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A nested randomised trial of the effect of tranexamic acid on intracranial haemorrhage and infarction in traumatic brain injury (CRASH-3 trial intracranial bleeding mechanistic study): Statistical analysis plan [version 1; referees: 1 approved, 1 approved with reservations]

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Abstract
Background: The CRASH-3 trial is a randomised trial on the effect of tranexamic acid (TXA) on death and disability in traumatic brain injury (TBI). The CRASH-3 intracranial bleeding mechanistic study (IBMS) is a randomised trial nested within the CRASH-3 trial to examine the effect of TXA on intracranial bleeding and infarction.

Methods: Patients eligible for the CRASH-3 trial, with a GCS of 12 or less or intracranial bleeding on a pre-randomisation CT scan are eligible for the IBMS. The occurrence of intracranial bleeding, infarction, haemorrhagic oedematous lesions, mass effect and haemorrhage evacuation is examined within 28 days of randomisation using routinely collected brain scans. The primary outcome is the volume of intracranial bleeding in patients randomised within three hours of injury (adjusted for prognostic covariates). Secondary outcomes include progressive and new intracranial bleeding, intracranial bleeding after neurosurgery and new cerebral infarcts up to 28 days post-randomisation. All outcomes will be compared between treatment groups.

Statistical analyses: The primary outcome will be analysed using absolute measures (ANCOVA) and relative measures (ratios). The same analysis will be done separately for patients who undergo haemorrhage evacuation post-randomisation. We will express the effect of TXA on new and progressive bleeding using relative risks and 95% CIs, and on cerebral infarcts using hazard ratios and 95% CIs. If any missing post-randomisation scans appear to be missing not at random, we will conduct sensitivity analyses to explore the implications.

Conclusion: The IBMS will provide information on the mechanism of action of TXA in TBI. This pre-specified statistical analysis plan is a technical extension of the published protocol.

Trial registration: The CRASH-3 trial was prospectively registered at the International Standard Randomised Controlled Trials registry (19 July 2011) and ClinicalTrials.gov (25 July 2011). The registries were updated with details for the IBMS on 20 December 2016.

Keywords
Traumatic brain injury, intracranial haemorrhage, tranexamic acid, statistical analysis plan
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Introduction

Worldwide over 50 million people experience traumatic brain injury (TBI) every year. TBI is the leading cause of death and disability in young adults, particularly in low-income and middle-income countries where rates of road traffic crashes are increasing. Falls are the most frequent cause of TBI in high-income countries. Intracranial bleeding is common after TBI, mostly in the first few hours after injury. The larger the bleed the greater the risk of death and long-term disability. To improve outcome from this life threatening and potentially disabling condition, effective treatments are needed to reduce intracranial haemorrhage expansion.

The permeability of the blood-brain barrier is compromised after TBI. Tranexamic acid could penetrate the blood-brain-barrier to enter the cerebrospinal fluid, inhibit the enzymatic breakdown of fibrin blood clots and reduce intracranial haemorrhage expansion. A recent systematic review identified two completed randomised trials of tranexamic acid in TBI. When the two trials were combined in a meta-analysis, there was a statistically significant reduction in intracranial haemorrhage growth (RR 0.75, 95% CI 0.58–0.98; P = 0.03) and mortality (RR 0.63, 95% CI 0.40–0.99; P = 0.05) with tranexamic acid. Neither trial found evidence for an increased risk of infarction with tranexamic acid (RR 0.51, 95% CI 0.20–1.32; P = 1.17) (0 infarcts – tranexamic acid group, 3 infarcts – placebo group). However, the confidence intervals are wide and the quality of this evidence is low. Therefore, the effect of tranexamic acid on mortality, intracranial bleeding and infarction in TBI remains uncertain.

