

Intravenous Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH 2): protocol for a randomised, placebo-controlled trial.

Version 1.2
15/01/2016

Correspondence:

Associate Professor Nikola Sprigg, Stroke, Division of Clinical Neuroscience, Clinical Science Building, Hucknall Road, Nottingham NG5 1PB, UK. Email Nikola.sprigg@nottingham.ac.uk

Key words:

hyperacute intracerebral haemorrhage, tranexamic acid, randomised trial, placebo controlled

Word count:

2528 not including references

Conflicts:

None declared

Authors statement: NS KR and PB drafted the manuscript. All authors reviewed and commented on the final manuscript. NS is corresponding author.

Abstract

Rationale

Outcome after intracerebral haemorrhage remains poor. Tranexamic acid is easy to administer, readily available, inexpensive and effective in other haemorrhagic conditions.

Aim

This randomised trial aims to test the hypothesis that intravenous tranexamic acid given within 8 hours of spontaneous intracerebral haemorrhage reduces death or dependency.

Design

Phase III prospective double-blind randomised placebo-controlled trial. Participants within 8 hours of spontaneous intracerebral haemorrhage are randomised to receive either intravenous tranexamic acid 1g 10-min bolus followed by 1g eight-hour infusion, or placebo.

Sample size estimates

A trial of 2,000 participants (300 from start-up phase, and 1,700 from main phase) will have 90% power to detect an ordinal shift of the modified Rankin Scale (mRS) with odds ratio 0.79.

Study outcomes

The primary outcome is death or dependency measured by the mRS at day 90. Secondary outcomes are neurological impairment at day 7; and disability, quality of life, cognition and mood at day 90. Safety outcomes are death, serious adverse events, thromboembolic events and seizures. Cost outcomes are length of stay in hospital, re-admission and institutionalisation.

Discussion

This pragmatic trial is assessing efficacy of tranexamic acid after spontaneous intracerebral haemorrhage. Recruitment started in 2013; as of 15th Jan 2016 1355 participants have been enrolled, from 95 centres in 7 countries. Recruitment is due to end in 2017. TICH-2 Trial is registered as ISRCTN93732214.

Introduction and rationale

Intracerebral haemorrhage (ICH) is a devastating form of stroke, with high early mortality; of those who survive, the majority remain disabled. Despite advances in management of ischaemic stroke, outcome following ICH has remained static for decades.(1) Around a quarter of ICH are complicated by haematoma expansion (HE); this most often occurs within the first few hours, but can occur up to 24 hours from spontaneous ICH (SICH) onset, and is associated with poor outcome.(2-4) Recent evidence has shown that intensive early blood pressure lowering can improve functional outcome, and this has been incorporated into clinical guidelines.(5)

Haemostatic drug therapies aimed at limiting HE have been tested in SICH, with recombinant factor VIIa being the most widely studied. Meta-analysis of these and other haemostatic therapies found no significant benefit on outcome.(6)

Tranexamic acid, an anti-fibrinolytic drug, significantly reduced mortality, with no increase in vascular occlusive events, in patients with major bleeding following trauma.(7) In a subgroup analysis of patients with traumatic ICH, tranexamic acid showed a non-significant trend to reduced mortality, and death or dependency.(8)

A meta-analysis of the only two trials of tranexamic acid in traumatic intracranial haemorrhage showed a significant reduction in post-traumatic intracranial bleeding.(9) However the confidence interval is wide and a larger trial is on-going.(10)

Tranexamic acid has also been tested in aneurysmal subarachnoid haemorrhage, where it reduced the risk of re-bleeding at the expense of increased risk of cerebral ischaemia.(11) However prolonged administration of tranexamic acid for 7 days, and the known risk of delayed cerebral ischaemia without tranexamic acid after aneurysmal subarachnoid haemorrhage, may explain the greater risk of vascular occlusive events.

