:1 ratio. Due to the emergency situation, a straightforward randomisation process will be used, where sites will simply select the next available treatment pack, which will be a numbered box containing either TXA or placebo according to a computer-defined sequence. Boxes will be identical with the exception of the treatment pack number. Randomisation will be stratified by site with supply to each site balanced for TXA and placebo, using random permuted blocks of varying size. Nottingham Stroke Trials Unit (NSTU) will provide the randomisation list to the IMP manufacturer Sharp Clinical Services UK.

Blinding: Sharp Clinical Services UK will prepare blinded individual treatment packs containing four 5ml glass ampoules of TXA 500mg or sodium chloride 0.9% which will be very similar in appearance. We do not specify the brand of TXA and saline glass ampoules to be used for IMP production in the protocol or IMP-D due to global availability and supply issues that may jeopardise IMP production. With a generic product it is not possible for the blinded glass ampoules to be absolutely identical. However, the blackout labels and heat shrink wrapping ensure the blinded IMP products are very similar in appearance meaning the risk of unblinding is very low. Furthermore, in the unlikely event that the person administering the IMP is unblinded, we believe the potential for this to negatively impact the integrity of the trial, either by influencing the primary outcome (death at day 7) or leading to allocation bias is negligible.

Allocation concealment: Participants, their families, research staff conducting the enrolment and prescribing treatment, the clinical team looking after the participant and research staff conducting the follow-up will be blinded to the treatment allocation for the duration of the study. The TMG and research staff at the coordinating centre will remain blind to treatment allocation until the data collection is complete, statistical analysis plan (SAP) finalised, and the database is locked. The DMC will have access to data split by treatment group, but will not be informed of group allocation, unless this is specifically requested. The TSC will remain blinded, unless a concern requiring unbinding is raised by the DMC. The TMG and the study statistician will only have access to data relating to the whole cohort. Reports split by intervention (as required by the DMC) will be prepared by an independent statistician in the Nottingham Clinical Trials Unit who will not have contact with participants.

Maintenance of randomisation codes and procedures for breaking code

Clinicians, patients and outcome assessors (clinical, radiological assessors) will be blinded to treatment allocation.

In general there should be no need to unblind the allocated treatment. If some contraindication to TXA develops after randomisation (e.g. clinical evidence of thrombosis), the trial treatment should simply be stopped. Unblinding should be done only in those cases when the doctor believes that clinical management depends importantly upon knowledge of whether the patient received TXA or placebo. The investigator can unblind if they believe it is in the best interest of a patient.

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. The rate of unblinding will be monitored and audited. The emergency contact details will be given to the investigators at participating sites.

In the event of breaking the treatment code this will normally be recorded as part of managing a SAE (see below for more details) and such actions will be reported in a timely manner. The Chief Investigator (delegated the sponsor's responsibilities) shall be informed immediately (within 24 hours) of any serious adverse events and shall determine seriousness and causality in conjunction with any treating medical practitioners.

TRIAL MANAGEMENT

The trial coordinating centre will be based in the Stroke Trials Unit at the University of Nottingham, UK. The trial will be managed by the chief investigator and the trial management group.
The Chief Investigator has overall responsibility for the study and shall oversee all study management.

The data custodian will be the Chief Investigator.

The sponsor will be University of Nottingham and the trial will be coordinated by Nottingham Stroke Trials Unit (NSTU) in conjunction with Nottingham Clinical Trials Unit (NCTU). This will include trial management, data management, database development, provision of the randomisation list to the IMP manufacturer and maintenance and statistical analyses and reporting. The Trial Management Group (TMG) will be responsible for the day-to-day management of the trial. The TMG will be responsible for ensuring project milestones are achieved, meeting at least monthly throughout the duration of the trial.

The trial will consist of a UK base with UK participating sites and an international element involving a number of international sites.

For non-UK countries National Coordinators will be appointed to facilitate obtaining their national and local approvals for site hospitals. In the EU Peter Kelly has been appointed as the EU Legal Representative to represent the UK Sponsor in the European Union. Separate local approvals will be sought for the international sites, all applicable local regulations will be adhered to, and a contract will be in place between the University of Nottingham and those sites apportioning liabilities and responsibilities for the conduct of the study.

A Trial Steering Committee (TSC) will be established to include an independent chair, two independent members and a patient representative in accordance with Sponsor and NIHR HTA guidance. The TSC will provide trial oversight, monitor trial progress and conduct and will act, when appropriate, on the recommendations of the Data Monitoring Committee (DMC). The TMG will report to the TSC. The TSC and DMC will meet before the trial commences to approve the protocol, then 6-monthly in the first instance and then at least yearly at their discretion.

An independent Data Monitoring Committee (DMC) will be established to include an independent chair, disease specific expert and statistician and will be privy to data as the trial progresses, with a remit of assessing safety events (including but not limited to seizures, thrombo-embolism, arterial occlusive events and death, SARS and SUSARs) and efficacy outcomes during trial recruitment. The Chair of the DMC will communicate with the Independent Chair of the TSC.
A DMC charter will be drawn up in line with the DAMOCLES Study Group guidance.("A proposed charter for clinical trial data monitoring committees: helping them to do their job well," 2005) The DMC Charter will define the schedule and format of DMC meetings, the method and timing of interim reports and stopping rules. The stopping rules are based upon a combination of presence

of ‘proof beyond a reasonable doubt’ and the likelihood that the results would change clinical practice. They are not purely mathematical stopping rules, but are strongly influenced by the Peto rule (Peto et al., 1977) where a difference would generally need to be of the magnitude of at least three standard errors. The frequency of such analyses will be determined by the DMC and does not need to be pre-specified, but the minimum frequency will be recorded in the charter. Any decision for premature disclosure of unblinded results to the TSC by the DMC would be justified on the basis of an appropriate combination of mathematical stopping rules and scientific judgment.

DURATION OF THE TRIAL / STUDY AND PARTICIPANT INVOLVEMENT

Participant Duration

The maximum duration of each participant’s involvement in the study will be 6 months.

Study Duration

Study duration will be 7 year 4 months.

End of the Trial

The end of the study will be database lock following completion of the last 6-month follow-up of the last participant.

SELECTION AND WITHDRAWAL OF PARTICIPANTS

Recruitment setting

Participants will be recruited from emergency departments, acute stroke services/units across the UK and worldwide. UK participants will be recruited from NIHR Clinical Research Network sites who have dedicated staff to facilitate recruitment and follow-up.
The study will be co-adopted by the NIHR Clinical Research Network Stroke and Injuries & Emergencies portfolios in the UK to enable efficient recruitment from the emergency department. Inclusion of sites outside the UK will both boost recruitment and enhance the external validity of the trial. While the majority of participants will be from the UK, it would not be possible to deliver a definitive study of this size without international enrolment. International sites will allow the question be answered more efficiently, increasing access to potentially eligible subjects, allowing us to reach the recruitment target quicker and provide better value for money.(Minisman et al., 2012) We have selected international sites that are comparable to those in the UK, with similar clinical pathways and models of care for ICH patients.

Care pathway: This pragmatic study is designed to match the clinical care pathway for acute stroke with rapid brain imaging to assess suitability for hyper acute treatments with a 4.5-hour time window such as thrombolysis. Patients will be assessed for eligibility immediately after the CT scan confirms diagnosis of ICH. The emergency consent procedure will facilitate enrolment out of hours and simple randomisation will enable the IMP to be given rapidly in the scanner, as with thrombolysis for ischaemic stroke. Enrolment into TICH-3 will be in addition to standard care, which includes lowering high blood pressure as recommended in clinical guidelines.(Hemphill et al., 2015; National Institute for Health and Care Excellence, 2019) This is important as blood pressure lowering was the significant interaction in TICH-2, and a synergistic relationship between blood pressure lowering and TXA is biologically plausible. For patients taking DOAC at time of enrolment, standard of care may include reversal of anticoagulation in accordance with clinical guidelines i.e with 4 factor PCC/ andexanet/ idarucizumab. We will record use of anticoagulant and any reversal treatment given as part of standard care prospectively on the case report form. Patients who receive Andexanet as part of the Annexa trial will not be eliglible for co-enrollment to TICH-3.

Equality diversity and inclusion for study participants: Historically women and patients from Black, Asian and minority ethnic (BAME) communities have been underrepresented in stroke trials. Our pragmatic inclusion criteria and emergency consent process, which does not require the availability of partner or relative to consent to enrolment should increase inclusivity. Furthermore, in the UK, in keeping with the NHS Long Term Plan around health inequality in research we embed a SWAT aimed at reducing inequalities in enrolling participants from minority communities. See later in protocol for details of SWAT.

Participants will be recruited from emergency departments, acute stroke services/units across the UK and worldwide. The initial approach will be from a member of the patient's usual care team (which may include the investigator). Due to the emergency nature of ICH we will use an ethically approved emergency consent process to allow enrolment of patients without the capacity to consent for themselves. We have worked closely with our UK stroke survivor group to develop the consent approach.

If needed, the usual hospital interpreter and translator services (as used in clinical practice) will be available to assist with discussion of the trial, the participant information sheets, and consent forms, but the consent forms and information sheets will not routinely be available printed in other languages. Provision of information sheets in other countries' languages shall be according to local national laws and ethical requirements.

It will be explained to the potential participant (or their legally designated representative 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. See below for further details regarding withdrawal.

