



METHOD ARTICLE

REVISED **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 2; peer review: 2 approved, 2 approved with reservations]**Abda Mahmood , Ian Roberts , Haleema Shakur-Still 

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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 intra-parenchymal bleeding in patients randomised within three hours of injury (adjusted for prognostic covariates). Secondary outcomes include a composite “poor” outcome, progressive and new intracranial bleeding, intracranial bleeding after neurosurgery and cerebral infarcts seen up to 28 days post-randomisation. All outcomes will be compared between treatment groups.




Statistical analyses: The primary outcome will be analysed using a covariate adjusted linear mixed model. The same analysis will be done separately for patients who undergo haemorrhage evacuation post-randomisation. We will express the effect of TXA on the composite outcome, new and progressive bleeding using relative risks and 95% CIs, and on cerebral infarcts using hazard ratios and 95% CIs. We will conduct sensitivity analyses assuming missing data are MCAR or MNAR.

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

Open Peer Review**Reviewer Status**    

	Invited Reviewers			
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version 3 (revision) 27 Nov 2019				 report
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version 1 13 Aug 2018	 report		 report	

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Any reports and responses or comments on the article can be found at the end of the article.

[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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Competing interests: No competing interests were disclosed.

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REVISED Amendments from Version 1

The main changes from Version 1 of the CRASH-3 Trial IBMS SAP and Version 2 are:

- 1) Primary outcome – a comparison of intra-parenchymal bleeding volume between treatment groups (rather than total intracranial bleeding volume).
- 2) Primary analysis – linear mixed model with pre-randomisation intra-parenchymal bleeding volume as an outcome (rather than previously proposed ANCOVA model that did not include pre-randomisation bleeding) (as per reviewer comments).
- 3) Elaborated on the proposed sensitivity analysis relative to the MNAR assumption (as per reviewer comments).
- 3) Other sensitivity analyses –
 - a. For the primary analysis assume missing data are MAR (assumption of linear mixed model) and do sensitivity analyses assuming they are MCAR or MNAR.
 - b. Remove neurosurgery patients from the primary analysis to reduce null bias from the bleeding related effects of neurosurgery and not TXA.
 - c. Remove neurosurgery patients from the cerebral infarction analysis to reduce null bias from infarction related effects of neurosurgery and not TXA.
- 4) Composite “poor outcome” (progressive bleeding, new bleeding, infarction, death or the need for neurosurgery). This would align the outcomes more with the main CRASH-3 trial.
- 5) Updated sample size and power calculation (as per reviewer comments).

The rationale for changes have been incorporated into the updated version of the SAP.

See referee reports

Introduction

Worldwide over 50 million people experience traumatic brain injury (TBI) every year¹. TBI is the leading cause of death and disability in young adults², particularly in low-income and middle-income countries where rates of road traffic crashes are increasing³. Falls are the most frequent cause of TBI in high-income countries⁴. Intracranial bleeding is common after TBI, mostly in the first few hours after injury⁵. The larger the bleed the greater the risk of death and long-term disability⁶. 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 TBI⁷. Tranexamic acid could penetrate the blood-brain-barrier to enter the cerebrospinal fluid^{8,9}, 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 TBI¹⁰. When the two trials were combined in a meta-analysis (n=478), 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 = 0.17)¹¹ (0 infarcts – tranexamic acid group, 3 infarcts – placebo group)¹². 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 TBI¹³. 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 elsewhere¹³.

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 bleeding¹⁴. 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 greatest⁵. On the other hand, tranexamic acid might increase the risk of cerebral thrombosis and infarction in TBI patients, potentially worsening neurological outcome^{15–17}. 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 coagulation¹⁵.

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)¹⁸. The IBMS evaluates the effect of tranexamic acid on bleeding expansion using a validated method (ABC/2)¹⁹ 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 injury²⁰. Because infarction takes longer to

manifest on CT imaging²¹, 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 results²². This pre-specified statistical analysis plan is a technical extension of the published protocol¹⁹.

Trial methods

The aims and methods for the IBMS are presented in detail elsewhere¹⁸.

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/NIHSEC/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 trials²³. 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 four hospitals in Malaysia to take part: Hospital Sungai Buloh, Penang General Hospital, Hospital Sultanah Nur Zahirah and Hospital Sultanah Bahiyah. We will report all participating sites in the final results publication.

Sample size

A trial with about 1,750 patients would have 95% power (at $\alpha = 0.05$) to detect the expected 15% reduction in intracranial bleeding volume with tranexamic acid¹¹. We expect around 75% of patients ($n=1300$) will be randomised within three hours of injury, and this sample will have 90% power to detect the expected treatment effect. Therefore, we will continue to collect data for the IBMS until we reach 2,000 patients or the CRASH-3 trial completes recruitment (scheduled end date: 31 January 2019).

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 protocol¹⁸.

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 intra-parenchymal bleeding will be compared between trial arms in patients randomised within three hours of injury, adjusting for prognostic covariates.

In the original IMBS protocol¹⁸, we said the total volume of intracranial bleeding would be compared between treatment groups. Since publishing the protocol, we have collected blinded data from 1700 trial patients, which suggest that any effect of tranexamic acid on intracranial bleeding expansion may only be reliably detected in intra-parenchymal bleeds. Intra-parenchymal bleeds are less likely to be surgically evacuated compared to subdural and epidural bleeds, which are often larger and therefore substantially increase intracranial pressure and require urgent neurosurgical evacuation. Large subdural and epidural bleeds are easier to evacuate because they occur outside of the brain tissue, whereas intra-parenchymal bleeds often occur deep within the brain tissue so it is difficult to evacuate them without causing further harm. Therefore, we may not be able to reliably examine the effect of tranexamic acid on subdural and epidural bleed

expansion given that large bleeds are often evacuated before we can examine any effect of tranexamic acid on them. Including bleeds that may not be affected by tranexamic acid in the primary outcome would dilute any effect of tranexamic acid on intracranial bleeding expansion to the null. Furthermore, when excluding patients who have undergone neurosurgery by the first rated post-randomisation scan, the proportional expansion of intra-parenchymal bleeding from pre- to post-randomisation is greater than for all other types of intracranial bleeding. Indeed, a recent randomised trial found a statistically significant reduction in intracerebral bleeding expansion with tranexamic acid²⁴. Finally, intra-parenchymal bleeds are often spherical in shape, so there is less measurement error with the ABC/2 method of volume estimation compared to subdural and epidural bleeds, which have concave and convex shapes, respectively. For these reasons, the primary outcome will examine the effect of tranexamic acid on the total volume of intra-parenchymal bleeding.