The CRASH-3 trial, with a planned sample size of 13,000 patients, will be the largest randomised trial into the effect of tranexamic acid in isolated TBI. The CRASH-3 trial is a prospective, international, multi-centre, parallel group, placebo-controlled randomised trial that examines the effects of tranexamic acid on death and disability in TBI. Patients who are within 8 hours of their TBI and have intracranial bleeding on a computed tomography (CT) scan or a Glasgow Coma Score (GCS) of 12 or less, and no significant extra-cranial bleeding, are potentially eligible for inclusion in the CRASH-3 trial. The original 8 hour time window for recruitment was restricted to 3 hours of injury in 2016 in order to reliably examine the effect of tranexamic acid given soon after injury. Eligible patients are randomly allocated (1:1) to receive tranexamic acid or matching placebo (0.9% sodium chloride). The 1 gram loading dose of the trial treatment is administered by intravenous injection within minutes of randomisation in hospital. The 1 gram maintenance dose is administered by intravenous infusion as soon as the loading dose has completed. Tranexamic acid or placebo are given as an additional treatment to the routine management of TBI. The aims and methods for the CRASH-3 trial are presented in detail elsewhere.

The CRASH-3 trial is based on the premise that intracranial bleeding contributes to head injury death and disability in patients with TBI. By inhibiting fibrinolysis, tranexamic acid is expected to reduce the extent of intracranial bleeding. Therefore, we expect to see less intracranial bleeding in head CT scans of patients treated with tranexamic acid, particularly in those treated soon after injury when the risk of haemorrhage expansion is greatest. On the other hand, tranexamic acid might increase the risk of cerebral thrombosis and infarction in TBI patients, potentially worsening neurological outcome. In this case, we expect to see more infarcts in patients treated with tranexamic acid, particularly in those treated after a prolonged period after injury when there is an increased risk of thrombotic disseminated intravascular coagulation.

The CRASH-3 Intracranial Bleeding Mechanistic Study (IBMS) is a randomised trial nested within the CRASH-3 trial and examines the effect of tranexamic acid on intracranial bleeding and infarction (protocol version 1.3 currently in use). The IBMS evaluates the effect of tranexamic acid on bleeding expansion using a validated method (ABC/2) to measure the total bleeding volume on routinely collected CT scans done soon after randomisation. The blinded data from ~1,000 patients in the IBMS so far suggests that this scan is done within a mean of 44 hours after randomisation. Bleeding is well visualised on CT in the early stage of injury. Because infarction takes longer to manifest on CT imaging, the effect of tranexamic acid on infarction is examined using all routinely collected brain imaging (including magnetic resonance imaging) done within 28 days of randomisation. The IBMS will provide information on the mechanism of action of tranexamic acid in TBI and could facilitate the generalisation of trial results. This pre-specified statistical analysis plan is a technical extension of the published protocol.

Trial methods

The aims and methods for the IBMS are presented in detail elsewhere.

Aim

The IBMS aims to examine the mechanism by which tranexamic acid exerts its effects in patients with isolated TBI. Specifically, we will assess the effect of tranexamic acid on intracranial bleeding and infarction.

Trial design and eligibility criteria

The IBMS is a randomised, placebo-controlled, parallel group, international, multi-centre, double-blind trial nested within the CRASH-3 trial. Patients who fulfil the eligibility criteria for the CRASH-3 trial, with a GCS of 12 or less or intracranial bleeding on a CT scan done before randomisation, are eligible for inclusion in the IBMS.

Trial registration

The CRASH-3 trial was prospectively registered at the International Standard Randomised Controlled Trials registry (ISRCTN15088122) on 19 July 2011, and ClinicalTrials.gov on 25 July 2011 (NCT01402882). The registries were updated with details for the IBMS on 20 December 2016.

Ethical approval

The UK Medical Research and Ethics Committee and Health Research Authority reviewed the protocol and supporting documents for the IBMS and provided a favourable ethical
opinion on 8 June 2016 (Research Ethics Committee Reference 12/EE/0274). All participating UK hospitals have provided Research and Development approvals and letters of access for the IBMS to be conducted at their respective sites. The Malaysian Medical Research and Ethics Committee reviewed the protocol and supporting documents for the IBMS and provided favourable ethical opinion on 16 May 2017 (Reference (25)KKM/NHSEC/P12-476). All relevant national and local ethical approvals will be gained from additional sites. Favourable ethical opinion was received from the Observational/Interventions Research Ethics Committee at LSHTM on 24 May 2016 (Reference 11535). The relevant Medical Research and Ethics Committees will review important protocol modifications for approval before implementation, and registries updated as appropriate.