Eligibility criteria

Inclusion criteria:

i. Adults (≥ 18 years)
ii. Presenting within 4.5 h of onset of acute spontaneous ICH
iii. ICH confirmed on brain imaging
iv. When onset of symptoms is unknown patient must be within 4.5 hours of symptom discovery and have no other exclusion criteria.
v. Patients taking direct oral anticoagulants can be included
vi. Informed consent according to Article 35 of (EU) No 536/2014
vii. EU country specific descriptions- see Appendix 2 and Part II document

Exclusion Criteria:

i. Patient with a known recommended indication for TXA treatment (e.g. traumatic brain injury).
ii. Patients with contraindication to TXA in view of treating physician should be excluded. I.e where the contraindication outweighs the risk of giving TXA to a patient as an emergency ICH treatment:
    a. Active seizures
    b. Current diagnosis of acute venous or arterial thrombosis
    c. Hypersensitivity to TXA
    d. Patients with known underlying structural abnormality such as arteriovenous malformation, aneurysm, tumor. An underlying structural abnormality does not need to be excluded before enrolment, but where known, patients should not be recruited.
iii. Patient known to be taking therapeutic anticoagulation at time of enrolment, with the exception of direct oral anticoagulants (patients taking direct oral anticoagulants are not excluded).
iv. Massive ICH for which haemostatic treatment seems futile (i.e. when haematoma volume is estimated as larger than 60ml).

v. Severe coma (Glasgow Coma Scale <5)
vi. Decision already taken for palliative (end of life) care with withdrawal of active treatment

Justification for inclusion/exclusion criteria:

Haematoma volume (HV): HV is one of the strongest predictors of haematoma growth and is independently associated with outcome after ICH. Previous work from us and others have suggested that patients with baseline HV >60 mls are destined to have a poor outcome (as assessed by a mRS of >3) and hence are to be excluded from TICH-3.
Measurement of HV can be done simply using the ABC/2 method(Kothari et al., 1996) in less than a few minutes. Whilst this measurement is pre-dominantly a research tool, it is increasingly used in clinical practice. If ABC/2 measurement is not possible in the time available a simple single measurement of the largest haematoma diameter provides an accurate estimate, if the length measurement is greater than 5cm the haematoma volume is likely to be greater than 60mls and the patient should be excluded(Bath et al., 2019).

Time: The risk of haematoma expansion is related to time from symptom onset, with risk of haematoma expansion being the highest in the first few hours and plateauing by 6 hours. Whilst other TXA studies have shown greatest efficacy when given within 3 hours of bleeding, these were in patients who did not have brain imaging available to target patient selection. By measuring HV on brain imaging we are able to exclude those who have already undergone significant expansion and least likely to benefit. We will include only those with HV < 60 mls who still have the potential to benefit from haemostatic therapy. Furthermore, 4.5 hours is the time window for thrombolysis in ischaemic stroke allowing us to mirror the clinical pathway for ischaemic and haemorrhagic stroke, making use of recent developments for rapid imaging and diagnosis in patients presenting within 4.5 hours of stroke onset.
Patients in whom time of symptom onset is unknown (such as wake up stroke) may be included provided that the CT scan does not show HV>60mls and as long as the patient is presenting within 4.5 hours of wake-up or discovery as they may have the potential to benefit from haemostatic therapy as they have not already undergone catastrophic haematoma expansion (as confirmed by HV < 60 mls).
Patients who are potential neurosurgical candidates will not be excluded from TICH-3 as the decision on whether a patient is a candidate for neurosurgery can take some time – and we do not want to encourage investigators to delay enrolment.
Patients with intra-ventricular haemorrhage (IVH) will not be excluded as they contribute approx. one third of patients with ICH. IVH volume is not routinely measured in clinical practice, and we believe any attempt to ask investigators to measure IVH volume will be unsuccessful and delay enrolment and treatment.

Direct oral Anticoagulatnts: Patients taking direct oral anticoagulants may be included as there is equipoise amongst clinicians around whether TXA is beneficial after ICH. The recently concluded TICH NOAC RCT (NCT02866838) confirmed that it is possible to randomise these patients to TXA or placebo. For patients taking DOAC at time of enrolment, standard of care may include reversal of anticoagulation in accordance with clinical guidelines i.e with 4 factor PCC, andexanet or idarucizumab. We will record use of anticoagulant and any reversal treatment given as part of standard care prospectively on the case report form. For the analysis, patients taking DOAC at baseline will be a pre-specified subgroup.

ICH in patients taking anticoagulants is ‘spontaneous’ as the underling aetiology is small vessel disease/CAA in the vast majority of patients(Seiffge et al., 2021). Most patients on VKA are within or below the therapeutic range when they bleed and the same is true for patients on DOACs (Seiffge et al., 2018)

Treatment with TXA does not deprive patients on DOACs from other reversal/antidote treatments (PCC, andexanet, idarucizumab) if local investigator assume this necessary. Actually, >40% of

patients in the “usual care” group of the currently ongoing ANNEXA-I RCT do not receive any “reversal” treatment. Patients that are part of the ANNEXA trials cannot be co-enrolled to TICH 3.

The TICH NOAC study (NCT02866838)[34] (publication currently in press) is the first study looking at the effects of TXA in DOAC associated bleeds. Regarding safety in patients receiving TXA while on DOACs, the TICH NOAC study observed no difference between the TXA and placebo groups in any serious adverse events (including major thromboembolic events, seizures and death) at day 7 or day 90. There was also no difference in major thromboembolic events in participants that received TXA and concomitant treatment with 4PCC. A subgroup analysis showed no signal for a synergistic effect between TXA and 4fPCC. All major thromboembolic events were observed in participants who had not been restarted on oral anticoagulation and occurred at least two weeks after ICH onset. The study concluded that there were no major safety concerns for the use of TXA in addition to standard care in patients with NOAC-associated ICH. This study also highlighted the need for further trials on haemostatic treatments to improve outcomes in NOAC-associated ICH, especially trials targeting an early treatment window.

There is little to no data available on concomitant use of reversal treatments such as PCC, andexanet, idarucizumab with tranexamic acid. Andexanet is only FDA approved and not widely available worldwide leaving factor Xa DOAC patients with very little treatment options.

Pregnancy: We have not excluded participants who are of childbearing age (fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause). We do not mandate pregnancy testing prior to enrolment as this is an emergency study and it is not possible to delay enrolment to check for pregnancy (see below regarding pregnancy testing). Pregnant women will be excluded if required by any EU country/member state as per their requirements.

If the patient is known to be pregnant the decision to include a participant is at the discretion of the treating physicians (stroke physician and/or obstetrician) and would take into account, the likely risk benefit to the mother. Exclusion of pregnant women with acute ICH from clinical trials has been a problem and should be avoid as recently recommended in the literature (Miller & Leffert, 2020)

The single dose is rapidly excreted and has an established safety profile, being utilised in pregnant women for the treatment of post-partum haemorrhage (Peitsidis & Kadir, 2011). IV TXA used off-label has been tested in randomised trials (WOMAN, CRASH, etc) for the treatment (WOMAN Trial Collaborators, 2017) (Ducloy-Bouthors 2011; WOMAN Trial Collaborators 2017) and prophylaxis of postpartum haemorrhage in females prior to vaginal or caesarean delivery (Novikova 2015; Saccone 2019; Sentilhes 2018; Simonazzi 2016; Xia 2020).

No cases of congenital malformation have been reported among the small number of cases that have been exposed to TXA in early pregnancy and no cases of intrauterine death have been reported among those exposed in later pregnancy ((UKTIS, 2022)). Additionally, according to the FDA, only animal studies have assessed TXA in early pregnancy with results showing no evidence TXA causes impaired fertility or harm to the foetus (Food & Drug Administration, 2013).

Meta-analyses did not find any significant increase in thrombotic events in pregnant women after the use of TXA during pregnancy (Abu-Zaid et al., 2022; UKTIS, 2022).

Possible serious adverse reactions related to tranexamic acid in pregnancy, fetal or maternal outcomes should be reported through appropriate channels (see Chapter on Reporting SARs and SUSARs)

Pregnancy Testing: Performing a pregnancy test in woman of child bearing age before enrolment is at the discretion of the treating physician unless mandated as a specific requirement in any EU country/ Member State. ICH is a medical emergency with the potential for rapid deterioration and the majority of ICH patients will be seen and treated in emergency departments. The time delay to intervention while awaiting a pregnancy test could create a time window during which haematoma expansion could occur, haematoma expansion is the commonest cause of death after ICH. The risk of haematoma expansion is likely to outweigh the risk of TXA in the first trimester of pregnancy. However, the final decision of eligibility is whether the treating physician/clinician's 'uncertainty' as to whether or not to use TXA in a particular patient with ICH.

Breastfeeding: TXA has been shown to be safe amongst women who are breastfeeding (Ahmadzia et al., 2021) both at the time of delivery as well as a follow up study 1-3 years post TXA administration which showed no adverse effects were reported to both mother and infant (Gilad et al., 2014). In TICH-3 breastfeeding will be stopped for a minimum of 3 days.

History of Seizures: High doses of TXA has been associated with increased risk of seizures in previous studies. Given that is has been previously established as a known adverse effect that has adverse neurological outcomes, longer hospital stays, and increased in-hospital mortality we will be excluding patients with active seizures and/or epilepsy. A prior history of epilepsy does not exclude patients from being enrolled, but is at the discretion of the treating physician.

However, a recent meta-analysis looking at the risks of seizures in patients taking 2g or less of TXA a day shows no increased risk of seizures(Murao et al., 2021). . All patients will be monitored accordingly and in the event of a seizure, this will be recorded and reported as a pre-specified safety event

Acute venous or arterial thrombosis: patients with a current diagnosis of acute venous or arterial thrombosis will be excluded. Previous venous and arterial thrombosis or known coagulopathic disorders will not be a prespecified exclusion criteria because in the setting of ICH with risk of haematoma expansion and early death, potential benefit is likely to far out weight the risk of propagating an venous or arterial thrombosis.

We know from meta-analysis of patients taking TXA for ICH have shown no increased risk of venous or arterial thrombosis in population of patients taking 2g/day or less of TXA The certainty of evidence was judged as high for thrombotic events (Murao et al., 2021; S. et al., 2021)

Given that it is an previously established side effect we will monitor our patients for acute venous and arterial occlusive events as a pre-specified safety outcome.

Expected duration of participant participation

Study participants will be participating in the study for a maximum of 6 months.

Removal of participants from therapy or assessments

Withdrawal

Participation in the trial is voluntary. Participants are free to withdraw from the trial at any time without giving a reason. The participants will be made aware that this will not affect their future care. Participants will be made aware (via the information sheet and consent form) that should they withdraw the data collected to date cannot be erased and may still be used in the final analysis.