In two small non randomised studies, tranexamic acid was reported to restrict haematoma expansion following ICH.(12, 13) In a subsequent small pilot randomised study, administration of tranexamic acid was feasible and well tolerated after ICH.(14) There have been recent calls for large trials to evaluate tranexamic acid in ICH, (15) and several phase II studies are on-going.(16, 17)

Methods:

Aim

TICH-2 aims to test the hypothesis that intravenous tranexamic acid is superior to placebo by reducing death or dependency at day 90 when given within 8 hours of SICH.

Design

TICH-2 is an international pragmatic double-blind randomised placebo-controlled parallel group, phase III trial. The pragmatic design ensures that the TICH-2 trial tests whether tranexamic acid is effective in clinical practice, balancing generalizability of results in real life with a sound scientific rationale in academic terms. We have designed the study to include participants who reflect the broad population with acute SICH, and have kept exclusion criteria to a minimum.(18)

Participants are randomised (1:1) to receive either tranexamic acid or matching placebo (0.9 % saline). Outcome is assessed face to face at the end of treatment (day 2) and day 7; central telephone follow up determines outcomes at days 90 and 365. Brain imaging (CT) is performed as part of routine care prior to enrolment; a second research CT scan is performed after 24 hours of treatment to assess haematoma expansion (figure 1).

Patient population

Inclusion criteria

Adults with acute SICH within 8 hours of stroke symptom onset or time last seen well.

Exclusion criteria

- 1) Patients with ICH secondary to anticoagulation, thrombolysis or known underlying structural abnormality such as arteriovenous malformation, aneurysm, tumour, or venous thrombosis. An underlying structural abnormality does not need to be excluded before enrolment, but where known, patients should not be recruited.
- 2) Contraindication to tranexamic acid.
- 3) Pre-morbid dependency (mRS>4).
- 4) Concurrent participation in another drug or device trial. Participants enrolled in TICH-2 may be enrolled into the RESTART trial [ISRCTN71907627 \(19\)](#) after 21 days.
- 5) Pre-stroke life expectancy <3 months (e.g. advanced metastatic cancer).
- 6) Coma – Glasgow coma scale <5
- 7) ICH was secondary to trauma
- 8) Women of childbearing potential, pregnant or breastfeeding at randomisation
- 9) Geographical or other factors that prohibit follow up at 90 days e.g. no fixed address or telephone contact number, or overseas visitor.

Informed Consent

All participants who have capacity need to provide consent before they enter the trial. However, the need for urgent treatment, means that it would be inappropriate to delay treatment when either impaired capacity (e.g. in cases of dysphasia or reduced conscious level) or lack of time prohibit obtaining written consent.

If the potential participant lacks capacity to give informed consent permission will be sought from a relative, or if no relatives are available, a doctor unconnected with the trial, acting as an independent legal representative.

If the time window does not allow investigators to seek full informed written consent, and if the attending clinicians consider it appropriate, patients or relatives (if the participant lacks capacity) will be approached to give oral assent. If oral assent for recruitment is given, participants (or relatives if the participant lacks capacity) will be approached to give written consent as soon as possible after recruitment.

Randomisation

All patients eligible for inclusion are randomised using a secure internet site in real-time. Trial web application/database programmers at University of Nottingham are responsible for the randomisation processing and security of the internet site in conjunction with University of Nottingham IT Services. Randomisation involves minimisation on key prognostic factors: age; sex; time since onset; systolic blood

pressure; stroke severity (National Institute Health Stroke Scale (NIHSS)); presence of intraventricular haemorrhage; known history antiplatelet treatment used immediately prior to stroke onset. Randomisation is stratified by country but not by site (to protect allocation concealment in small sites). The randomisation algorithm code calculates an imbalance score to decide to which group the new subject must be allocated, to have the minimum amount of imbalance, in terms of prognostic factors. In the case that the groups are evenly matched, a group is selected at random. At random, the opposite group will be selected approximately 5% of the time to reduce predictability and bias.⁽²⁰⁾ Out of the treatment packs available at the participant's hospital, one is selected at random which matches the selected treatment group. Randomisation generates a unique number corresponding to a treatment pack. The selected treatment pack is then allocated to the participant's unique trial number. Balance between the treatment groups is monitored by programmers and statisticians during the recruitment phase.