Consent to participate

TBI patients are physically and mentally incapable of providing informed consent to participate in a clinical trial. As acknowledged in the Declaration of Helsinki, patients who are incapable of giving consent are an exception to the general rule of informed consent in clinical trials\(^1\). In the CRASH-3 trial, patients are unable to provide consent and so consent is sought from the patient’s relative, legal representative or the responsible clinician. If and when the patient regains capacity to provide informed consent, they are informed about the trial and written consent sought to continue their participation in the trial. If a patient or patient representative declines consent, they are withdrawn from the trial. For patients who were included in the trial but did not regain capacity, written informed consent is sought from a relative or legal representative. Written informed consent from patients, their relatives, legal representatives or the responsible clinician includes consent for the publication of anonymised patient data. The requirements of relevant local and national ethics committees are adhered to at all times.

The CRASH-3 trial includes consent to extract data from patient medical records. Collecting brain imaging data for the IBMS is consistent with the consent procedure used in the CRASH-3 trial. It would be impractical to re-consent patients or relatives/legal representatives to brain imaging, particularly for patients who have deceased or are disabled as a result of their injuries where re-consent would be distressing and unwelcome. The LSHTM and national Ethics Committees extended their approvals to extract brain imaging data from CRASH-3 trial patients without further patient consent. Patients who withdrew from the main CRASH-3 trial would not be included in the IBMS.

Participating hospitals

The hospitals participating in the IBMS were selected based on the number of patients enrolled in the CRASH-3 trial, the availability of electronic imaging at site and the willingness of the trial principal investigator at site to take part. We invited ten of the highest recruiting CRASH-3 trial hospitals in the United Kingdom (UK) to take part (Queen Elizabeth Hospital, Birmingham; Royal London Hospital; University Hospital Coventry; Salford Royal Hospital; St George’s Hospital, London; King’s College Hospital, London; St Mary’s Hospital, London; Addenbrooke’s Hospital, Cambridge; John Radcliffe Hospital, Oxford, Southmead Hospital, North Bristol). We also invited Hospital Sungai Buloh in Malaysia to take part. We will invite other hospitals participating in the CRASH-3 trial to meet the planned sample size for the IBMS. We will report all participating sites in the final results publication.

Sample size

A study with about 1,500 patients would have 80% power (at alpha = 0.05) to detect a 15% reduction in intracranial bleeding volume with tranexamic acid. We expect around 75% of patients will be randomised within three hours of injury. Therefore, we will continue to collect data for the IBMS until we reach 2,000 patients or the CRASH-3 trial completes recruitment.

Interim analyses and unblinding

The treatment allocation is double-blinded such that trial team members, outcome assessors and patients are unaware of whether a trial patient will receive tranexamic acid or placebo. There are no interim analyses planned. The final analysis of the unblinded results will take place after recruitment is complete, the data have been cleaned and the trial database has been locked as per the procedures detailed in the Data Management Plan (DMP) (version 1.0) and protocol\(^15\).

Data management and integrity

All trial data are managed in accord with the IBMS DMP which is stored in the Trial Master File. The DMP working procedures are produced in conjunction with the London School of Hygiene and Tropical Medicine (LSHTM) policies and procedures, the Clinical Trials Unit and trial specific working procedures, and regulatory requirements. The web database was built to comply with ICH-GCP guidelines and uses MySQL for data storage. Hypertext Preprocessor (PHP) was used to develop the dynamic web pages for the user interface.