The participant will be asked if they wish to withdraw from any or all; of follow-up with participant contact, or follow-up without participant contact. Unless the participant withdraws from follow-up, this will be continued as per protocol even if they have withdrawn from treatment. If the participant declines continued personal participation but allows data collection from other sources (such as the

general practitioner and hospital databases) follow-up data will be collected via this route. If the participant is temporarily withdrawn from trial medication by a member of the clinical team, they may restart the trial treatment within the original timescale. Withdrawal, and the reasons for withdrawal, if given, will be documented in the CRF.

Participants will be made aware (via the information sheet and consent form) that should they withdraw the data collected to date cannot be erased and may still be used in the final analysis.

Participant removal from the trial due to adverse events: In any participant who experiences an adverse event the trial medication may be withdrawn permanently or temporarily halted at the discretion of the clinical team. Should the participant not receive the complete intervention, they will remain in the trial and be followed up until the end of the trial, as completeness of follow-up is essential.

Loss to follow-up

Every effort will be made to trace participants lost to follow-up. Hospital databases, records from the general practitioner and details of third persons given by the participant will be checked to determine whether the participant is alive, what his/her health status is, and whether there are any new contact details. Participants will only be defined as lost to follow-up once phone calls, texts messages and letters to the participant and next of kin have not been responded to.

Participants may be withdrawn from the trial either at their own request or at the discretion of the Investigator.

Informed consent

ICH is an emergency condition, that requires urgent treatment, and there is evidence from trials in traumatic extracranial bleeding that TXA is more effective when given early [25]. The need for urgent treatment in the TICH-3 trial means that the implementation of the research should not be delayed and that it would be inappropriate to delay treatment until fully informed written consent can be obtained, either from a patient, relative or other legal representative (Legal representative defined according to the EU's Clinical Trial Regulation (No.534/2014). Rules concerning the determination of the legally designated representatives of incapacitated persons vary depending on the Member States. It should therefore be left to Member States to determine the legally designated representatives of incapacitated persons and minors.

Therefore, oral consent from the patient themselves or their legal representative will be used in the first instance in order to not delay the treatment and so that the treatment pack can accompany the patient to the CT scan to be administered as soon as possible after confirmation of the ICH.

The following processes are to be followed: (For non-UK countries, where possible and where local laws and ethical approval allows):

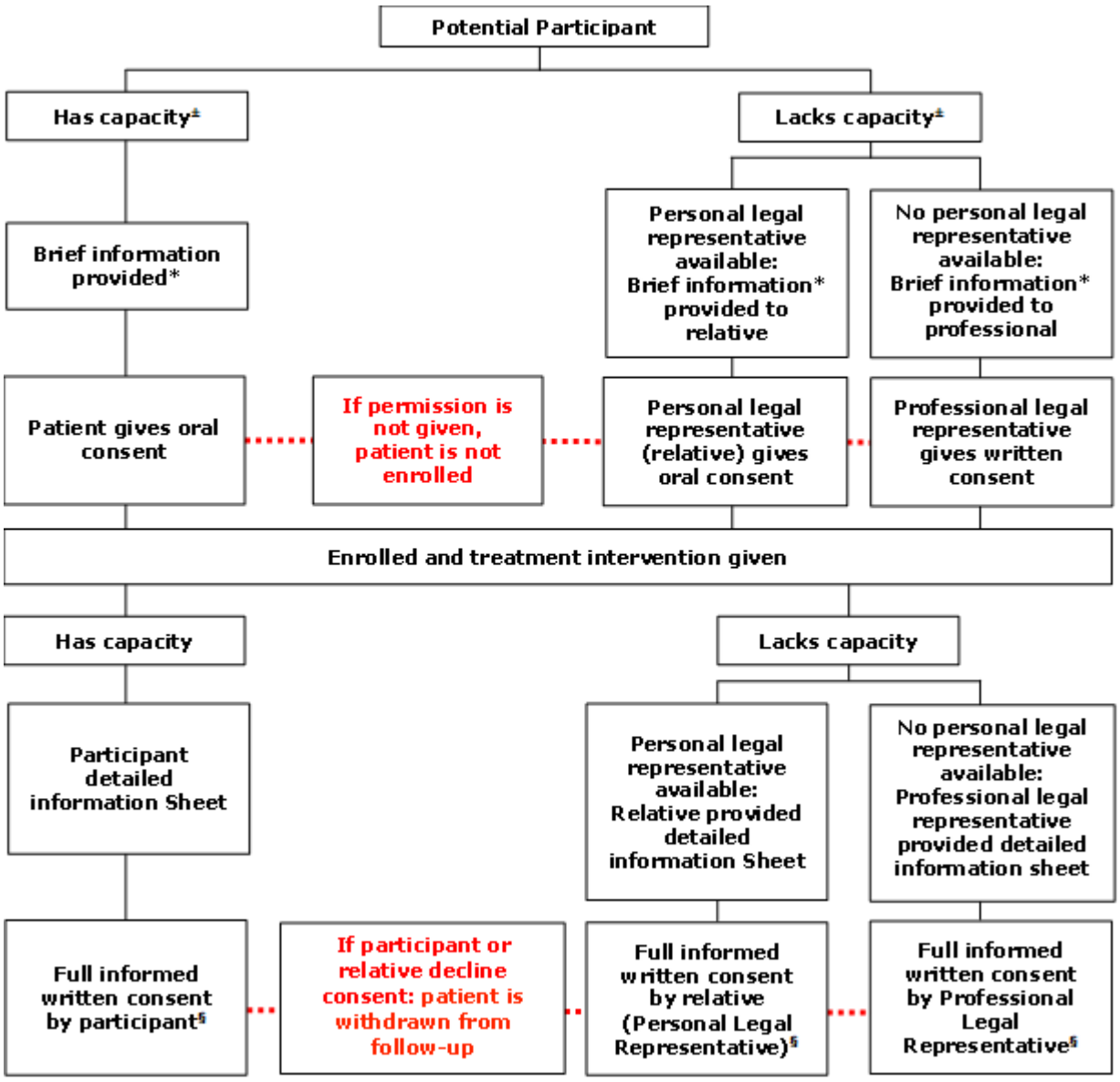
Note: All local/national regulations and ethical expectations surrounding the assessment of capacity and any hierarchy of whom can consent on behalf of a trial participant who lacks capacity to consent for themselves must be adhered to. Information and clarification can be sought from the National Coordinator, and/or the national REC and national competent authorities granting approvals.

Patient has capacity: The emergency nature of ICH means that time prohibits obtaining full written consent even if the participant has capacity. The participant's attending clinical care team will determine if the patient has capacity to consent. If the attending clinician considers it appropriate, the potential participant will be asked if they are willing to be recruited. Specifically, the responsible doctor or delegate will explain that the patient has had stroke caused by bleeding in the brain known as intracerebral haemorrhage (ICH) and will receive the usual emergency treatments for ICH. That, in addition to the usual care, the patient may be enrolled in a research study that aims to improve the treatment of patients with ICH once confirmed by a brain scan. It will

be explained that the study is being done to see whether using a drug called TXA 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 TXA or a dummy medicine (a liquid which does not contain TXA, called a placebo). The doctor will explain that TXA 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 TXA will improve recovery after ICH, at present we cannot be sure about this. A brief information sheet will be provided but detailed written information will only be provided if the patient requests at this point. If time allows, written consent will be obtained. If not, verbal consent will be obtained followed by written consent.
If requested, the detailed information sheet will be provided. If they say yes, the potential participant will be randomised **using this initial oral consent**. The case report form and medical records will record that initial oral consent was given. 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. This approach has been successfully in other hyperacute stroke studies.

Time: Potential participants will be given as long as they need to consider whether they wish to go ahead with study treatment, however we recommend that a maximum of approximately 10 minutes should be taken obtaining initial oral permission (consent). It will be explained to the potential participant that as this is an emergency treatment, with a small potential therapeutic time window. If the potential participant does not want to decide in such a short time frame they will not be enrolled.

Figure 2 Consent arrangements in the UK and Non-UK countries only where applicable. In non-UK countries, local/national regulations and ethical expectations surrounding the assessment of capacity and any hierarchy of whom can consent on behalf of a trial participant who lacks capacity to consent for themselves must be adhered to. We have further elaborated member state specifics in Appendix 2.



□Assessment of capacity is the responsibility of the treating clinical team
*Further written information provided if requested or required and questions answered. Independent doctor will sign at this stage. Rules concerning the determination of the legally designated representatives of incapacitated persons diverge in Member States. It should therefore be left to Member States to determine the legally designated representatives of incapacitated persons.
§If the patient dies before written consent can be obtained, the participant data collected to date is utilised – to exclude this data would introduce bias in the trial
$If the patient does not regain capacity and has no legally designated representative, the participant data is utilised – to exclude this data would introduce bias in the trial

Patient lacks capacity to give consent

The participant's attending clinical care team will determine lack of capacity. If the potential participant lacks capacity to give meaningful consent (e.g. in cases of dysphasia, confusion, or reduced conscious level) the following procedure will be employed:

Legally designated representative present: If a legal representative (relative, personal legal representative or other person suitable to act as a legal representative in the country/EU state and able to represent the patient's presumed views and wishes) is present or can be contacted rapidly by telephone in the time frame required, bearing in mind the emergency nature of the clinical situation, they will be provided with brief information about the trial.

Specifically, the responsible doctor or delegate will explain that the patient has had a stroke suspected to be caused by bleeding in the brain known as intracerebral haemorrhage (ICH) and will receive the usual emergency treatments for the stroke. In addition to the usual care, if ICH is confirmed then the patient may be enrolled in a research study that aims to improve the treatment of patients with ICH. It will be explained that the study is being done to see whether using a drug called TXA 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 TXA or a dummy medicine (a liquid which does not contain TXA, called a placebo). The doctor will explain that TXA 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 TXA will improve recovery after ICH, at present we cannot be sure about this. A brief information sheet will be provided if practicable and time allows but further detailed written information will only be provided on request at this point. If the legal representative objects to the inclusion of the patient in the trial, their views will be respected, and the patient not enrolled

Inclusion of incapacitated adults complies with article 31 as the benefits of the trial are expected to outweigh any risks and it is not possible therein apply to this trial. This is in compliance with the EU regulations, and we have made provision for when national law contradicts the EU law.