Treatment

Blinded individual treatment packs contain four 5ml glass ampoules of tranexamic acid 500mg or sodium chloride 0.9%, which are identical in appearance. Trial treatment is administered as 10ml (tranexamic acid 1g or placebo) in 100ml sodium chloride 0.9% infusion bag intravenously as a loading dose infusion over 10 minutes, followed by infusion of 10ml (tranexamic acid 1g or placebo) in 250ml sodium chloride 0.9% infusion bag over 8 hours.

Allocation concealment: Clinicians, patients and outcome assessors (research nurse and radiologist) are blinded to treatment allocation for the duration of the study. Unblinding should be done only in those rare cases when the doctor believes that clinical management depends importantly upon knowledge of whether the patient received antifibrinolytic or placebo. In those few cases when urgent unblinding is considered necessary, the emergency telephone number should be contacted, giving the name of the doctor authorising unblinding and the treatment pack number. Unblinding will be monitored and audited.

Primary outcome

Death or dependency using the 7-level modified Rankin Scale (mRS) at day 90.

Secondary outcomes

1. Neurological impairment (NIHSS⁽²¹⁾) at day 7 (or discharge if sooner).
2. Outcome: Disability (Barthel index⁽²²⁾), dependency (mRS⁽²³⁾), Quality of Life (EuroQol, EQ-5D and EQ-VAS⁽²⁴⁾), Cognition (Telephone Interview Cognition Score-Modified⁽²⁵⁾) and mood (Zung Depression Scale⁽²⁶⁾) at days 90 and 365.
3. Costs: Length of stay in hospital, re-admission, institutionalisation.
4. Radiological efficacy/safety (CT scan): Change in haematoma volume from baseline to 24 hour scan, haematoma location and new infarction. Details of haematoma volume calculation to be given in Statistical Analysis plan.
5. Safety endpoints recorded until day 90: Death (cause); venous thromboembolism; vascular occlusive events (stroke/transient ischaemic attack/myocardial infarction/peripheral artery disease); seizures. Serious adverse events in first 7 days.

6. MRI substudy: Prevalence of remote diffusion weighted imaging hyperintense lesions, perihematoma oedema volume and diffusion restriction on day 5 MRI scan, and combined volume of the residual hematoma cavity and abnormal signal on the Day 90 MRI scan.

Serious Adverse Events

Serious adverse events (SAE) are defined as any untoward medical occurrence or effect that at any dose results 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. Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered an SAE 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.

SAEs and safety endpoints are reported in line with expedited reporting regulations and then adjudicated by an independent panel.

All SAEs occurring within the first 7 days will be recorded and reported to the competent authority Medicine Healthcare Regulatory Authority (MHRA) and Regional Ethics Committee (REC) as part of the annual reports. Suspected Unexpected Serious Adverse Reactions (SUSARS) will be reported within the statutory timeframes to the MHRA and REC.

Data Monitoring

An independent Data & Safety Monitoring Committee (DSMC) receives safety reports every six months, or more frequently if requested, and assesses unblinded efficacy and safety data. The DSMC will perform a formal interim analysis after 800 participants have been recruited and followed-up at 90 days. A DSMC Charter contains details of membership, terms and conditions, and guidelines for stopping the trial. The DSMC reports their assessment to the independent chair of the TSC (with a copy to the CI) and a copy is then sent to the funder (NIHR HTA). With respect to safety, the following outcomes will initiate discussion for recommending early stopping or continuation of the study:

- The primary outcome ('shift' in mRS) favours the active group (benefit), $P < 0.001$ (2-sided).
- The primary outcome ('shift' in mRS) favours the control group (hazard), $P < 0.02$ (2-sided).
- Analysis of death favours the control group (hazard) with $P < 0.02$ (2-sided).