Data are collected at each participating site and directly uploaded into the web database. A number of computerised validation checks have been built into the database to ensure all required fields are complete and irregular entries are flagged. In rare cases of poor internet connection or inadequate facilities, paper versions of the Case Report Forms (CRFs) are completed and transcribed into the web database as soon as possible. A delegate cross-checks the transcription between paper and web CRFs and any detected errors are amended on paper and/or web CRFs immediately. Any revisions to a submitted form are saved automatically in a database log with details of who edited the data and when edits were made. Any changes made from the initial form submission are highlighted in each amended version of a form. All other data checks and cleaning are performed by the IBMS lead. This includes using a download report facility within the database to review the data for inconsistencies and resolve queries as per the procedures detailed in the DMP. The final database lock will take place at the end of the trial within three months of the end of data collection. Data will be exported for statistical analysis in Stata Version 15 [StataCorp LP, College Station, Texas, USA].
Primary outcome
The mean volume of intracranial bleeding will be compared between trial arms (using absolute and relative measures) in patients randomised within three hours of injury, adjusting for prognostic covariates.

In the original IBMS protocol, the primary outcome included all patients randomised within 8 hours of injury. Since the protocol was published, an individual patient data meta-analysis was published which included 40,138 patients with acute severe bleeding enrolled in randomised trials of tranexamic acid. This meta-analysis showed that immediate treatment improved the odds of survival by more than 70% (OR 1.72, 95% CI 1.42–2.10; p<0.0001). Therefore, the survival benefit decreased by about 10% for every 15 minutes of treatment delay until 3 hours, after which there was no benefit. To quantify any reduction in bleeding volume with tranexamic acid compared to placebo in the IBMS, we must examine the primary outcome during the interval where bleeding is at greatest risk of expansion. If there is a minimal change in bleeding volume after three hours of injury, including patients treated after three hours of injury in the primary analysis will dilute any effect of tranexamic acid towards the null. Therefore, we will restrict the analysis of the primary outcome to three hours of injury.

Secondary outcomes
(a) Frequency and volume of progressive bleeding in patients randomised within 3 hours of injury: number of patients with a post-randomisation scan with a total bleeding volume of more than 25% of the volume on the pre-randomisation scan;
(b) Frequency and volume of new bleeding in patients randomised within 3 hours of injury: number of patients with haemorrhage on the post-randomisation scan that was not seen on the pre-randomisation scan;
(c) Number of patients with cerebral infarcts seen on a post-randomisation scan and not known to be present pre-randomisation;
(d) Mean volume of intracranial bleeding seen after randomisation in patients who undergo neurosurgical haemorrhage evacuation.

All outcomes for patients treated after three hours of injury will be presented separately.

Trial status
We are currently collecting data for the IBMS and at the time of writing a total of 1,250 patients’ scans have been examined.

Statistical analysis plan
Trial profile
We will show the flow of trial patients in the Consolidated Standards of Reporting Trials (CONSORT) diagram. This will include the total number of patients randomised into the IBMS divided by treatment arm. Each treatment arm will detail the number of patients who received the loading and maintenance doses, the number of patients for whom clinical baseline and outcome data was collected, and the number of patients who were scanned before randomisation and/or after randomisation. We will report the number of patients included in the primary and secondary analyses, the reasons for any post-randomisation exclusions and the number lost to follow-up. If after a patient is randomised into the trial, it is found that they did not meet the eligibility criteria or did not receive their allocated treatment, they are considered to have deviated from the trial protocol. Data from patients who have deviated from the protocol will be included in the intention to treat analysis. If a patient or their representative withdraws consent for data collection, we will use only data up to the point of withdrawal in the analysis.

Baseline characteristics
We will report baseline characteristics, including, age, sex, GCS, systolic blood pressure, mean number of hours from injury to pre-randomisation scan, mean (and median) haemorrhage volume, different types of haemorrhage (intra-parenchymal, intra-ventricular, subdural, epidural, subarachnoid and petechial), cerebral infarction, oedematous lesions, mass effect findings, and the Marshall classification. To check that randomisation produced similar groups, we will describe the baseline characteristics of each treatment group with frequencies and percentages.