If no relatives (or other legally designated representative able to represent the patient's presumed views and wishes) are immediately available, the clinical team can seek the opinion of an independent qualified doctor who is prepared to act as the legally designated representative (professional legal representative) and sign a consent form if in line with national requirements. Rules concerning the determination of the legally designated representatives of incapacitated persons diverge in Member States. It should therefore be left to Member States to determine the legally designated representatives of incapacitated persons and minors. Incapacitated subjects. The independent qualified doctor will not interfere with the investigator decision to enrol a participant in the trial, in line with CTR 536/2014 Article 35.
The independent doctor must be a qualified and registered practitioner and work in accordance with the regulations in the EU/member state.They would usually be a registrar or consultant level.

For participants who were enrolled following agreement by an independent doctor, as soon as relatives are contacted or when the patient regains capacity, a detailed information sheet will be provided, and written consent sought for continuation in the trial.
In event of a patient dying after being enrolled by a professional legal representative but before relatives can be contacted for consent the clinical team should inform the relatives of the patient's involvement in the study and provide information about the study as appropriate, either using approved written information or verbally as per the relatives wishes.

During the process of recruitment and randomisation, the type of consent taken will be documented and monitored to ensure all those with initial oral consent are followed up with written consent, where possible.

Where obtaining this written confirmation of fully informed consent if it is not possible for practical reasons despite all reasonable attempts, such as when the patient does not regain capacity, or if no relatives are available, the patient will remain in the trial unless they (or a relative/legal representative acting on the patient's behalf in the event of lack of capacity) subsequently express a wish to withdraw from the trial. Participants or their legal representative will be informed that they are free to withdraw from the trial at any time without giving a reason and made aware that this will not affect their future care. The participants' decision to withdraw would overrule the decision of the legal representative.

Telemedicine: Where the independent doctor assesses the patient via telemedicine, verbal consent will be obtained and witnessed by someone present in the hospital and this will be recorded in the medical notes. If the independent doctor does not wish to decide via telemedicine the patient will not be enrolled.

If the patient has capacity to consent but is unable to sign because of impairments (e.g. dominant hand weakness), where possible a mark will be made by the participant, verbal consent obtained, witnessed and signed by an independent observer.
If is not possible for the legal representative to provide consent in person, witnessed consent will be obtained via the telephone or videoconference with a witness. This is particularly important if access to hospital for relatives is restricted due to Covid-19 or other emergencies.

One copy of the consent form will be kept by the participant/legal representative, one will be kept by the Investigator, and a third will be retained in the patient's hospital records.
Should there be any subsequent amendment to the final protocol, which might affect a participant's participation in the trial, continuing consent will be obtained using an amended consent form which will be signed by the participant.

TRIAL / STUDY TREATMENT AND REGIMEN

Appendix 1 shows a schematic diagram of screening, procedures and stages, randomisation, trial treatments, baseline & intermediate visits, final visit, and long-term follow-up.

Study Treatment

Trial treatment is administered as intravenous TXA 2g through a venous cannula with a 1g loading dose infusion (10ml in 100ml sodium chloride 0.9% infusion bag) over 10 minutes followed by 1g infusion (10ml in 250ml sodium chloride 0.9% infusion bag) over 8 hours. Placebo treatment replaces TXA with sodium chloride 0.9%.

As this is a single intravenous injection for a specific time-period and continuing use of this drug is not expected as part of any ongoing or further treatment of the patient then there are no specifications for ongoing medical management of the patients within this trial regimen. All further or additional treatment of individual patients is at the discretion of the treating clinician.

Justification of dose: A 2g dose will produce plasma concentrations sufficient to inhibit fibrinolysis. In the emergency situation a fixed dose is more practical, the fixed dose chosen is both efficacious and safe for large patients and small patients.

In TICH-2 95% of participants received both the bolus and infusion dose, 5% did not receive the infusion dose. Risk of seizures has been demonstrated with TXA use in cardiac surgery where high doses of TXA are used (up to 9g); TXA doses exceeding 80mg/kg were associated with seizures, and risk of seizures were higher with infusion than bolus.(Sharma et al., 2014) The proposed TICH-3 dose 2g will generate doses of 17mg to 50mg/kg assuming weight range of 40-120kg, which will generate plasma concentrations above the range 10-15mg/l needed to inhibit fibrinolysis well below the dose 100mg/kg associated with increased seizure risk..

The dose regime chosen was utilised in CRASH-2, CRASH-3, WOMAN and TICH-2 (approximately 55,000 patients) and was safe and well tolerated with no increase in SAE's, VTE or seizures.

Whilst there is the potential risk of accumulation in patients with renal impairment, as TXA is eliminated through renal excretion, the dosing regimen in this trial is a single dose, such that accumulation is expected to be minimal. Hence, dose adjustment is not required in patients with renal impairment. Only a very small proportion of TXA is metabolized by the liver, thus there is no need for dose adjustment in those with liver impairment.

Assessments

Local investigators will collect and enter data over the internet. Data collection is to be kept to a minimum but includes ethnicity, pre-morbid dependency, medical history (hypertension, prior

stroke, prior Myocardial Infarction, prior Venous Thrombotic Event) and language spoken. Data will be collected within the first 24 hours but does not need to be done prior to randomisation in order to allow rapid enrolment and treatment.

Assessments	Screening	Baseline Data	Day 7	Death/Discharge	Day 180
Clinical Assessment	x[$]		x		
Eligibility screening	x				
Consent	x				
Randomisation		x			
Administer IMP		x			
NIHSS		x[$]	x[$]		
GCS	x[$]		x[$]		
Blood pressure		x[$]	x[$]		
Anticoagulation and anticoagulation reversal use		x[$]	x[$]		
Safety outcomes		x	x	x	
mRS		pre-stroke status			x
EuroQoL (EQ5d 5L)		pre-stroke status		x	x
EuroQoL (VAS)		pre-stroke status		x	x
Cognition (AD-8)					x
Resource use			x	x	x
Patient Self report Health Resource Use Questionnaire					x

mRS modified Rankin scale; NIHSS National institute of Health Stroke Score; GCS Glasgow Coma Scale, Safety outcomes: including SAEs: serious adverse events; [$]Routine clinical assessment.
Safety outcomes: seizures, thrombo-embolism, arterial occlusive events and death within hospital.

Data collection at follow-up

Following consent, participants will be assessed by the clinical team for baseline characteristics, and on day 1, day 7 and at discharge from hospital. Follow up at day 180 will be via a postal questionnaire or telephone interview as is standard practice in clinical stroke trials. Follow up will also comply with the national laws of each country where the trial takes place i.e., France will undergo the 180-day follow up in person as required by law.

Local investigators will collect and enter data and images via the secure internet link 7 days after randomisation: (or at death if sooner) length of stay, disposition.

The National Coordinating Centre will collect information (blinded to treatment allocation) on primary and secondary outcomes at day 180 (end of follow-up) by postal questionnaire (or by telephone or in person depending on national laws)).

Health economic data: We will prospectively collect data on participants' pre-morbid function (mRS) and HRQoL (EQ-5D 5L and VAS), where possible from the participant if not a relative/friend. Subsequent health care use whilst an in-patient: antihypertensive therapy, do not attempt resuscitation orders (DNAR), admission to intensive care unit, neurosurgical intervention,

hospital length of stay, discharge disposition. At day 180 we will collect data on readmissions, institutionalization, days at home and HRQoL (EQ-5D 5L), health and social use using brief patient data proforma (see later for details of health economic outcomes.

Neuroimaging: As part of standard care for acute stroke, all participants will have had a pre-recruitment cranial CT or MRI scan on admission to hospital (prior to enrolment) to confirm the presence of ICH. CT is standard in most UK hospitals. Pre-recruitment CT scans will be collected after recruitment into the trial is confirmed (encrypted data via internet or post) to allow accurate and consistent imaging phenotyping, particularly in respect of HV. Estimation of haematoma size (ABC/2 rule or A< 5cm) will be performed by investigators at sites prior to enrolment. We will not routinely perform follow-up imaging due to the high cost and burden on sites involved.

Follow Up

Performed centrally with postal (or telephone) follow up at day 180.
Postal questionnaires are used widely in clinical trials and measurement of mRS via this method is valid and reliable. In previous studies we have used telephone questionnaires as they allow assessment of cognition and other outcomes, however they are more time consuming and costly. Furthermore, stroke survivors told us they find communication by post less intrusive than phone calls. Hence, we plan to use a postal questionnaire but in participants where this is not returned will confirm participant status and then attempt to contact participants by phone and complete the questionnaire over the phone. The questionnaire can be completed by the participant or a proxy. This approach was successfully used in 8000 participants with stroke in the HTA funded study, SO2S (Roffe et al., 2017).

There are increasing calls to measure cognition after stroke and ICH, as patients are at increased risk of dementia. The measurement of cognition through an informant is validated, and the Washington University Dementia Screening Tool AD-8(Galvin et al., 2007) is a self-rating tool that can be used by patient or informant, hence making it suitable as an affordable tool in this large pragmatic study. AD-8 has been validated in a number of languages.(James E. Galvin & Zweig)

Concomitant and Rescue Medications and Treatments

Enrolment into TICH-3 will be in addition to standard care, which includes lowering high blood pressure as recommended in clinical guidelines.(Hemphill et al., 2015; National Institute for Health and Care Excellence, 2019) Antihypertensive treatment will be given according to clinical need at the discretion of the treating clinician, in accordance with clinical guidelines. We will record BP and use of acute BP lowering treatment as part of the case report form. Subjects using therapeutic anticoagulation other than DOACs at enrolment are excluded from the study. There are no other prohibited concomitant treatments. For patients taking DOAC at time of enrolment, standard of care may include reversal of anticoagulation in accordance to clinical guidelines (this may include 4 factor PCC, andexanet, idarucizumab). We will record use of anticoagulant and any reversal treatment given as part of standard care prospectively on the case report form. Patients who receive Andexanet as part of the Annexa trial will not be eligible for co-enrolment to TICH-3.

Accountability for drugs & placebos

Each site will maintain an accountability log and be responsible for the storage and issue of study medication. Following a brain scan that confirms ICH, consent and randomisation, treatment will be prescribed. The research team will record administration of the drug to the patient on the participant's CRF. Unused and partially used supplies will be returned to pharmacy. This will be recorded in the pharmacy study log.