Sample size estimates

The null hypothesis (H_0) is that tranexamic acid does not alter death or dependency at day 90, in participants with acute SICHD. The alternative hypothesis (H_A) is that death or dependency at day 90 differ between those participants randomised to tranexamic acid versus placebo. A total sample size of 2,000 (1,000 per group) participants with acute SICHD are required, assuming overall *significance (alpha) = 0.05; power (1-beta) = 0.90; ordinal odds ratio of 0.79; increases due to losses to follow-up of 5%; and a reduction of 20% for baseline covariate adjustment.*[\(27\)](#)

Statistical analyses

Detailed information regarding analyses will be in the statistical analysis plan, which will be finalised before database lock.

Primary outcome: Death or dependency (ordinal shift analysis of the 7 level mRS) at day 90 will be compared between tranexamic acid and placebo by intention-to-treat, without imputation, using ordinal logistic regression, with adjustment for minimisation factors. The assumption of proportional odds will be tested using the likelihood ratio test.

Sub-group analyses: The comparison of tranexamic acid and placebo on the primary outcome will be performed in pre-specified subgroups, including the minimisation criteria, and: start of treatment (≤ 3 , > 3 hours), CT angiography (yes, no), spot sign (yes, no), haematoma location (lobar, deep, infra-tentorial), geographical region (UK, other), and ethnicity (white, other). The interpretation of any subgroup effects will be based on interaction tests (i.e. evidence of differential treatment effects in the different subgroups). The scientific rationale for the subgroup analysis and predicted direction of effects will be covered in detail in the statistical analysis plan.

Secondary analyses: Binary logistic regression will be used for binary outcomes, including SAEs and thromboembolic events. Cox regression will be used for time to event analyses, including death. Analysis of covariance will be used for continuous measures, including haematoma expansion. Wilcoxon rank sum test will be used for continuous measures which are not normally distributed, including Barthel Index. Regression analyses will be performed with adjustment for minimisation factors.

Study organization and funding

The University of Nottingham is sponsor for the study with funding from National Institute of Health Research Health Technology Assessment (NIHR HTA project code 11_129_109). The study has been adopted in the UK by the NIHR Clinical Research Network (CRN) portfolio and participants will be recruited from acute stroke units at NIHR CRN sites in the UK and acute stroke units in participating centres worldwide. UK sites have dedicated Stroke CRN staff to facilitate recruitment and follow-up. Trial coordination will be performed by staff at the University of Nottingham. Outside the United Kingdom, International sites will have a National Coordinating Centre and the National Coordinators will form the International Advisory Committee. The study received approval from the MHRA on 23rd October 2012, REC on 23rd November 2012, and the respective National Health Service (NHS) Research & Development (R&D) department on 15th February 2013. The study was prospectively registered with the ISRCTN on the 17th January 2013 (No. 93732214).

Recruitment started in 2013; as of 15th Jan 2016 1355 participants have been enrolled, from 95 centres in 7 countries. Recruitment is due to end in 2017.

Additional funding for conductance of the trial in Switzerland was provided by a grant from the Swiss heart foundation.

Discussion

ICH is a medical emergency for which treatment needs to be given urgently. Haematoma expansion is most likely to occur in the first few hours after ICH, but extends up to 24 hours later,⁽³⁾ and is associated with poor functional outcome.

Tranexamic acid is inexpensive and easy to administer, and potentially safe, based on data from other studies. In CRASH-2, tranexamic acid was most effective when given rapidly; delayed administration was associated with lack of efficacy and potential harm.⁽²⁸⁾ TICH-2 will include patients as soon as possible after stroke onset, but allow a pragmatic time window of 8 hours.