Primary analysis
Analysis of covariance (ANCOVA) will compare the mean volume of intracranial bleeding seen after randomisation between treatment groups, adjusting for the time from injury to CT scan, GCS, age and systolic blood pressure. A linear regression analysis using the blinded imaging data from 1,000 patients indicated that these variables are significantly predictive of post-randomisation bleeding volume (p<0.05). The primary analysis will be adjusted, using these covariates and the stratification factor (treatment site). Baseline adjustment eliminates conditional bias arising from a chance difference in covariates between treatment groups, and increases precision in the treatment effect by factoring out the covariance between baseline factors and post-randomisation bleeding volumes.

We will use histograms and normal probability plots to examine whether regression residuals are normally distributed. If not, we will check for outliers and report 95% bootstrap confidence intervals. We will present ratios and 95% confidence intervals to examine the relative effect of tranexamic acid (versus placebo) on mean bleeding volume.

In the previously published protocol, we stated that the primary analysis would also be adjusted for using the pre-randomisation bleeding volume. Since then, we have collected blinded imaging data from 1,000 patients and found that only 50% of patients were scanned both before and after randomisation. A 50% reduction in power as a result of missing scans would outweigh the 30% increase in power from baseline adjustment. Therefore, we will not adjust the primary analysis using the pre-randomisation bleeding volume.
In line with the CONSORT guidelines\textsuperscript{28}, we will also report the unadjusted analysis to facilitate synthesis and comparability with other studies that may not adjust for the same covariates. An independent samples t-test will compare the mean volume of intracranial bleeding between treatment groups.

**Secondary analyses**

**Progressive haemorrhage, new haemorrhage, haemorrhagic oedematous lesions and mass effect:** We will express the effect of tranexamic acid on the occurrence of dichotomous endpoints between trial arms, including the frequency of progressive haemorrhage, new haemorrhage, haemorrhagic oedematous lesions, and mass effect outcomes (sulcal effacement, ventricular effacement, midline shift), using relative risks and 95% confidence intervals estimated using generalised linear models. We will express the effect of tranexamic acid on the degree of midline shift (measured in millimetres) using ANCOVA, adjusting for the time from injury to scan, GCS, age and systolic blood pressure. We will use histograms and normal probability plots to examine whether regression residuals are normally distributed. If not, we will check for outliers and report 95% bootstrap confidence intervals.

Cerebral infarction: We will express the effect of tranexamic acid on cerebral infarcts measured at up to 28 days post-randomisation and not known to be present pre-randomisation using hazard ratios and 95% confidence intervals. We will conduct a survival analysis using the interval between the time of randomisation and the time of the scan on which the infarct was detected. We will plot the survival curves in the two treatment groups using a Kaplan-Meier plot. The time to the scan on which the infarct was detected will be compared between treatment groups using a log-rank test. We will conduct a Cox regression analysis to quantify any difference between treatment groups in the hazard of detecting an infarct up to 28 days post-randomisation.

Neurosurgical haemorrhage evacuation after randomisation: Tranexamic acid received soon after injury could reduce intracranial haemorrhage expansion and affect the propensity for neurosurgery. But if randomisation and the decision for neurosurgery occur at the same time, tranexamic acid may not have sufficient opportunity to influence this decision, although it could affect bleeding during neurosurgery. Patients who receive tranexamic acid may have less blood on a post-surgery scan compared to patients who receive placebo. Therefore, patients who undergo haemorrhage evacuation before a post-randomisation scan was done will be considered in a separate analysis. We will express the effect of tranexamic acid on the volume of haemorrhage measured on a post-surgery scan using ANCOVA (adjusting for time from injury to scan, GCS, age and systolic blood pressure) because there could be baseline differences between randomised groups when the analysis is restricted to those who undergo neurosurgery. The blinded data collected so far suggests that 26% of patients who underwent haemorrhage evacuation after randomisation were not scanned before randomisation so pre-randomisation bleeding could not be measured. We will not adjust for pre-randomisation bleeding because although it could increase power by 13\%\textsuperscript{27}, this would be offset by a 26\% reduction in power from missing baseline data.