Management of study drug overdose

No specific antidotes are available. The study drug will be administered by slow intravenous injection by qualified nursing staff so the potential for overdose is not anticipated.

Urgent Safety Measures

An Urgent Safety Measure is a procedure taken to protect a research participant when that participant is identified as being at risk of harm in relation to their involvement in a research project and urgent action, which deviates from the approved protocol, is required to manage the event and protect the participant

TXA has been used extensively and has an established safety profile. See literature review in protocol.
Urgent safety measures will be taken as necessary to protect a research participant when that participant is identified as being at risk of harm in relation to their involvement in the study.

Urgent safety measures will be communicated to the competent authority immediately. The sponsor or their delegate (EU legal representative or National Coordinator) shall communicate with the relevant competent authority according to local procedures. The Sponsor shall be informed and any necessary amendments to the protocol will be made and all participating countries informed.

Protocol Deviations And Violations

Protocol Deviations
A protocol deviation is a minor move away from described procedures as an action or event that does not affect the scientific soundness of the research plan or the rights, safety, or welfare of human subjects.

Examples of Deviations are given below but this is not exhaustive:

- Conducting a study follow up outside of the required timeframe;
    - 7-day follow-up: >3days past the due date
    - Discharge and death form: >7days past the due date
- Trial medication administered incorrectly, despite correct prescription e.g infusion lasting 12 minutes not 10. Minor increase or decrease in infusion delivery time (+/-10%) with no impact on safety or efficacy. If the infusion is administered faster than 10 minutes this would have potential safety implications and is a protocol violation.
- Using non-consecutive treatment packs instead of lowest numbered consecutive treatment packs as instructed. Randomisation occurs when the investigator opens the lowest numbered consecutive treatment pack and administers it to the participant. When the investigator opens a treatment that is not the lowest treatment pack number, this is non consecutive and constitues a minor protocol deviation as it will not affect the safety of the participant or scientific integrity of the study in this double blind CTIMP.

Protocol deviations do not require reporting electronically but will be documented with a file note. Investigators should discuss with the trial office who will advise whether an event requires reporting.

Protocol Violation
A protocol violation is a major variation in practice from the trial protocol, for example:

- Enrolling a participant who did not meet all the inclusion/exclusion criteria i.e after 4.5 hours symptom onset
- Failing to obtain or document informed consent
- Dispensing or dosing error for study medication/drug;
- Using trial medication for non trial patient
- Failing to report unanticipated problems involving risks to participants or others to the appropriate authorities

- Failing to follow safety monitoring plan;
- Implementing unapproved recruitment procedures;
- Allowing an unauthorised person to obtain informed consent;
- Multiple follow ups missed or outside permissible windows
- Materially inadequate record keeping
- Intentional deviation from protocol, good clinical practice, or regulations by study personnel
- Subject repeated non-compliance with study requirement

All suspected protocol violations must be reported to the Chief Investigator, via the online electronic case report form and/or telephone call. The sponsor (or CI as delegate) will decide if a protocol violation is major and or constitutes a GCP breach. 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 (via the EU portal), internal audit of the trial and seeking counsel of the trial committees.

Review of Protocol Violations and Deviations

Protocol deviations and Violations will be reviewed at least annually by both the Data Safety Monitoring Committee (using unblinded data) and the Trial Steering Committee (with blinding to treatment assignment). In addition to this the trial management team with review all deviations and report them to sponsor who will assess to see if they constitute breaches of good clinical practice. This will be recorded in the TMF along with any actions taken regarding education/training at sites. Any sites with frequent protocol violations earlier will be subject to training/education and if necessary, would be closed to recruitment.

Criteria for terminating trial

The trial may be terminated by either the TSC, the sponsor or the funders if there is overwhelming evidence of major safety concerns, new information, or issues with trial conduct (e.g. poor recruitment, loss of resources). The trial may be stopped at individual centres due to unacceptable performance in recruitment and/or failure to comply with protocol.

Any unused and partially used drug and placebo shall be returned to the local pharmacy.

RADIATION EXPOSURE

Details of diagnostic or therapeutic ionising radiation

A pre-recruitment CT head scan is performed at the time of presentation with acute stroke as routine clinical care, whether or not the patient goes on to participate in the trial. This is not considered to be a research-related exposure, although information from the scan is subsequently used to establish eligibility (i.e. by confirming acute ICH).

Patients who are enrolled into the trial may subsequently undergo further CT head scans based on clinical need (for example if there is a clinical deterioration) or based on local clinical practice. These scans are considered to be standard of care (SoC). There will be no additional radiation exposure due to the study.

Trial Procedures

Single run non-contrast CT head scan performed as SoC.
There will be no additional radiation exposure due to the study.

STATISTICS

STATISTICS

Methods

Statistical analysis will be performed by the trial statistician or their delegate(s) using validated statistical analysis software such as Stata or SAS. All variables will be summarised using descriptive statistics appropriate to their distribution.

The analysis and presentation of the trial results will be in accordance with the CONSORT guidelines and a full Statistical Analysis Plan (SAP) based on the approved protocol will be published prior to database lock. The primary objective of the trial is to determine the effectiveness of TXA versus placebo and as such, the principal approach to the primary comparative analysis will be to analyse as randomised without imputation of missing data, with due emphasis being placed on the confidence intervals for the between arm comparisons. Sensitivity and secondary analyses will be considered supportive to the primary. Similarly, analyses of secondary outcomes, will be considered supportive to the results of the analysis of the primary outcome.

Interim analyses of the primary outcome will be performed for review by the DMC only. The frequency of such analyses will be determined by the DMC and will not be pre-specified. They will use this, and other evidence provided in confidential reports presenting data by treatment group, prepared by a statistician independent from the trial, to determine whether the trial should continue. Recommendations to stop, in addition to safety concerns, will be based upon a combination of presence of 'proof beyond a reasonable doubt' and the likelihood that the results would change clinical practice. Such a decision would not be purely mathematical but will be strongly influenced by the Peto rule(Peto et al., 1977) where a difference would generally need to be of the magnitude of at least three standard errors. Examples of where consideration would be given to the trial stopping include, but are not limited to, the following:

- Analysis of death favours the control (hazard) with P<0.02 (2-sided)
- Analysis of death favours the active (benefit) with P<0.001 (2-sided).
- Shift analysis of mRS favours the active (benefit) with P<0.001 (2-sided). The significance level of P<0.001 amounts to 'proof beyond reasonable doubt'.
- Shift analysis of mRS favours the control (hazard) with P<0.02 (2-sided)

Sample size and justification

The null hypothesis is that TXA does not alter death by day 7 in participants with acute ICH. Assuming 10.31% of participants in the placebo group die by day 7 (the proportion observed in TICH-2 participants who would be eligible for TICH-3) 2688 participants per group would allow detection of a difference of 2.57% in the proportion of deaths between the placebo and TXA groups (i.e.7.74% deaths on TXA, OR of 0.73), at the 5% significance level 2-sided with 90% power. This difference is considered by patients and their relatives to be important, clinicians feel that it would change clinical practice, and is plausible, as demonstrated in the sub-group analysis of TICH-2 and the CRASH-II trial. As the primary outcome is death it is anticipated that there will be minimal loss to follow up; in TICH-2 (Sprigg et al., 2018) none of 2325 participants were lost to follow up by 7 days, and in CRASH-3("Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial," 2019) <1% of 12737 participants were lost to follow up. It is therefore planned to include a total of at least 5500 participants with at least 2750 in each treatment arm.

Literature has investigated the reduction in sample size which can be gained by including co-variates in the model for different outcomes: 20% for ordinal analysis of mRS (Peto et al., 1977),

between 15% and 44% for survival data(Minisman et al., 2012) and from 3-46 % for dichotomous outcomes (National Institute for Health and Care Excellence, 2019) have been suggested.

Given the uncertainty around the magnitude of a co-variate adjustment to the sample size, a formal reduction will not be made. However, the table below shows the detectable differences with a final sample size of 2688 participants per arm where a co-variate adjustment has been made. All calculations assume a control rate of 10.31%, 90% power and 5% significance level 2-sided. It can be seen that although the required sample size was determined based on an OR 0.73, when covariate adjustment is applied, and sample size is maintained at 2688/arm for analysis, it may be possible to detect a smaller effect. For example, a 20% reduction in sample size due to covariate adjustment would allow detection of an effect size of OR 0.757.

Reduction in required sample size resulting from co-variate adjustment	% deaths in control group	% deaths in TXA group	Detectable effect when sample size maintained at 2688/arm	
			Risk Difference	Odds Ratio
None	10.31%	7.74%	2.57%	**0.73**
5%	10.31%	7.80%	2.51%	0.736
10%	10.31%	7.87%	2.44%	0.743
15%	10.31%	7.93%	2.38%	0.749
20%	10.31%	8%	2.31%	0.757
25%	10.31%	8.07%	2.24%	0.764
30%	10.31%	8.14%	2.17%	0.771
35%	10.31%	8.21%	2.10%	0.778
40%	10.31%	8.30%	2.01	0.787

Sample size calculations were performed using PASS software.

Baseline characteristics
Characteristics of randomised participants will be compared between the two trial arms at baseline, using appropriate descriptive statistics.

Assessment of efficacy

Primary outcome: Early death up to and including day 7 after ICH onset.
The evaluation of the primary outcome will be performed using regression models for binary outcomes, with adjustment for key prognostic factors. The model will be fully specified in the SAP. Absolute and relative measures of effect and 95% confidence intervals will be presented. The primary outcome will also be investigated in pre-specified subgroups using appropriate interaction terms. The subgroups will be specified in the SAP and will, at a minimum include age, sex, systolic blood pressure, HV, GCS, the start of treatment (≤2, ≤3, >3 hours), antiplatelet (yes no), direct oral anticoagulation (yes, no) and intraventricular haemorrhage (yes, no). The trial is powered to detect overall differences between groups rather than interactions of this kind, therefore the analyses will be regarded as exploratory.

Secondary outcomes
Pre-specified secondary outcome of importance: functional outcome: Dependency assessed by modified Rankin Scale(mRS) (Peto et al., 1977) at 180 days using a postal questionnaire (or telephone if postal not possible).