In the original IBMS protocol¹⁸, 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 acid²⁵. 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; $p < 0.0001$). Thereafter, 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.
- (e) Composite poor outcome: progressive bleeding (“a” above), new bleeding (“b” above), cerebral infarction

(“c” above), death or the need for neurosurgery within 28 days of injury.

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 1,700 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 classification¹⁸. To check that randomisation produced similar groups, we will describe the baseline characteristics of each treatment group with frequencies and percentages.

Primary analysis

Linear mixed model²⁶ will be used to compare the mean change in intra-parenchymal haemorrhage volume from pre- to post-randomisation between treatment groups. The basic model includes pre- and post-randomisation volumes as correlated outcomes with mean post-randomisation volumes allowed to differ by treatment group but mean pre-randomisation volumes constrained to be the same, and with variances of pre- and post-randomisation volumes allowed to differ. In the absence of missing data, this linear mixed model gives identical estimates of the treatment effect, and near identical standard errors to the more standard ANCOVA analysis. The advantage of the linear mixed model approach is that patients with missing pre- or post-randomisation scans can be included in the analysis, potentially reducing bias and increasing efficiency²⁶.

A linear regression analysis of the blinded data indicated that time from injury to CT scan, GCS, age and systolic blood pressure are significantly predictive of the pre- and post-randomisation bleeding volumes ($p < 0.05$). These covariates and the stratification factor (treatment site)²⁷ will be included in the analysis to improve the precision of the effect estimate. This will be done by extending the basic linear mixed model described above to include each covariate and its interaction with bleeding volume (pre- versus post-randomisation). This gives treatment effect estimates that are identical to those from the standard ANCOVA model in the absence of missing data. We expect the covariates to affect bleeding volumes in different ways (e.g. older people are likely to have larger bleeds at baseline, more severely unconscious people (low GCS) are likely to have larger bleeds at baseline). In line with the CONSORT guidelines²⁸, we will also report the results from the linear mixed model without covariate adjustment to facilitate synthesis and comparability with other trials that may not include the same covariates.

The blinded data indicates that pre- and post-randomisation bleeding volumes are positively skewed. We will log transform these values and report the primary outcome as a proportion.

In the original protocol, we planned to analyse the primary outcome using ANCOVA. Since publishing the protocol, we learnt that less than 50% of patients were scanned both pre- and post-randomisation. Because the pre-randomisation mean bleeding volume of the observed data may be different from the true pre-randomisation mean bleeding volume, the estimates from the ANCOVA model may be biased. Compared to ANCOVA, linear mixed models are more powerful and typically less biased when there are missing data²⁶.

Sensitivity analysis

Exclude patients who underwent neurosurgical haemorrhage evacuation after randomisation: The blinded data shows that after randomisation 14% of patients had neurosurgery before undergoing the first rated post-randomisation scan. In these cases, it is difficult to use the post-randomisation and post-neurosurgery scan to estimate the treatment effect because any change seen in intracranial haemorrhage expansion or infarction could be due to the effect of tranexamic acid or neurosurgery. The inclusion of these patients in the primary analysis may dilute any treatment effect towards the null. Therefore, we will conduct a sensitivity analysis excluding patients who underwent neurosurgery before a post-randomisation scan was done.

Secondary analyses

Composite poor outcome, 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 the composite “poor” outcome, 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 a basic linear mixed model, with pre-randomisation midline shift included as an outcome (as described above). We will extend this model to include covariates and their interaction with midline shift: time from injury to scan, GCS, age and systolic blood pressure.

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. We will conduct a sensitivity analysis excluding the patients who underwent neurosurgery.

Neurosurgical haemorrhage evacuation after randomisation: If tranexamic acid received soon after injury reduces intracranial haemorrhage, a patient who received tranexamic acid may be less likely to undergo neurosurgery to evacuate haemorrhage compared with a patient who received placebo. However, in an emergency trauma setting, the decision for neurosurgery occurs at the same time or very soon after the time of randomisation. Therefore, tranexamic acid received soon after injury may not affect the propensity for neurosurgery. But it could affect intracranial bleeding during neurosurgery.

We hypothesise that patients who receive tranexamic acid may have less blood on a post-randomisation and post-neurosurgery scan compared to patients who receive placebo. We will express the effect of tranexamic acid on the total volume of intracranial haemorrhage measured on a post-randomisation and post-neurosurgery scan using a linear mixed model as above. If the patient has been scanned pre-randomisation (and pre-neurosurgery), we will include the pre-randomisation bleeding volume as an outcome in the linear mixed model as above. To improve the precision of the effect estimate, we will extend this model to include each covariate and its interaction with bleeding volume: time from injury to scans, time from neurosurgery to scan, GCS, age and systolic blood pressure.

We will conduct a survival analysis using the time from randomisation to neurosurgery. The time to neurosurgery will be compared between treatment arms using a log-rank test. Because the log-rank test will only indicate whether there is a significant difference between treatment arms in the time to neurosurgery, we will also conduct a Cox regression analysis to quantify any difference in the hazard of neurosurgery between arms.

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^{5,25,29,30}. 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 hours²⁵, 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 injury¹⁵. 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)³¹.

Types of haemorrhage: We will conduct the linear mixed model analysis specified in the primary analysis section separately for subdural, epidural and intra-ventricular bleeds.

Missing data from scans not done before or after randomisation

Not all trial patients will be scanned before and after randomisation. We will report the number of patients without scans²⁸ and baseline data for patients included in the analysis to help identify any selective missingness of outcomes by treatment arm³². We will examine whether missing scans are missing equally between treatment arms and appear to be missing completely at random (MCAR). In this case, although missing data reduces the precision of the analysis, it does not bias the treatment effect³³.

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 (MAR)³³. 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 MAR. In this case, a regression analysis which takes GCS group into account should give unbiased estimates of the treatment effect³⁴.