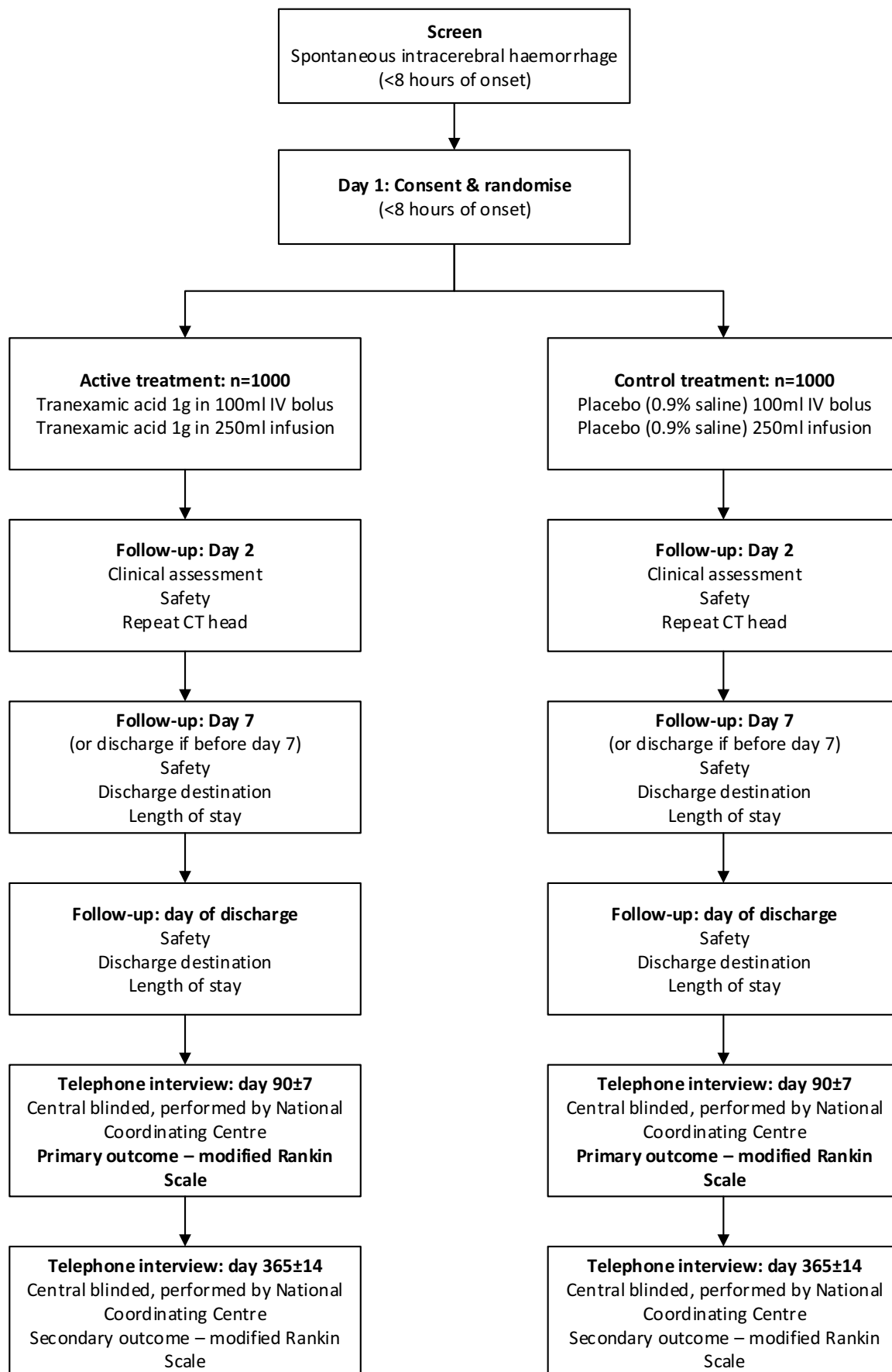
Contrast extravasation within the haematoma during contrast-enhanced CT, and CT angiography (the “spot sign”) predict haematoma expansion,⁽²⁹⁻³¹⁾ although there is currently wide variation in the use of these techniques in routine clinical practice. Nevertheless, other clinical trials assessing tranexamic acid in ICH are selecting participants on the basis of contrast extravasation, recruiting ‘spot positive’ patients.^(16, 17) However, as the spot sign has limited specificity for haematoma expansion, and CTA is not used routinely in many patients with ICH, we chose not to limit selection to those with spot sign positive ICH.