Additional secondary outcomes:
Death up to and including Day 2 after ICH onset.
Quality of Life (EQ-5D-5L) at Day 180,
Cognition (AD-8) at Day 180.

Secondary outcomes will be analysed using appropriate (depending on outcome type and distribution) regression models adjusting for predefined key prognostic factors. Regression models will be used for binary outcomes such as death at Day 2. Dependency at Day 180 measured using the mRS will be analysed using ordinal logistic regression adjusting for key prognostic factors. The results of these analyses will be considered supportive to the primary.

Assessment of safety

The following pre-specified safety events will be reported by investigators as part of the electronic case report form recorded in the first 7 days:
1) venous thromboembolism
2) arterial occlusive events
3) seizures
4)All fatal events occurring before hospital discharge will also be collected.
These will be summarised using appropriate descriptive statistics according to the treatment the participant received irrespective of randomisation. Where a participant did not receive any intervention, they will be summarised separately. Where a participant did not receive a full dose of the intervention, they will be summarised as though they had.

Justification for safety monitoring/pre-specified safety outcomes:
AEs and SAEs that do not meet the criteria for safety events will not be collected unless they are suspected SARS or SUSARS which should be reported at any time point. SUSARS will be subject to expedited reporting requirements and reported to EudraVigilance as per regulatory requirements.

TXA has an established safety record in 50,000 non-surgical patients(Devlin et al., 2018) and was safe in TICH-2 where patients randomised to TXA had less SAEs at day 2, 7 and 90. Given the participants are in the acute stage of an ICH, there will be a significant number of SAEs and AEs that are related to the stroke but not TXA. We believe that collecting large numbers of unrelated SAEs will adversely increase burden on sites and the trial team without increasing safety for participants. Focus is therefore on events that are highly likely to be related to the study medication. In view of this we will not collect all SAEs unless they are suspected SARS or SUSARS which should be reported at any time point – however we will collect data reported by investigators as part of the electronic case report form on pre-specified safety outcomes (seizures, thrombo-embolism, arterial occlusive events and death (the primary outcome) occurring within the first 7 days. This approach has been taken by other investigators.

Procedures for missing and spurious data

It is expected that missing primary outcome data will be minimal, and the primary analysis will use all available data i.e. missing data will not be imputed.
Analysis of secondary outcomes will also not use any methods of imputation for missing data.
All efforts will be made to obtain missing data and to query spurious data.
Further information will be included in the SAP.

Definition of populations analysed

Intention-to-treat dataset: All randomised participants
Per protocol dataset: All participants in the intention-to-treat population who are deemed to have no major protocol violations that could interfere with the objectives of the study. The per-protocol population will be defined in a blinded review prior to database lock
Safety dataset: All randomised participants.

The primary and secondary outcomes will be analysed according to the Intention to Treat principle using all available data from randomised participants and analysing according to treatment

allocation, irrespective of treatment received (the intention to treat dataset). Sensitivity analyses of the primary and key secondary outcomes will be performed using the per protocol dataset. Safety data will be summarised using the safety dataset, according to the treatment the participant received irrespective of randomisation. Where a participant did not receive any intervention, they will be summarised separately. Where a participant did not receive a full dose of the intervention, they will be summarised as though they had.

Further details will be provided in the SAP.

Internal Pilot:

Objective – to determine the feasibility of the main trial meeting its recruitment target.

Feasibility assessment (Stop-go Decision)

Decision to proceed to main phase – The recommendation to proceed from the internal pilot phase to the main phase of the trial will be made by the TSC approximately 18 months after recruitment start. It will be based on safety (as assessed by the DMC) and information about recruitment. The recommendation will be provided to HTA for ratification.

It is assumed that non-UK sites should have been recruiting for 6 to 12 months when the stop-go decision takes place.

Table shows the decision matrix to be used for the recommendation to proceed.

	Red	Amber	Green
% Threshold	<50%	>50-99%	100%
Recruitment	<500	500 -999	1000*
Active sites	<43	43-84	85*
Rate/site/month	<0.35	0.35-0.64	0.65
Action	Discuss trial viability with TSC and HTA	Continue – action needed: protocol TSC meeting, protocol review, assess & resolve barriers, assess feasibility of increased recruitment at active sites, review site selection, increase site numbers	Continue

Note: As a minimum requirement 65% of the active sites (55 sites) and 65% of the participants (650) will need to be UK-based in order to meet the green criteria.

It is important to note there will be no break in recruitment unless the stopping criteria are met.

HEALTH ECONOMICS

The primary health economics analysis will take an NHS and personal social services cost perspective, in accordance with NICE guidance. Secondary analysis will take wider societal perspective to capture the broader effects of TXA versus Usual care including out of pocket expenses and potential effect on carers and families. This will enable a broader societal perspective to be reported alongside a health service perspective.

Cost

Health resource data will be collected from a hospital perspective from first admission to discharge this will include Length of Stay (LOS); ICU stay; neurosurgical intervention; antihypertensive therapy and Do Not Attempt to Resuscitate orders (DNARs).

A purposely designed self-reported Health Resource Use Questionnaire will be used to capture participant-level resource information for health care use at day 180 for the previous 3 months. Whilst we know this is not ideal, we have the intense period for cost comparison whilst a hospital inpatient. We do not want to ask the patient to record longer than 3 months at day 180, as patient memory is poor beyond this point and asking for a longer recall imposes a greater patient burden.

Two intense cost collection periods enable health economic analysis to be performed on TXA versus usual care base between the groups based on initial inpatient stay and day 90 to 180 costs. The 180-day questionnaire will collect data on all aspects of participant treatment and follow-up including inpatient and readmissions and outpatient hospital visits, medication, rehabilitation and primary and community care use over the last 3 months. The questionnaire will be designed with input from the trial patient advisory group and seek to capture all relevant resource drivers yet minimise burden on the participants. The Health Resource Use Questionnaire (to be submitted to the UK health economists DiRUM database) will ensure the key resource implications for TXA versus control are captured. This resource data will then form the units on which cost data, using sources such as the Unit Cost of Health and Social Care, Personal Social Services Research Unit (PSSRU) of the British National Formulary (BNF), and national reference costs can be attached.

Outcome
The main outcome measures for the economic evaluation will be the QALY (EQ5D-5l) at day 180 and discharge.
Secondary measures will include time at home (or usual residence) at day 180
Discharge destination post I/P stay

Analysis
A number of health economic analysis will be performed.

1. Interim cost effectiveness analysis from a health and social care perspective at discharge.
2. Cost effectiveness analysis of TXA versus usual care at day 180 from a societal perspective based on days at home / discharge destination.
3. Cost utility analysis of TXA versus usual care at day 180 from a societal perspective.

An incremental analysis will be used between the two trial arms. The net monetary benefit framework will be used to estimate the extent to which, and the probability that, TXA is cost effective option compared to usual care. An Incremental Cost Effectiveness Ratio (ICER) will be calculated, if appropriate, in the 12 months from randomisation. Cost Effectiveness Acceptability Curves (CEACs) showing the probability of effectiveness versus willingness to pay at the NICE threshold of £20,000-£30,000 per QALY will be constructed. Key cost drivers will be examined using probabilistic sensitivity analysis.

ADVERSE EVENTS

Definitions

An adverse event is any unfavourable and unintended sign, symptom, syndrome or illness that develops or worsens during the period of observation in the study.
An AE does include a / an:

1. exacerbation of a pre-existing illness.

2. increase in frequency or intensity of a pre-existing episodic event or condition.

3. condition detected or diagnosed after medicinal product administration even though it may have been present prior to the start of the study.

4. continuous persistent disease or symptoms present at baseline that worsen following the start of the study.

Known side effects of TXA: Gastrointestinal disorders (nausea, vomiting, diarrhoea) may occur but disappear when the dosage is reduced. Hypotension has occasionally been reported after rapid intravenous infusion. Rare instances of colour vision disturbances have been reported following long-term use. Rare cases of thromboembolic events have been reported. Rare cases of allergic skin reactions have also been reported.

TXA will counteract the thrombolytic effect of fibrinolytic preparations, but these would be contra-indicated in patients with haemorrhagic stroke.

Reference safety information: Section 4.8 of the SmPC for TXA, Section 10: date of last revision 02 February 2021, will act as the reference safety information.

An AE does not include a / an:

1. medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion); but the condition that lead to the procedure is an AE.

2. pre-existing disease or conditions present or detected at the start of the study that did not worsen.

3. situations where an untoward medical occurrence has not occurred (e.g., hospitalisations for cosmetic elective surgery, social and / or convenience admissions).

4. disease or disorder being studied, or sign or symptom associated with the disease or disorder unless more severe than expected for the participant's condition.

5. overdose of concurrent medication without any signs or symptoms.

A Serious Adverse Event (SAE) is any adverse event occurring following study mandated procedures, having received the IMP or placebo that results in any of the following outcomes:

1. Death

2. A life-threatening adverse event

3. Inpatient hospitalisation or prolongation of existing hospitalisation

4. A disability / incapacity

5. A congenital anomaly in the offspring of a participant

Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

All adverse events will be assessed for seriousness, expectedness and causality by local investigator. If the event is suspected to be a pre-specified safety event, or a suspected SAR or a SUSARs it must be recorded and reported – see below.

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined using the criteria above. Hence, a severe AE need not necessarily be serious.

Causality

Not related or improbable: a clinical event including laboratory test abnormality with temporal relationship to trial treatment administration which makes a causal relationship incompatible or for which other drugs, chemicals or disease provide a plausible explanation**.** This will be counted as "unrelated" for notification purposes.

Possible: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, but which could also be explained by other drugs, chemicals or concurrent disease. This will be counted as “related” for notification purposes.

Probable: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, and is unlikely to be due to other drugs, chemicals or concurrent disease. This will be counted as “related” for notification purposes.

Definite: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, and which can definitely not be attributed to other causes. This will be counted as “related” for notification purposes.

An AE whose causal relationship to the study IMP is assessed by the Chief Investigator as “possible”, “probable”, or “definite” is an Adverse Drug Reaction.

With regard to the criteria above, medical and scientific judgment shall be used in deciding whether prompt reporting is appropriate in that situation.