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 (MNAR) (i.e. even when accounting for the fully observed data, the reason for missing observations still depends on the unseen values)³³.

Because injury severity can partly explain missingness and there are unknown reasons for some missingness, it is difficult to confirm whether our missing data will be MAR or MNAR. For the purpose of the primary analysis, we will assume missing data are MAR. To examine how robust the primary analysis is to the chosen method of handling missing data, we will conduct sensitivity analyses assuming missing data are MCAR or MNAR. Under the MCAR assumption, we will compare haemorrhage volumes between treatment groups without accounting for missingness. Under the MNAR assumption, we will compare haemorrhage volumes between treatment groups and explore the possibility that missingness of the outcome data is related to prognostic characteristics as well as to the trial treatment. If tranexamic acid reduces intracranial haemorrhage expansion and the risk of death, patients who receive tranexamic acid may be more likely to be scanned post-randomisation compared to those who receive placebo. On the other hand, if tranexamic acid reduces or prevents intracranial haemorrhage expansion, post-randomisation scanning may not be clinically indicated in these patients. We will conduct sensitivity analyses excluding patients with a low pre-randomisation GCS who may have large haemorrhage expansion and therefore not survive to have a post-randomisation scan. We will conduct sensitivity analyses excluding patients with a high pre-randomisation GCS who may have smaller haemorrhage expansion and therefore not require a post-randomisation scan.

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 TBI³⁵. 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 protocol¹⁸. The main changes are: an increased sample size from 1,000 to a maximum of 2,000 patients, a comparison of intra-parenchymal bleeding expansion between treatment groups for the primary outcome, the use of covariate adjusted linear mixed models for the primary analysis and relevant secondary analyses, and restriction of the analysis of the primary and secondary

outcomes (new and progressive bleeding) to patients treated within three hours of injury. 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.

Author contributions

Abda Mahmood leads the CRASH-3 IBMS and is a PhD Candidate in the Department of Population Health at LSHTM. Ian Roberts is Chief Investigator of the CRASH-3 Trial, Co-Director of the Clinical Trials Unit and Professor of Epidemiology and Population Health at LSHTM. Haleema Shakur-Still is Co-Director of the Clinical Trials Unit and Professor of Epidemiology and Population Health at LSHTM.

Grant information

The JP Moulton Charitable Trust (United Kingdom) is funding the run-in costs for the CRASH-3 trial and the recruitment of up to 500 patients. Full funding for the main trial is provided through joint funding by the UK Department for International Development/Medical Research Council/Wellcome Trust through the Joint Global Health Trials Scheme in low-middle income countries (Grant number MR/M009211/1) and by the National Institute for Health Research, Health Technology Assessment programme for the UK (Grant number 14/190/01). The CRASH-3 IBMS is fully funded by LSHTM (Grant reference EPAA6020). The design, management and interpretation of the CRASH-3 IBMS are entirely independent of the manufacturers of tranexamic acid or the funders.

All funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgements

We are grateful to all patients who participated in the CRASH-3 trial and whose brain scans were examined for the purpose of the IBMS. We are grateful to all clinical research staff, and administrative, management and support staff who work on the CRASH-3 trial and have supported the IBMS. We thank all members of the administrative team, data team, information technology team, and trial management team at the Trial Co-ordinating Centre of the Clinical Trials Unit (CTU) at LSHTM. We are grateful to Dr Phil Edwards and Dr Dan Altmann for their statistical support during the conception of this trial, and Professor James Carpenter for his statistical support during the early stage of this trial (Medical Statisticians at LSHTM). We are grateful to Amy Mulick and Professor Chris Frost (Medical Statisticians and Research Fellow at LSHTM) for their continued support with statistical analysis.

We are grateful to all UK sites participating in the IBMS: Queen Elizabeth Hospital Birmingham (Principal Investigator: Professor Antonio Belli), Royal London Hospital (Principal

Investigators: Professor Tim Harris & Dr Ben Bloom), University Hospital Coventry (Principal Investigator: Dr Caroline Leech), Salford Royal Hospital (Principal Investigator: Dr Fiona Lecky), St George's Hospital London (Principal Investigator: Dr Phil Moss), King's College Hospital London (Principal Investigator: Dr Phillip Hopkins), St Mary's Hospital London (Principal Investigator: Professor Mark Wilson), Addenbrooke's Hospital Cambridge (Principal Investigator: Dr Adrian Boyle), John Radcliffe Hospital Oxford (Principal Investigator:

Dr Melanie Darwent), Southmead Hospital Bristol (Principal Investigator: Dr Jason Kendall). We are grateful to all Malaysian sites participating in the CRASH-3 IBMS: Hospital Sungai Buloh (Principal Investigator: Dr Sabariah Faizah Jamaluddin), Penang General Hospital (Principal Investigator: Dr Darin Wong), Hospital Sultanah Nur Zahirah (Principal Investigator: Dr Hamzah Lotfi) and Hospital Sultanah Bahiyah (Principal Investigator: Dr Fatahul Laham Mohamed). These sites actively recruit for the CRASH-3 trial.