The dosing regime used in TICH-2 produces plasma concentrations sufficient to inhibit fibrinolysis; higher doses do not provide any additional haemostatic benefit.⁽³²⁾ In the emergency situation administration of a fixed dose is more practicable and the fixed dose chosen is efficacious for large patients and safe for small patients.

Summary and conclusion

SICH is a devastating form of stroke, in which haematoma expansion plays a key role in high morbidity and poor outcome. TICH-2 is a large pragmatic randomised controlled trial assessing the efficacy of tranexamic acid, an anti-fibrinolytic drug, on death and dependency in SICH. If effective, tranexamic acid is inexpensive, easy to administer and widely available – and could be combined with other treatments such as antihypertensives, which are now recommend in clinical guidelines⁽⁵⁾, in an attempt to target multiple pathophysiological targets to improve outcome from SICH.

Trial flow chart



REFERENCES

1. van Asch CJ, Luitse MJ, Rinkel GJ, van der Tweel I, Algra A, Klijn CJ. Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. *Lancet Neurol.* 2010;9(2):167-76.
2. Steiner T, Bosel J. Options to Restrict Hematoma Expansion After Spontaneous Intracerebral Hemorrhage. *Stroke.* 2010;41:402-9.
3. Kazui S, Naritomi H, Yamamoto H, Sawada T, Yamaguchi T. Enlargement of spontaneous intracerebral hemorrhage. Incidence and time course. *Stroke.* 1996;27(10):1783-7.
4. Brott T, Broderick J, Kothari R, Barsan W, Tomsick T, Sauerbeck L, et al. Early hemorrhage growth in patients with intracerebral hemorrhage. *Stroke.* 1997;28(1):1-5.
5. Hemphill JC, 3rd, Greenberg SM, Anderson CS, Becker K, Bendok BR, Cushman M, et al. Guidelines for the Management of Spontaneous Intracerebral Hemorrhage: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke.* 2015.
6. Al-Shahi Salman R. Haemostatic drug therapies for acute spontaneous intracerebral haemorrhage. *Cochrane Database of Systematic Reviews* 2009 Issue 4.
7. CRASH-2 trial collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet.* 2010;Epub Jun 14.
8. CRASH-2 Collaborators (Intracranial Bleeding Study). Effect of tranexamic acid in traumatic brain injury: a nested randomised, placebo controlled trial (CRASH-2 Intracranial Bleeding Study). *BMJ.* 2011;343(d3795).
9. Zehtabchi S, Abdel Baki SG, Falzon L, Nishijima DK. Tranexamic acid for traumatic brain injury: a systematic review and meta-analysis. *Am J Emerg Med.* 2014;32(12):1503-9.
10. Dewan Y, Komolafe EO, Mejia-Mantilla JH, Perel P, Roberts I, Shakur H. CRASH-3 - tranexamic acid for the treatment of significant traumatic brain injury: study protocol for an international randomized, double-blind, placebo-controlled trial. *Trials.* 2012;13:87.
11. Roos Y, Rinkel G, Vermeulen M, Algra A, van Gijn J. Antifibrinolytic Therapy for Aneurysmal Subarachnoid Hemorrhage: A Major Update of a Cochrane Review *Stroke.* 2003;34:2308-9.
12. Ojacastrro MF TM, Dulos ID, Tabuena RP. . Efficacy of tranexamic acid in reducing hematoma volume in patients with hypertensive intracerebral hemorrhage.2008;3 Suppl 1:197-8. *International Journal of Stroke.* 2008;3(Suppl)(1):197-8.
13. Sorimachi T FY, Morita K, Tanaka R. . Rapid administration of antifibrinolytics and strict blood pressure control for intracerebral hemorrhage. 2005;57(5):837-44. *Neurosurgery.* 2005;57(5):837-44.
14. Sprigg N, Renton CJ, Dineen RA, Kwong Y, Bath PMW. Tranexamic Acid for Spontaneous Intracerebral Hemorrhage: A Randomized Controlled Pilot Trial (ISRCTN50867461). *Journal of Stroke and Cerebrovascular Diseases.* 2014;23(6):1312-8.
15. Roos Y. EDITORIAL:Tranexamic acid for traumatic brain injury. *BMJ.* 2011;343:d3958.
16. Meretoja A, Churilov L, Campbell BC, Aviv RI, Yassi N, Barras C, et al. The spot sign and tranexamic acid on preventing ICH growth--AUStralasia Trial (STOP-AUST): protocol of a phase II randomized, placebo-controlled, double-blind, multicenter trial. *Int J Stroke.* 2014;9(4):519-24.
17. Glad SB. NOR ICH - a RCT of tranexamic acid for ICH. Personal communication. 2014.
18. Fonville AF, Samarasekera N, Hutchison A, Perry D, Roos YB, Al-Shahi Salman R. Eligibility for Randomized Trials of Treatments Specifically for Intracerebral Hemorrhage: Community-Based Study. *Stroke.* 2013;44(10):2729-34.
19. Al-Shahi Salman R, Dennis MS. Antiplatelet therapy may be continued after intracerebral hemorrhage. *Stroke.* 2014;45(10):3149-50.
20. Saghaei M. An overview of randomization and minimization programs for randomized clinical trials. *Journal of medical signals and sensors.* 2011;1(1):55-61.