Reporting of suspected SAR and SUSARs

A serious adverse reaction is any serious untoward and unintended response to an investigational medicinal product related to any dose administered which resulted in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect) that has had its causality assessed as possible, probable or definite. All serious adverse reactions must be recorded and reported.

Local investigators will be asked to contact the study site immediately in the event of any suspected serious adverse reaction or SUSAR. All serious adverse reactions will be recorded and closely monitored until resolution, stabilisation, or until it has been shown that the study medication or treatment is not the cause. The Chief Investigator (delegated responsibility by the Sponsor) shall be informed immediately (within 24 hours) of any serious adverse reactions and shall determine seriousness and causality in conjunction with any treating medical practitioners, as per CT regulation 536/2014 chapter 7, article 41. “The causal relationship is usually assessed by the investigator. The sponsor can upgrade it (from unrelated to related) but cannot downgrade it. The sponsor shall keep detailed records of all adverse events reported to it by the investigator.

For SUSARs, when the sponsor disagrees with the causal relationship expressed by the investigator on the IMP, the opinions of the investigator and the sponsor should be recorded in the Individual Case Safety Report (ICSR) in line with ICH E2B." In Europe this will be in accordance with article 42 of the Regulation (EU) No. 536/2014 to EudraVigilance.

In the event of a pregnancy occurring in a trial participant or the partner of a trial participant further specific monitoring shall not occur during the pregnancy and or after delivery due to the short half-life of TXA and its frequent use in obstetrics unless mandated by a specific EU country/member state. However, any suspected serious adverse reactions will be recorded and reported to the competent authority as below. The definition of SAEs listed in the protocol includes congenital anomaly in the offspring of a participant. Other potential adverse events that maybe reported after pregnancy would include, fetal or pre-term death, miscarriage, low birth weight.

All pre-specified safety events, suspected SARS and SUSARS will be recorded and reported to the competent authority as part of the annual Development Safety Update Reports. SUSARs will be reported within the statutory timeframes to the competent authority, in Europe this will be in accordance with article 42 of the Regulation (EU) No. 536/2014 to EudraVigilance and RECs as stated below. The Sponsor shall ultimately be responsible for adverse event reporting. A

SUSARs

Definition: A serious adverse event that is either sudden in its onset, unexpected in its severity and seriousness or not a known side effect of the IMP *and* related or suspected to be related to the IMP is classed as Suspected Unexpected Serious Adverse Reaction and requires expedited reporting as per the clinical trials regulations. In Europe this will be in accordance with article 42 of the Regulation (EU) No. 536/2014 to EudraVigilance.

All serious adverse events that fall or are suspected to fall within these criteria shall be treated as a SUSAR until deemed otherwise.

The event shall be reported immediately (within 24 hours) of knowledge of its occurrence to the Chief Investigator.

The Chief Investigator will:

- Assess the event for seriousness, expectedness and relatedness to the study IMP
- Take appropriate medical action, which may include halting the trial and inform the Sponsor of such action
- If the event is deemed a SUSAR, shall, within statutory timeframes, enter the required data on the competent authority's reporting platform. In Europe this will be in accordance with article 42 of the Regulation (EU) No. 536/2014 to EudraVigilance.
- Shall inform the REC as required according to national law.
- Shall, within the statutory timeframe send any follow-up information and reports to the competent authority and REC.
- Make any amendments as required to the study protocol and inform the ethics and competent authorities as required

Participant removal from the study due to adverse events

Any participant who experiences a serious adverse reaction may be withdrawn from the study at the discretion of the Investigator. Clinical need and participant safety will be the priority. However, as the treatment is given in first 8 hours only it is likely that the intervention will have been completed – and withdrawal from follow up may not be appropriate. The participant (or legal representative) retains the right to withdraw at any time without giving a reason.

ETHICAL AND REGULATORY ASPECTS

ETHICS COMMITTEE AND REGULATORY APPROVALS

The trial will not be initiated before the protocol, informed consent forms and participant and GP information sheets have received approval / favourable opinion from the individual country/member state competent authority, individual country/member state Research Ethics Committee (REC), each respective National Health Service (NHS) or other healthcare provider's Research & Development (R&D) department (or equivalent), if required according to individual country/ member state law. Should a protocol amendment be made that requires subsequent approvals, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant and GP information sheets (if appropriate) have been reviewed and received

approval / favourable opinion from the authorizing bodies. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the competent authority, healthcare provider and national REC are notified as soon as possible, and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the authorizing bodies will be informed in accordance with local rules

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, in accordance with Regulation (EU) no. 536/2014 any other national laws, subsequent amendments and local healthcare policies as applicable to each country.

INFORMED CONSENT AND PARTICIPANT INFORMATION

The process for obtaining participant informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced but reflect the emergency situation and time critical nature of the intervention, in accordance with Article 35 of (EU) No 536/2014. EU country specific informed consent procedures will be followed by national co-ordinators (appendix 2)

The participant will receive a copy of the signed and dated forms and the original will be retained in the Trial Master File. A second copy will be filed in the participant's medical notes and a signed and dated note made in the notes that informed consent was obtained for the trial.

The decision regarding participation in the study is entirely voluntary. The investigator or their nominee shall emphasize to them that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled.

The investigator will inform the participant of any relevant information that becomes available during the course of the study, and will discuss with them, whether they wish to continue with the study. If applicable they will be asked to sign revised consent forms.

If the Informed Consent Form is amended during the study, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Informed Consent Form by the REC and use of the amended form (including for ongoing participants).

RECORDS

Case Report Forms

Each participant will be assigned a trial identity code number (country number, centre number and randomisation number), allocated at randomisation, for use on CRFs other trial documents and the electronic database. The documents and database will also use their initials (of first and last names separated by a hyphen or a middle name initial when available). The date of birth (dd/mm/yyyy) is entered into the database once for the use of data verification and is not visible when entering study data.

CRFs will be treated as confidential documents and held securely in accordance with regulations. The investigator will make a separate confidential record of the participant's name, date of birth, local hospital number or NHS number, and Participant Trial Number (the Trial Recruitment Log), to permit identification of all participants enrolled in the trial, in case additional follow-up is required.

CRFs shall be restricted to those personnel approved by the Chief or local Principal Investigator and recorded on the 'Trial Delegation Log.'

Source documents

Source documents shall be filed at the investigator's site and may include but are not limited to, consent forms, current medical records, laboratory results and pharmacy records. A CRF may also completely serve as its own source data and shall be identified as such. For example, day 180 from will serve as source document. Only trial staff as listed on the Delegation Log shall have access to trial documentation other than the regulatory requirements listed below. Source documents will be filed in the trial site file and retained for 25 years archiving.

Direct access to source data / documents

The CRF and all source documents, including progress notes and copies of laboratory and medical test results shall made be available at all times for review by the Chief Investigator, Sponsor's designee and inspection by relevant regulatory authorities according to local laws. .

DATA PROTECTION

All trial staff and investigators will endeavour to protect the rights of the trial's participants to privacy and informed consent, and will adhere to the EU General Data Protection Regulations (EU Regulation 679/2016) , 2018 and local national data protection laws for non-EU countries. The University of Nottingham's Trial database (CRFs) will only collect the minimum required information for the purposes of the trial. Paper CRFs (such as the returned day 180 follow up forms which will be collected by the national coordinator or a designated qualified coordinator by the national coordinator) will be held securely, in a locked room, or locked cupboard or cabinet. In countries where national laws do not allow telephone or any form of remote follow up (I.e. France), data will be collected in person by the national coordinator or a designated qualified coordinator appointed by the national coordinator.

Access to the information will be limited to the trial staff and investigators and relevant regulatory authorities (see above). Electronic CRFs will be stored on a secure dedicated web server. Access to the information will be limited to the trial staff and investigators and relevant regulatory authorities (see above). Computer held data including the trial database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one-way encryption method). Information about the trial in the participant's medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information.

Electronic data held at the University of Nottingham will be backed up every 24 hours to both local and remote media in encrypted format.

QUALITY ASSURANCE & AUDIT

INSURANCE AND INDEMNITY

The University of Nottingham as research Sponsor indemnifies its staff with both public liability insurance and clinical trials insurance in respect of claims made by research subjects. Our clinical trials policy is worldwide but separate local national policies have been purchased according to local national requirements to indemnify the University of Nottingham for claims made for proven

negligent harm. It is expected that all participating healthcare providers hold indemnity insurance to cover claims made as a result of their own negligence

TRIAL CONDUCT

Trial conduct will be subject to systems audit of the Trial Master File for inclusion of essential documents; permissions to conduct the trial; Trial Delegation Log will be stored on-line (secure dedicated web server) in addition to record of training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, correct randomisation, timeliness of visits); adverse event recording and reporting; drug accountability, pharmacy records.

TRIAL DATA

The Nottingham Coordinating Centre (NCC) is responsible for on-going monitoring of TICH-3 trial data for the duration of the study. In an international context, TICH-3 will comply with the national laws and competent authority regarding monitoring (i.e., GCP units in Denmark will co-monitor TICH-3 at their sites.)

Monitoring of trial data shall include confirmation of informed consent; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. The Trial Coordinator, or where required, a nominated designee of the Sponsor, shall carry out monitoring of trial data as an ongoing activity.

GCP section 5.18.3 states in regard to monitoring that, “the determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size and endpoints of the trial. In general there is a need for on-site monitoring, before, during, and after the trial; however in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigators training and meetings, and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP. Statistically controlled sampling may be an acceptable method for selecting the data to be verified.”

The TICH-3 trial is a large, pragmatic, randomised double blind placebo controlled trial. The intervention (tranexamic acid) has marketing authorisation in many countries and has been in clinical use for decades.

Its safety profile is well established and no significant serious adverse events associated with its use have been identified. The trial will collect data on pre-specified serious adverse events for the first seven days after enrolment which may theoretically be associated with this product and the condition under investigation, and these will be reviewed by the independent Data Monitoring Committee (DMC). The trial procedures are based on routine clinical procedures and include (1) the intravenous administration of the trial drug using routine clinical use; (2) collecting routine clinical information from the medical records; and (3) informed consent. There are no complex procedures or interventions for the participants or investigators in this trial. Clinical management for underlying conditions will remain as per each hospital’s standard protocol. Based on these factors, the probability of harm or injury (physical, psychological, social or economic) occurring as a result of participation in this research study has been assessed as low in each of these categories. Based on the low risks associated with this trial, the Monitoring Procedure to assure appropriate conduct of the trial will utilise 100% central data monitoring in conjunction with procedures such as investigator training and meetings and written guidance.