References

- Maas AIR, Menon DK, Adelson PD, *et al.*: **Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research.** *Lancet Neurol.* 2017; **16**(12): 987–1048.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Berkner J, Mannix R, Qiu J: **Clinical Traumatic Brain Injury in the Preclinical Setting.** *Methods Mol Biol.* 2016; **1462**: 11–28.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Mathers CD, Loncar D: **Projections of global mortality and burden of disease from 2002 to 2030.** *PLoS Med.* 2006; **3**(11): e442.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Roozenbeek B, Maas AI, Menon DK: **Changing patterns in the epidemiology of traumatic brain injury.** *Nat Rev Neurol.* 2013; **9**(4): 231–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Homnick A, Sifri Z, Yonclas P, *et al.*: **The temporal course of intracranial haemorrhage progression: how long is observation necessary?** *Injury.* 2012; **43**(12): 2122–5.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Davis SM, Broderick J, Hennerici M, *et al.*: **Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage.** *Neurology.* 2006; **66**(8): 1175–81.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Chodobska A, Zink BJ, Szymdynger-Chodobska J: **Blood-brain barrier pathophysiology in traumatic brain injury.** *Transl Stroke Res.* 2011; **2**(4): 492–516.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Abou-Diwan C, Sniecinski RM, Szlam F, *et al.*: **Plasma and cerebral spinal fluid tranexamic acid quantitation in cardiopulmonary bypass patients.** *J Chromatogr B Analyt Technol Biomed Life Sci.* 2011; **879**(7–8): 553–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Lecker I, Wang DS, Romaschin AD, *et al.*: **Tranexamic acid concentrations associated with human seizures inhibit glycine receptors.** *J Clin Invest.* 2012; **122**(12): 4654–66.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Mahmood A, Roberts I, Shakur H, *et al.*: **Does tranexamic acid improve outcomes in traumatic brain injury?** *BMJ.* 2016; **354**: i4814.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Perel P, Al-Shahi Salman R, Kawahara T, *et al.*: **CRASH-2 (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage) intracranial bleeding study: the effect of tranexamic acid in traumatic brain injury—a nested randomised, placebo-controlled trial.** *Health Technol Assess.* 2012; **16**(13): iii-xiii, 1–54.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Yutthakasemsunt S, Kittiwatanagul W, Piyavechvirat P, *et al.*: **Tranexamic acid for patients with traumatic brain injury: a randomized, double-blinded, placebo-controlled trial.** *BMC Emerg Med.* 2013; **13**: 20.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Dewan Y, Komolafe EO, Mejía-Mantilla JH, *et al.*: **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.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Bingham E, editor: **Experimental investigations upon the flow of liquids in tubes of very small diameter.** by Dr Jean Leonard Marie Poiseuille (1846) translated by W.H. Herschel. 1st ed. Lancaster: Lancaster Press Inc; 1940.
[Reference Source](#)
- Gando S, Sawamura A, Hayakawa M: **Trauma, shock, and disseminated intravascular coagulation: lessons from the classical literature.** *Ann Surg.* 2011; **254**(1): 10–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Mazzeo AT, Kunene NK, Choi S, *et al.*: **Quantitation of ischemic events after severe traumatic brain injury in humans: a simple scoring system.** *J Neurosurg Anesthesiol.* 2006; **18**(3): 170–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Hulka F, Mullins RJ, Frank EH: **Blunt brain injury activates the coagulation process.** *Arch Surg.* 1996; **131**(9): 923–7; discussion 7–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Mahmood A, Roberts I, Shakur H: **A nested mechanistic sub-study into the effect of tranexamic acid versus placebo on intracranial haemorrhage and cerebral ischaemia in isolated traumatic brain injury: study protocol for a randomised controlled trial (CRASH-3 Trial Intracranial Bleeding Mechanistic Sub-Study [CRASH-3 IBMS]).** *Trials.* 2017; **18**(1): 330.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Kothari RU, Brott T, Broderick JP, *et al.*: **The ABCs of measuring intracerebral hemorrhage volumes.** *Stroke.* 1996; **27**(8): 1304–5.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Currie S, Saleem N, Straiton JA, *et al.*: **Imaging assessment of traumatic brain injury.** *Postgrad Med J.* 2016; **92**(1083): 41–50.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Fiebach JB, Schellinger PD, Jansen O, *et al.*: **CT and diffusion-weighted MR imaging in randomized order: diffusion-weighted imaging results in higher accuracy and lower interrater variability in the diagnosis of hyperacute ischemic stroke.** *Stroke.* 2002; **33**(9): 2206–10.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Roberts I, Prieto-Merino D: **Applying results from clinical trials: tranexamic acid in trauma patients.** *J Intensive Care.* 2014; **2**(1): 56.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- World Medical Association: **World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects.** *JAMA.* 2013; **310**(20): 2191–4.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Sprigg N, Flaherty K, Appleton JP, *et al.*: **Tranexamic acid for hyperacute primary Intracerebral Haemorrhage (TICH-2): an international randomised, placebo-controlled, phase 3 superiority trial.** *Lancet.* 2018; **391**(10135): 2107–15.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Gayet-Ageron A, Prieto-Merino D, Ker K, *et al.*: **Effect of treatment delay on the effectiveness and safety of antifibrinolytics in acute severe haemorrhage: a meta-analysis of individual patient-level data from 40 138 bleeding patients.** *Lancet.* 2018; **391**(10116): 125–32.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Liu GF, Lu K, Mogg R, *et al.*: **Should baseline be a covariate or dependent variable in analyses of change from baseline in clinical trials?** *Stat Med.* 2009; **28**(20): 2509–30.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Kahan BC, Morris TP: **Analysis of multicentre trials with continuous outcomes: when and how should we account for centre effects?** *Stat Med.* 2013; **32**(7): 1136–49.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Moher D, Schulz KF, Altman DG: **The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials.** *Lancet.* 2001; **357**(9263): 1191–4.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Mayer SA, Brun NC, Begtrup K, *et al.*: **Recombinant activated factor VII for acute intracerebral hemorrhage.** *N Engl J Med.* 2005; **352**(8): 777–85.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Oertel M, Kelly DF, McArthur D, *et al.*: **Progressive hemorrhage after head trauma: predictors and consequences of the evolving injury.** *J Neurosurg.* 2002; **96**(1): 109–16.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Ker K, Prieto-Merino D, Sprigg N, *et al.*: **The effectiveness and safety of antifibrinolytics in patients with acute intracranial haemorrhage: statistical analysis plan for an individual patient data meta-analysis [version 1]; referees:**

- 2 approved].** *Wellcome Open Res.* 2017; **2**: 120.
[Publisher Full Text](#)
32. Groenwold RH, Moons KG, Vandenbroucke JP: **Randomized trials with missing outcome data: how to analyze and what to report.** *CMAJ.* 2014; **186**(15): 1153–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
33. Rubin DB: **Inference and missing data.** *Biometrika.* 1976; **63**(3): 581–92.
[Publisher Full Text](#)
34. Carpenter J, Kenward M: **Missing data in randomised controlled trials: a practical guide.** *UK: Health Technology Assessment Methodology Programme.* 2007.
[Reference Source](#)
35. Lingsma HF, Roozenbeek B, Perel P, *et al.*: **Between-centre differences and treatment effects in randomized controlled trials: a case study in traumatic brain injury.** *Trials.* 2011; **12**: 201.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

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Christian Gluud

The Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen, Denmark

Mahmood and colleagues have developed a statistical analysis plan for their nested CRASH-3 randomised clinical trial assessing tranexamic acid versus placebo for people with intracranial haemorrhage in traumatic brain injury. The primary outcome is the volume of intra-parenchymal bleeding in participants randomised within three hours of injury. The patients included will be up to 2000 participants out of the total of almost 13,000 participant randomised in the CRASH-3 trial which ended early 2019. The trial is of utmost importance. So is this nested sub-study, dealing with the population that were the only population randomised in the trial from 10th of November 2015. The statistical analysis plan is well written and clear. I only read the version 2, which has undergone amendments since first publication in August 2018. However, I have some points where it is difficult for me to fully understand the plan.