21. National Institute of Health NINDS Stroke Scale. http://www.ninds.nih.gov/doctors/NIH_Stroke_Scale.pdf.
22. Mahoney FI, Barthel DW. Functional evaluation: The Barthel Index. *Md State Med J*. 1965;61-5.
23. Bath PM, Lees KR, Schellinger PD, Altman H, Bland M, Hogg C, et al. Statistical analysis of the primary outcome in acute stroke trials *Stroke*. 2012 43(4):1171-8.
24. EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. The EuroQol Group. *Health Policy*. 1990;16(3):199-208.
25. de Jager CA, Budge MM, Clarke R. Utility of TICS-M for the assessment of cognitive function in older adults. *Int J Geriatr Psychiatry*. 2003;18(4):318-24.
26. Zung WWK. A self-rating depression scale. *Arch Gen Psychiatry*. 1965;12:63-70.
27. The Optimising Analysis of Stroke Trials (OAST) Collaboration. Should stroke trials adjust functional outcome for baseline prognostic factors? *Stroke*. 2009;40:888-94.
28. The CRASH-2 collaborators. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet*. 2011;377(9771).
29. Delgado Almandoz JE, Yoo AJ, Stone MJ, Schaefer PW, Goldstein JN, Rosand J, et al. Systematic Characterization of the Computed Tomography Angiography Spot Sign in Primary Intracerebral Hemorrhage Identifies Patients at Highest Risk for Hematoma Expansion. *Stroke*. 2009;40(9):2994-3000.
30. Delgado Almandoz JE, Yoo AJ, Stone MJ, Schaefer PW, Oleinik A, Brouwers HB, et al. The Spot Sign Score in Primary Intracerebral Hemorrhage Identifies Patients at Highest Risk of In-Hospital Mortality and Poor Outcome Among Survivors. *Stroke*. 2010;41(1):54-60.
31. Ederies A, Demchuk A, Chia T, Gladstone DJ, Dowlatshahi D, BenDavut G, et al. Postcontrast CT Extravasation Is Associated With Hematoma Expansion in CTA Spot Negative Patients. *Stroke*. 2009;40(5):1672-6.
32. Horrow JC, Van Riper DF, Strong MD, Grunewald KE, Parmet JL. The dose-response relationship of tranexamic acid. *Anesthesiology*. 1995;82:383-92.