Consent Forms will be monitored centrally by the coordinating centre (where permission is given to do so). Investigators/institutions are required to provide direct access to source data/documents for trial-related monitoring, audits, ethics committee review and regulatory inspection.

Routine source data verification will not take place except in exceptional circumstances. This is partly due to COVID-19 and partly due to efficiency given the pragmatic design of the trial.

In exceptional circumstances, NSTU may arrange monitoring visits to sites as considered appropriate based on perceived training needs and the results of central statistical monitoring of study data. The purpose of such visits will be to ensure that the study is being conducted in accordance with the protocol, to help site staff to resolve any local problems, and to provide extra training focused on specific needs. Therefore, no routine source data verification will take place.

A triggered monitoring visit may be performed on request by the Trial Management Committee (TMC), or where concerns have been raised during a central monitoring review. Any SMVs that are deemed necessary with be highlighted during a TMC meeting so that the decision is minuted. On-site monitoring visit triggers may include (but are not limited to):

- A high frequency of protocol queries from site staff
- A high level of findings through central monitoring oversight
- A high number of protocol violations
- Poor data quality (long data entry delays, high query rate and high percentage of missing data)
- Poor adherence to the trial interventions
- High staff turnover

Where corrections are required, these will carry a full audit trail and justification.

Trial data and evidence of monitoring and systems audits will be made available for inspection by the competent authority as required.

The monitoring plan will be compliant with the TICH-3 Working Practice Document (WPD) UK Site Monitoring (tich-3.ac.uk/documents.) and in accordance with EU Member States' rules and regulations

Urgent medical enquires can be contacted via the emergency mobile numbers found on the TICH-3 Website (https://stroke.nottingham.ac.uk/sif/live/)

COVID-19

This trial will take into consideration the impact of COVID-19 on clinical trials worldwide by taking into consideration the European Medical Agency's 'GUIDANCE ON THE MANAGEMENT OF CLINICAL TRIALS DURING THE COVID-19 (CORONAVIRUS) PANDEMIC' Version 5 10/02/2022.

RECORD RETENTION AND ARCHIVING

. In line with CTR Article 58, all records and documents will be retained for at least 25 years in all EU/Member States.

If the responsible investigator is no longer able to maintain the study records, a second person shall be nominated to take over this responsibility. The University of Nottingham will collect records of where local documents have been archived.

The Trial Master File and trial documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at the University of Nottingham. This archive shall include all trial databases and associated meta-data encryption codes. International records shall be retained for 25 years.

DISCONTINUATION OF THE TRIAL BY THE SPONSOR

The Sponsor reserves the right to discontinue this trial at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice from the Trial Steering Committee and Data Monitoring Committee as appropriate in making this decision.

STATEMENT OF CONFIDENTIALITY

Individual participant medical information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted above. Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare. If information is disclosed during the study that could pose a risk of harm to the participant or others, the researcher will discuss this with the CI and where appropriate report accordingly.

Data generated as a result of this trial will be available for inspection on request by the participating physicians*, the University of Nottingham representatives, the REC*, local healthcare R&D Departments (or equivalent) and the regulatory authorities.

*Data only pertaining to those countries/sites

PUBLICATION AND DISSEMINATION POLICY

Simultaneous oral presentation at a large international stroke conference, publication in high impact journal will ensure maximum impact and rapid dissemination with incorporation into guidelines. Stroke survivors and carers will inform dissemination to patients and public which is likely to include social media and a roadshow.

Participants will not be identified in any publications.

Publications that result from the trial will be submitted to CTIS within 1 year from end of trial.

USER AND PUBLIC INVOLVEMENT

This trial builds on work with stroke survivors and their carers in previous studies (TICH-1 and TICH-2), with particular focus on emergency consent methods and choice of outcome measures. We will continue to work with stroke survivors and their carers throughout the trial. In addition, we are committed to increasing inclusivity and representation in our trial and have invited a member of the Leicester BAME PPI group to join the TSC.

Results will be presented to stroke survivors and the public at multiple forums, including the Stroke Assembly lay conference in the UK and across Europe using the Stroke Alliance For Europe (SAFE) network.

Dissemination plan will be developed with the PPI group. Likely to involve a results 'Roadshow' of meetings to lay members around the UK.

Web-hosted lay summary in text and video format developed with the stroke survivor group and Black, Asian and Minority ethnicity Applied Research Collaboration group. Use of social media, Twitter, news broadcasters (with a press release as for TICH-2 and CRASH-3).

STUDY FINANCES

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SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator: (name)_____

Signature:_____

Date: _____

Trial Sponsor : (name)_____

Signature:_____

Date: _____

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Appendix 1:

List of events that are common after stroke and do not need expedited reporting unless they are thought to be a serious adverse reaction or SUSAR. This list is not exhaustive and intended as a guide only. Section 4.8 of the SmPC for TXA is the reference safety information, Section 10: date of last revision 02 February 2021, will act as the reference safety information.

EXPECTED EVENTS NOT SUBJECT TO EXPEDITED SUSAR REPORTING			
After tranexamic acid the following events are expected and therefore not subject to expedited SUSAR reporting:			
Gastro-intestinal	**Cardiovascular**	**Central nervous system**	**General**
Diarrhoea	Arterial thrombosis any site	Convulsions/ Seizure	Anaphylaxis
Nausea	Venous thrombosis any site	Disturbance in colour vision	Fatigue
Vomiting	Collapse	Dizziness	Flushing
	Hypotension		Hypersensitivity including oropharyngeal swelling, urticaria, angioedema
			Rash

Appendix 2: Member State Specific Requirements.

Please note this protocol will adhere to the national member state requirements. A national coordinator representing each country where TICH-3 is taking place informs the TICH-3 trial team in the UK of the regulatory and ethical requirements which we have provided in part II of the application. Additionally, all mandatory investigator training will be catered to each country's requirements. We have detailed some of these requirements below.

France

Statement from the French competent authority: Protected populations (referred to in articles L1121-5 to L1121-8-1 of the Public Health Code of France) * must be clearly mentioned in the non-inclusion criteria of the protocol and its summary:

o Pregnant women, parturient, breastfeeding mothers

o Minors o Persons deprived of liberty

o Persons under psychiatric care

o Persons admitted to a health or social institution for purposes other than research

o Adults under legal protection or unable to express their consent

o Persons in an emergency situation who are unable to express their prior consent

o Non-affiliated or non-beneficiary of a social security system (derogation of the CPP mandatory which authorizes the inclusion of these persons if article L1121-8-1 is respected)

NB: inclusion is possible but must be justified * Articles L1121-5 to L1121-8-1 of the Public Health Code: Protected populations may participate in IR or MDR only under the following conditions:

• either the importance of the expected benefit for these persons is such as to justify the foreseeable risk incurred;

• or the research is justified in terms of the expected benefit for other persons in the same situation, provided that research of comparable effectiveness cannot be carried out on another category of the population. In this case, the foreseeable risks and constraints of the research must be minimal.

Response from the TICH-3 Team: TICH-3 will abide by the national laws and competent authorities of the country it takes part in. According to Articles L1121-5 to L1121-8-1 of the Public Health Code of France, TICH-3 will include protected persons specifically persons in an emergency situation who are unable to express their prior consent. This is due to patients having suffered an intracerebral stroke that has caused bleeding in the brain and therefore may not have the capacity to give prior consent (i.e. unconscious).

As per the Public Health Code of France, the research is justified on the grounds that the intervention Tranexamic Acid has a good established safety profile, is effective in other bleeding conditions (traumatic brain injury, port partum haemorrhage, etc) and may reduce mortality in intracerebral haemorrhage (Guo et al., 2021). We have further updated these points in the TICH-3 Protocol.

Denmark

Statement from the EC of Denmark: The protocol section on “Selection and withdrawal of participants” contains information on informed consent processes in the trial. The processes are not completely in accordance with national law in Denmark. Compliance with the requirements for informed consent will be assessed in detail upon assessment of part II of the application. It is recommended to include in the protocol that compliance with national requirements will be described in part II of the application. It is also noted that the EU Clinical Trial Regulation (CTR) only describes informed consent by a “legally designated representative”. The requirements for who can act as a legally designated representative are described in national legislation.

Response from the TICH-3 Team: We included in the TICH-3 protocol titled ‘International Draft Version 2.0 09/11/22’ that TICH-3 will comply with national law requirements of the country it participates in. Additionally, the National Coordinator of Denmark has uploaded a document in Part II of the CTIS application detailing the compliance, procedures and requirements of how TICH-3 will be undertaken in Denmark.

The TICH-3 trial team has asked the national coordinator of each country, where applicable, to upload a supporting document in the relevant Part II CTIS section addressing their respective national competent authority’s considerations in relation to the trial.

Finland

Due to the emergency nature of the trial, deferred consent will be sought. We have uploaded supporting documents in Part II of the CTIS application signed by the national coordinator and representative of Finland. All procedures will be in accordance with Finland’s ethical laws and considerations.

Ireland

Pregnancy: The decision of testing pregnancy in Ireland is made at the discretion of the treating physician (Stroke physician and/or obstetrician) and study investigator. This information will be relayed in the TICH-3 Ireland SIV investigator training.

Sweden

Professional Legal Representative: As per information received from the national coordinator of Sweden and its regulatory body, appointing a professional legal representative can only be done so via a court in Sweden. As per the national coordinator's decision, TICH-3 Sweden will not be appointing a professional legal representative and will only use the participant or participant's relative in the consent process.

Spain

Professional Legal Representative: As requested by the Spanish Ethical body, a professional legal representative is unacceptable and therefore TICH-3 Spain will not be utilising a professional legal representative and we were advised that in the event that the participant is unable to give consent and no relative is available, the study team should do everything possible to contact a relative (i.e., telephone).