My suggestions for further explanations or clarity are:

1. The sample size estimation may still have some problems. When one has a volume, it is like a continuous outcome, giving the best power. As the data are skewed, I understand the logarithmic transformation. But why then dichotomise the transformed data? Is it easier for the reader to understand? Or is it in order to calculate a number needed to treat? Then I maybe understand a little. Usually, I would recommend to use the original volume in mL for the calculation of the sample size based on the assumed minimal relevant difference as well as a plausible standard deviation. Moreover, if you really want to dichotomise it, then you need to give a proportion in the control group having a bleed larger than e.g. three mL, and then take your relative risk reduction or increase based on that. As I see it this control proportion is missing.
2. On p 5, the authors say they will adjust their analysis for prognostic factors. I see no mention of site here. Moreover, the selection of the prognostic factors going into the analysis could become clearer?
3. On p.6, participants that are operated become a sensitivity analysis, whereas earlier they were presented as the primary analysis?
4. On p.7, pre-randomisation bleeding volume is called 'an outcome'. Should that not become a 'variable'?

5. On p. 8 MAR, MNAR, and MCAR are used extensively. But I am not sure how to interpret the likely multiple differing outcomes. Maybe, the potential impact of missingness could be examined by just applying 'best-worst' and 'worst-best' scenario analyses?
6. In the title and in the Abstract, I lack information on the fact that you examine the effect of tranexamic acid versus placebo. This is a central advantage of this trial that can only be mentioned too seldomly.
7. In the Abstract, the primary outcome is said to be the volume, which seems to contrast with the sample size calculation (see point 1).
8. On p. 3, it says: "in a meta-analysis, there was a statistically significant reduction in intracranial haemorrhage growth". Considering that the reader does not know the bias risks of the trials and that the confidence interval is the naïve 95%, maybe it could be formulated a bit weaker? E.g., "in a meta-analysis, there seemed to be a reduction in"?
9. The present status of the trial needs to become clearer. As I understand it, all randomisation has stopped earlier this year?
10. On p 7, first column, lower third. Here 'compared to' should become 'compared with'?
11. I understand that this SAP has been submitted during 2018, well before randomisation was stopped and data examined. This also needs to be clearly discussed in the light that the trial has now sized randomisation and the data likely been analysed?
12. The alpha level chosen for this analysis of the primary outcome is 0.05. As this is an extra analysis, one could have chosen a more stringent level to keep the type 1 family wise error under 0.05. This needs to be discussed.
13. The remaining statistical analyses including subgroup and sensitivity analyses all seem also to be conducted at the alpha level of 0.05. This is likely ok but should one not then stress that all these analyses will be viewed as exploratory analyses due to the high risks of type I errors?

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

Yes

Is the description of the method technically sound?

Partly

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?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: I am a clinician with trial expertise. I am not a statistician.

I confirm that I have read this submission and 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.

Author Response 21 Nov 2019

Abda Mahmood, London School of Hygiene & Tropical Medicine, London, UK

Author response:

Thank you for your detailed review of the analysis plan for the CRASH-3 IBMS. We have responded to the below queries and hope this makes the analysis plan clearer. Please note that we received this report after the trial unblinded, and are not able to make substantial changes to the analysis plan at this stage.

Reviewer comment:

My suggestions for further explanations or clarity are:

- The sample size estimation may still have some problems. When one has a volume, it is like a continuous outcome, giving the best power. As the data are skewed, I understand the logarithmic transformation. But why then dichotomise the transformed data? Is it easier for the reader to understand? Or is it in order to calculate a number needed to treat? Then I maybe understand a little. Usually, I would recommend to use the original volume in mL for the calculation of the sample size based on the assumed minimal relevant difference as well as a plausible standard deviation. Moreover, if you really want to dichotomise it, then you need to give a proportion in the control group having a bleed larger than e.g. three mL, and then take your relative risk reduction or increase based on that. As I see it this control proportion is missing.

Author response:

The relevant section of the SAP is: "The blinded data indicates that pre- and post-randomisation bleeding volumes are positively skewed. We will log transform these values and report the primary outcome as a proportion."

There has been some confusion in interpretation, probably because of a lack of clarity on our part. We do not plan to dichotomise the log transformed bleeding volume. Bleeding volume is continuous and measured in millilitres (ml). Because bleeding volumes are skewed, this data will be log transformed before entered into the linear mixed model. The anti-log of the treatment effect estimate and its corresponding 95% confidence intervals (CIs) will be presented to aid interpretation. The treatment effect estimates will provide an estimate of the relative increase or decrease in haemorrhage volume with tranexamic acid. The text in the manuscript has been amended for clarity.

This does not affect the sample size calculation.

Reviewer comment:

- On p 5, the authors say they will adjust their analysis for prognostic factors. I see no mention of site here. Moreover, the selection of the prognostic factors going into the analysis could become clearer?

Author response:

We stated in the primary analysis section that Site will be included in the model. We clarified in response to reviewer 3's query that the main effect of site is accounted for in the primary analysis.

The selection of prognostic factors is based on the established association between time from injury to scan, GCS, age and systolic blood pressure on bleeding volume. The blinded data support this association and so these covariates will be included in the model. This is noted in the primary analysis section.

Reviewer comment:

- On p.6, participants that are operated become a sensitivity analysis, whereas earlier they were presented as the primary analysis?

Author response:

The primary analysis includes all patients and its sensitivity analysis excludes patients who underwent neurosurgical haemorrhage evacuation. A secondary analysis looks at the effect of tranexamic on bleeding in patients who underwent neurosurgical haemorrhage evacuation.