Because any change in intracranial haemorrhage expansion or infarction on a post-surgery scan could be due to the effect of tranexamic acid or surgery, patients who undergo neurosurgery will not be included in the primary analysis. The inclusion of these patients could increase the number of false positives and dilute any effect of tranexamic acid to the null. If patients have been scanned after randomisation, and before and after surgery, they can be included in both the primary analysis and the neurosurgery analysis, respectively.

Subarachnoid haemorrhage: We will express the effect of tranexamic acid on the size (small-medium, large) and spread (focal-multiple, diffuse) of subarachnoid haemorrhage between trial arms, using relative risks and 95% confidence intervals estimated using generalised linear models.

**Subgroup analyses**

**Time from injury to randomisation:** Most intracranial bleeding occurs within hours of injury\textsuperscript{24,29,30}. Subgroup analyses will examine whether the effect of tranexamic acid on intracranial haemorrhage is modified by the time from injury to randomisation (≤1 hour, >1 to 3 hours, >3 to 8 hours). If there is minimal haemorrhage expansion after 3 hours\textsuperscript{24}, we expect tranexamic acid will have a lesser effect in reducing haemorrhage expansion in this group compared to the groups treated within 3 hours. We will conduct a linear regression analysis with an interaction between treatment (tranexamic acid, placebo) and time to randomisation (≤1 hour, 1–3 hours, >3–8 hours) to examine whether the effect of tranexamic acid on intracranial haemorrhage volume varies according to the time from injury to randomisation.

There may be an increase in the frequency of cerebral infarction with tranexamic acid in those treated after 3 hours of injury compared to those treated within 3 hours of injury\textsuperscript{15}. We will use relative risks and 95% confidence intervals estimated using generalised linear models to examine whether the effect of tranexamic acid on cerebral infarction varies within subgroups of time from injury to randomisation (≤3 hours, >3 hours). However, given the lower prevalence of cerebral infarction compared to intracranial bleeding, it will be difficult to reliably examine the effect of tranexamic acid on cerebral infarction within time strata. We will examine whether tranexamic acid increases the risk of adverse events in an individual patient data meta-analysis of 15,000 patients with TBI or spontaneous intracerebral haemorrhage (published separately)\textsuperscript{31}.
Types of haemorrhage: Tranexamic acid could reduce parenchymal haemorrhage expansion. The blinded data collected so far suggests that 70% of patients have parenchymal haemorrhage at baseline which expands from 3ml to 7ml in those randomised within three hours of injury (excluding those who have undergone haemorrhage evacuation). Other types of haemorrhage have lower expansion rates or are more likely to be surgically evacuated. We will expand the model used in the primary analysis to include an interaction between haemorrhage type and treatment group, and examine the effect of tranexamic acid on each haemorrhage type using dummy variables.

Missing data from scans not done before or after randomisation
All trial patients will not be scanned before and after randomisation. We will report the number of patients without scans and baseline data for patients included in the analysis to help identify any selective missingness of outcomes by treatment arm. If scans are missing equally between treatment arms and appear to be missing completely at random, we will continue with the planned analyses because although this missing data reduces the precision of the analysis, it does not bias the treatment effect.

However, if haemorrhage expansion is associated with the reason the data are missing (patients with haemorrhage expansion may die before the second scan, patients without haemorrhage may not need to be re-scanned), imbalance in missing data by treatment arm can cause bias. We will examine whether the occurrence of missing scans is influenced by fully observed baseline variables (e.g. GCS), using relative risks and 95% confidence intervals estimated using generalised linear models. If they are, and within defined groups data are missing completely at random, the data could be missing at random. For example, if missingness depends on GCS, but within mild, moderate and severe GCS groups missingness is unrelated to haemorrhage or infarction, the data are missing at random. In this case, a regression analysis which takes GCS group into account should give unbiased estimates of the treatment effect.

However, we suspect that within GCS groups, missingness could be related to haemorrhage volume (i.e. low GCS patients are expected to have a greater haemorrhage volume than high GCS patients). In this case, the data would be missing not at random (i.e. even when accounting for the fully observed data, the reason for missing observations still depends on the unseen values), and we would conduct sensitivity analyses to explore the implications.