Reviewer comment:

- On p.7, pre-randomisation bleeding volume is called 'an outcome'. Should that not become a 'variable'?

Author response:

In the mixed model literature, pre-randomisation data is often referred to as an "outcome". We understand that this can be confusing as it is not measured after randomisation, and so we will change this to "variable" as suggested.

Reviewer comment:

- On p. 8 MAR, MNAR, and MCAR are used extensively. But I am not sure how to interpret the likely multiple differing outcomes. Maybe, the potential impact of missingness could be examined by just applying 'best-worst' and 'worst-best' scenario analyses?

Author response:

Thank you for your suggestion. We tried to methodically explain why we don't think missing data will be from a random subset of trial patients (i.e. it will not be missing completely at random), it may not be fully explained by baseline prognostic characteristics (i.e. it may not be missing at random), but it may be related to prognostic characteristics as well as to the trial treatment (i.e. it may be missing not at random). Your suggestion for applying best-worst and worst-best sensitivity analyses is helpful, and we will do this to help assess the impact of missingness on effect estimates. But a large proportion of patients were not scanned post-randomisation in the CRASH-3 IBMS, and so best-worst and worst-best scenarios may merely indicate the best case scenario (benefit with trial treatment) and worst case scenario (harm with trial treatment) by definition of how the missing values are imputed. For these outcomes, the results of the complete case analyses may be more useful, in the context of a clear discussion of the resulting interpretative limitations of missing post-randomisation scans (Jakobsen *et al.*, 2017).

Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be used for handling missing data in randomised clinical trials - a practical guide with flowcharts. *Bmc*

Medical Research Methodology. 2017 Dec 6;17

Reviewer comment:

- In the title and in the Abstract, I lack information on the fact that you examine the effect of tranexamic acid versus placebo. This is a central advantage of this trial that can only be mentioned too seldomly.

Author response:

We have amended the abstract accordingly.

Reviewer comment:

- In the Abstract, the primary outcome is said to be the volume, which seems to contrast with the sample size calculation (see point 1).

Author response:

Please see our response to point 1.

Reviewer comment:

- On p. 3, it says: "in a meta-analysis, there was a statistically significant reduction in intracranial haemorrhage growth". Considering that the reader does not know the bias risks of the trials and that the confidence interval is the naïve 95%, maybe it could be formulated a bit weaker? E.g., "in a meta-analysis, there seemed to be a reduction in"?

Author response:

We have amended this accordingly.

Reviewer comment:

- The present status of the trial needs to become clearer. As I understand it, all randomisation has stopped earlier this year?

Author response:

Yes, the trial finished recruitment on 31 January 2019 and unblinded on 31 May 2019. The "trial status" section has been updated for clarity.

Reviewer comment:

- On p 7, first column, lower third. Here 'compared to' should become 'compared with'?

Author response:

This has been amended accordingly.

Reviewer comment:

- I understand that this SAP has been submitted during 2018, well before randomisation was stopped and data examined. This also needs to be clearly discussed in the light that the trial has now sized randomisation and the data likely been analysed?

Author response:

The analysis plan was submitted and published before the trial unblinded. We received this referee report after the trial unblinded. We have not made any substantial changes to the analysis plan as per this review. We only respond to acknowledge and address the queries raised, and update the

relevant sections of the SAP for clarity as requested. The “trial status” section has been updated to clarify.

Reviewer comment:

- The alpha level chosen for this analysis of the primary outcome is 0.05. As this is an extra analysis, one could have chosen a more stringent level to keep the type 1 family wise error under 0.05. This needs to be discussed.

Author response:

Although this trial is nested within the CRASH-3 trial, it has a different purpose. The CRASH-3 trial examines the effect of tranexamic acid versus placebo on death and disability in TBI patients, whereas the mechanistic study examines intracranial bleeding and other neuro-radiological characteristics in these patients.

We will consider the implications of type 1 error when interpreting the results and include this in the discussion of any results publication.

Reviewer comment:

- The remaining statistical analyses including subgroup and sensitivity analyses all see also to be conducted at the alpha level of 0.05. This is likely ok but should one not then stress that all these analyses will be viewed as exploratory analyses due to the high risks of type I errors?

Author response:

We acknowledge that we are examining the effect of the trial treatment on a number of endpoints and so there is a high risk of type 1 error. We will consider the implications of type 1 error when interpreting the results and stress that these analyses are exploratory in the final results publication.

Many thanks for your thorough review.

Competing Interests: No competing interests were disclosed.

Reviewer Report 21 May 2019

<https://doi.org/10.21956/wellcomeopenres.16363.r35529>

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Stephen Senn 

Independent Consultant Statistician, Strassen, Luxembourg

Introduction

This is a careful and detailed description of an important clinical trial. I claim no knowledge of the medical specialty and, as befits a statistician, limit myself to a discussion of statistical aspects only.

Power calculation

The acid test is “can the calculation be repeated?” Unfortunately, the answer is “no”. What is missing is the standard deviation of the reduction. I calculate that if the SD were 87 for an effect of 15 then about 1750 patients would be needed to give 95% power and that a reduction of sample size to 1300 would have about 87% power. However, a standard deviation that is 87% of the mean control value size is very large and implies a lack of Normality, which in turn suggest that a log-transformation might be needed. In fact, later we encounter the statement: “*The blinded data indicates that pre- and post-randomisation bleeding volumes are positively skewed. We will log transform these values and report the primary outcome as a proportion.*” Whatever the explanation, the necessary detail is lacking.

Statistical analysis

This is a multi-centre trial. Reference is made to a treatment by centre interaction being investigated but the reference to modelling the main effect of centre is imprecise; it is stated “*stratification factor (treatment site) 27 will be included in the analysis to improve the precision of the effect estimate*”, which uses terminology that is inconsistent with that used for interaction. The plan does not say how the main effect of centres will be allowed for. There are two standard ways to include the main effect of centre in the model. One is to treat the centre effect as fixed and the other as random¹. If there are many small centre and if there is some imbalance, the former may be inefficient. The latter requires care when covariates are involved because regression terms should, in theory, be allowed for at two levels: both between and within centres. An analogous problem occurs in cross-over trials. A useful reference is that of Kenward and Roger².

Also, it is not clear to me what this statement means: “*This will be done by extending the basic linear mixed model described above to include each covariate and its interaction with bleeding volume (pre-versus post-randomisation).*”

References

1. Senn S: A note regarding ‘random effects’. *Statistics in Medicine*. 2014; **33** (16): 2876-2877 [Publisher Full Text](#)
2. Kenward MG, Roger JH: The use of baseline covariates in crossover studies. *Biostatistics*. 2010; **11** (1): 1-17 [PubMed Abstract](#) | [Publisher Full Text](#)

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?

Yes

Competing Interests: I was once involved in a programme to develop a treatment for hereditary angiodema in which tranexamic acid was used as a comparator. I don't think that that constitutes a conflict but mention it in case. I maintain a full declaration here:

http://www.senns.demon.co.uk/Declaration_Interest.htm

Reviewer Expertise: Medical statistics, in particular as applied to drug development, including design and analysis of clinical trials and development programmes, ethics, personalised medicine and statistical inference.

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

Author Response 21 Nov 2019

Abda Mahmood, London School of Hygiene & Tropical Medicine, London, UK

Reviewer: Introduction

This is a careful and detailed description of an important clinical trial. I claim no knowledge of the medical specialty and, as befits a statistician, limit myself to a discussion of statistical aspects only.

Reviewer: Power calculation

The acid test is “can the calculation be repeated?” Unfortunately, the answer is “no”. What is missing is the standard deviation of the reduction. I calculate that if the SD were 87 for an effect of 15 then about 1750 patients would be needed to give 95% power and that a reduction of sample size to 1300 would have about 87% power. However, a standard deviation that is 87% of the mean control value size is very large and implies a lack of Normality, which in turn suggest that a log-transformation might be needed. In fact, later we encounter the statement: “*The blinded data indicates that pre- and post-randomisation bleeding volumes are positively skewed. We will log transform these values and report the primary outcome as a proportion.*” Whatever the explanation, the necessary detail is lacking.

Author response

Thank you for your comment. The sample size calculation has been clarified below, and we hope this now passes the acid test.

We originally planned for the IBMS to be conducted in 1,000 CRASH-3 trial patients. This sample size was based on the reduction in bleeding volume seen with tranexamic acid in the CRASH-2 Intracranial Bleeding Sub-study (Perel *et al.*, 2012). We expected a 15% reduction in intracranial bleeding with tranexamic acid (24ml tranexamic acid, 28ml placebo), a correlation of 0.6 between pre- and post-randomisation bleeding volumes, and a standard deviation of 28ml. This gave an unadjusted sample size estimate of 1542, which was reduced to 987 with adjustment ($1542 * (1 - (0.6^2))$) (Borm *et al.*, 2007).

Due to the large amount of missing data (only around half of patients were scanned both pre-randomisation and post-randomisation), we increased the sample size for the CRASH-3 IBMS to include a maximum of 2000 patients. This was the approximate maximum number of patients the scan assessor could feasibly collect data from before the CRASH-3 trial completed

recruitment. It was not expected that the scan assessor would be able to collect data from 2,000 patients (due to many international sites not using electronic imaging, and the limited time and resources for this study). This upper bound was chosen to prevent delays in data collection as a result of protocol amendments that would be needed should the sample size be increased again. More realistically, we expected around 1,700 patients could be included in the CRASH-3 IBMS. Using the same expected treatment effect, standard deviation, correlation and baseline adjustment values as the original sample size calculation, this increased power to 95%. If only considering those treated within 3 hours of injury ($n=1300$), there is 90% power to detect the expected treatment effect. However, this calculation is not adjusted for missing data. If we assume that 47% of patients will be dropped from the analyses, this leaves a study with 901 patients scanned both pre-randomisation and post-randomisation. Using the same standard deviation (adjusted for baseline), correlation and baseline adjustment values as the original sample size calculation, a study with 901 patients would have 76% power to detect the expected treatment effect. In case it is helpful, the relevant Stata code is below:

Original calculation

```
power twomeans 24 28, sd(28) // sample size estimate (n=1542)
di 1542*(1-0.6^2) // adjusted sample size estimate (n=987)
```

Variance deflation factor adjustment

```
di sqrt(28^2*(1-0.6^2)) // SD=22.4
```

Estimated power of expected sample size

```
power twomeans 24 28, sd(22.4) n(901) // 76% power
```

The sample size section of the SAP has been amended.

Reviewer: Statistical analysis

This is a multi-centre trial. Reference is made to a treatment by centre interaction being investigated but the reference to modelling the main effect of centre is imprecise; it is stated “*stratification factor (treatment site) will be included in the analysis to improve the precision of the effect estimate*”, which uses terminology that is inconsistent with that used for interaction. The plan does not say how the main effect of centres will be allowed for. There are two standard ways to include the main effect of centre in the model. One is to treat the centre effect as fixed and the other as random¹. If there are many small centre and if there is some imbalance, the former may be inefficient. The latter requires care when covariates are involved because regression terms should, in theory, be allowed for at two levels: both between and within centres. An analogous problem occurs in cross-over trials. A useful reference is that of Kenward and Roger².

Author response:

Thank you for your detailed comment. The specified linear mixed model analyses, which compare bleeding volume between treatment groups, include an interaction between centre and whether bleeding volume was measured before and/or after randomisation. Therefore, the main effect of centre (which is treated as fixed) is accounted for in the model. Because we have relatively few centres ($n=14$) compared to the number of patients ($n \approx 1750$), we expect any loss in efficiency from this method (compared to the random centre effects method) to be minimal.

Although we noted in the SAP that we would include an interaction between centre and treatment in the model, we do not expect between centre differences in unfavourable outcome to affect the chance of demonstrating a treatment effect (Lingsma *et al.*, 2011). There is also low power for a

between-centre interaction. Therefore, we will not include the interaction between centre and treatment in the model. The relevant sections of the SAP have been amended.

Reviewer comment:

Also, it is not clear to me what this statement means: “*This will be done by extending the basic linear mixed model described above to include each covariate and its interaction with bleeding volume (pre- versus post-randomisation).*”

Author response:

In linear mixed model analyses, which compare bleeding volume between treatment groups, we have pre-specified an interaction between each covariate and whether bleeding volume was measured before and/or after randomisation. The “basic linear model” does not include covariates. The model we will use for the primary analysis and relevant secondary analyses include covariates. The relevant section of the SAP has been amended. We hope this is clearer.