Between-centre effects
Randomisation into the CRASH-3 trial is stratified according to participating centres. We do not expect between-centre differences in unfavourable outcome to affect the chance of demonstrating a treatment effect in TBI. Nonetheless, for transparency we will report the interaction between centre and treatment effect using a linear mixed model with an interaction between centre and treatment.

Conclusion
This statistical analysis plan updates our previously published protocol. The main changes are: an increased sample size from 1,000 to 2,000 patients, restriction of the analysis of the primary outcome and secondary outcomes (new and progressive bleeding) to patients treated within three hours of injury, and not adjusting the primary analysis and secondary neurosurgery analysis using the pre-randomisation bleeding volume. We present our plan for the statistical analyses in advance of the database lock and un-blinding to guard against data dependent analyses. The CRASH-3 IBMS should provide reliable evidence on the effect of tranexamic acid on intracranial bleeding and infarction in TBI.

Data availability
No data are associated with this article.
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The paper is clearly written and overall I would consider the analysis plan for this study appropriate. Specific suggestions and points that could be clarified are as follows:

1. What was the reason for 80% power rather than 90% (as is typical in a trial)? If this is justified in the protocol that is fine, but could be referred to in the present paper.

2. In the section on interim analyses it is stated no interim analysis is planned. However, in the primary analysis section (p5) a 1000 blinded subset of data was used to identify predictors of brain volume. I would have expected these to be defined a priori. Is there a justification / precedent for identifying candidate predictors as the authors have?

3. In terms of missing data, if there are many missing pre-randomisation scans it would be possible to include baseline as an outcome in a repeated measures linear mixed model, cf. Dinh & Yang (2010). The advantage of this approach is that linear mixed models can estimate the maximum likelihood function over missing (and non-missing) data and so subjects with either missing baseline or outcome scans could be included in the analysis. Treatment effects are defined by an interaction between treatment arm and time.

4. Could the authors elaborate on the proposed sensitivity analysis relative to the MNAR assumption.

5. On p3 in the 2nd paragraph of the introduction, the p-value for reference 11 is quoted as 1.17 which is greater than 1.

Is the rationale for developing the new method (or application) clearly explained?
Yes

Is the description of the method technically sound?
Yes

Are sufficient details provided to allow replication of the method development and its use by others?
Partly

If any results are presented, are all the source data underlying the results available to ensure full reproducibility?
No source data required
Are the conclusions about the method and its performance adequately supported by the findings presented in the article?
Partly

**Competing Interests:** No competing interests were disclosed.

**Referee Expertise:** Statistics

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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This is an interesting study to verify relevant clinical contexts with reference to the pre-specified statistical analysis. We could not investigate the mechanism of underlying intracranial bleeding directly by therapeutic trial design of both CRASH3 and this study. However it could help for exploring and generating hypothesis about mechanisms of pharmacological action by different statistical plan in the study patients. In my opinion, the analytical plan of CRASH3 trial and related studies 1-3 are comparable to the concept in meta analysis that exploring the clinical heterogeneity and statistical heterogeneity 4-5 among the studies of antifibrinolytic treatment for acute traumatic brain injury by the finding of reporting evidences. I look forward to seeing the result and encourage to continue such workings hereby. Finally, the concordant result among studies including explorative details in both treatment and control groups could have more evidences for traumatic intracranial bleeding.

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Is the rationale for developing the new method (or application) clearly explained?
Yes

Is the description of the method technically sound?
Yes

Are sufficient details provided to allow replication of the method development and its use by others?
Yes

If any results are presented, are all the source data underlying the results available to ensure full reproducibility?
No source data required

Are the conclusions about the method and its performance adequately supported by the findings presented in the article?
Partly

**Competing Interests:** No competing interests were disclosed.

**Referee Expertise:** Neurosurgery : Traumatic Brain Injury, Hemorrhagic stroke

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.