References

Perel P, Al-Shahi Salman R, Kawahara T, Morris Z, Prieto-Merino D, Roberts I, et al. CRASH-2 (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage) intracranial bleeding study: the effect of tranexamic acid in traumatic brain injury--a nested randomised, placebo-controlled trial. *Health Technol Assess.* 2012;16(13):iii-xii, 1-54

Borm GF, Fransen J, Lemmens WA. A simple sample size formula for analysis of covariance in randomized clinical trials. *J Clin Epidemiol.* 2007 Dec;60(12):1234-8

Lingsma HF, Roozenbeek B, Perel P, *et al.*: Between-centre differences and treatment effects in randomized controlled trials: a case study in traumatic brain injury. *Trials.* 2011; 12: 201.

Competing Interests: No competing interests were disclosed.

Version 1

Reviewer Report 18 October 2018

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John Hodson 

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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.

Reviewer Expertise: Statistics

I confirm that I have read this submission and 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.

Author Response 18 Dec 2018

Abda Mahmood, London School of Hygiene & Tropical Medicine, London, UK

Thank you for your valuable feedback on our paper. We have responded to each of your points below and all relevant changes have been incorporated into the revised version of the manuscript (version 1.1).

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.

In the published protocol, we said that a trial with at least 1000 patients will have 80% power (at $\alpha = 0.05$) to detect a 15% lower bleeding volume in the tranexamic acid group at follow-up (i.e., 24 mL tranexamic acid vs. 28 mL placebo). This was based on the treatment effect observed in a smaller randomised trial of tranexamic acid in traumatic brain injury (CRASH-2 Trial Intracranial Bleeding Study; Perel et al., 2012). Since publishing the protocol, we increased the sample size from 1,000 to around 1,750 patients, and thereby the power from 80% to 95%, which will be further improved by covariate adjustment.

Because the primary analysis will be based on patients randomised within 3 hours of injury, of which at the time of writing the first version of the SAP we expected there to be 1000, we reported the power of the primary analysis to detect the expected treatment effect. However, the power of the total sample is greater than this. We have amended the SAP to clarify (page 8).

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?

We plan to adjust the primary analysis using appropriately selected prognostic covariates. Time from injury to scan, age, GCS and systolic blood pressure have been shown to predict intracranial haemorrhage volume (Narayan et al., 2008; Yadav et al., 2006). We used our blinded data from 1000 patients to examine whether this finding was replicated in our trial because adjusting for non-prognostic covariates can lead to a reduction in power (Kahan et al., 2014). We found that the selected fully observed covariates are predictive of intracranial haemorrhage volume so we pre-specified that we will adjust for these covariates to improve the precision of the effect estimate.

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.

Thank you for suggesting this alternative more powerful approach. We will use linear mixed models for the primary analysis and relevant other analyses, as specified in the updated version of the SAP.

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

We have updated the relevant section of the SAP accordingly (page 18).

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.

Thank you for picking up this typo. The p-value has been corrected to 0.17 (page 3).

References

Narayan RK, Maas AI, Servadei F, Skolnick BE, Tillinger MN, Marshall LF, et al. Progression of traumatic intracerebral hemorrhage: a prospective observational study. *J Neurotrauma*. 2008;25(6):629-39.

Kahan BC, Jairath V, Dore CJ, Morris TP. The risks and rewards of covariate adjustment in randomized trials: an assessment of 12 outcomes from 8 studies. *Trials*. 2014;15:139.

Perel P, Al-Shahi Salman R, Kawahara T, Morris Z, Prieto-Merino D, Roberts I, et al. CRASH-2 (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage) intracranial bleeding study: the effect of tranexamic acid in traumatic brain injury--a nested randomised, placebo-controlled trial. *Health Technol Assess*. 2012;16(13):iii-xii, 1-54.

Yadav YR, Basoor A, Jain G, Nelson A. Expanding traumatic intracerebral contusion/hematoma. *Neurol India*. 2006;54:377-81.

Competing Interests: None

Reviewer Report 17 September 2018

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Surakrant Yutthakasemsunt 

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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 studies¹⁻³ are comparable to the concept in meta analysis that exploring the clinical heterogeneity and statistical heterogeneity⁴⁻⁵ 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.

References

1. Roberts I, Belli A, Brenner A, Chaudhri R, et al.: Tranexamic acid for significant traumatic brain injury (The CRASH-3 trial): Statistical analysis plan for an international, randomised, double-blind, placebo-controlled trial. *Wellcome Open Res.* 2018; **3**: 86 [PubMed Abstract](#) | [Publisher Full Text](#)
2. Mahmood A, Roberts I, Shakur H: A nested mechanistic sub-study into the effect of tranexamic acid versus placebo on intracranial haemorrhage and cerebral ischaemia in isolated traumatic brain injury: study protocol for a randomised controlled trial (CRASH-3 Trial Intracranial Bleeding Mechanistic Sub-Study [CRASH-3 IBMS]). *Trials.* 2017; **18** (1). [Publisher Full Text](#)
3. Ker K, Prieto-Merino D, Sprigg N, Mahmood A, et al.: The effectiveness and safety of antifibrinolytics in patients with acute intracranial haemorrhage: statistical analysis plan for an individual patient data meta-analysis. *Wellcome Open Res.* 2017; **2**: 120 [PubMed Abstract](#) | [Publisher Full Text](#)
4. Thompson SG: Why sources of heterogeneity in meta-analysis should be investigated. *BMJ.* 1994; **309** (6965): 1351-5 [PubMed Abstract](#)
5. Thompson SG, Sharp SJ: Explaining heterogeneity in meta-analysis: a comparison of methods. *Stat Med.* 1999; **18** (20): 2693-708 [PubMed Abstract](#)

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.

Reviewer Expertise: Neurosurgery : Traumatic Brain Injury, Hemorrhagic stroke

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

Author Response 08 Jan 2019

Abda Mahmood, London School of Hygiene & Tropical Medicine, London, UK

Thank you for reviewing our paper and for your thoughtful comments. We look forward to sharing the results in the near future!

Competing Interests: None

