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**Effect of tranexamic acid on intracranial haemorrhage and
infarction in patients with traumatic brain injury:
a randomised trial.**

Abda Mahmood

Thesis submitted in accordance with the requirements for the degree of

Doctor of Philosophy

University of London

December 2019

Clinical Trials Unit

Department of Population Health

Faculty of Epidemiology and Population Health

London School of Hygiene and Tropical Medicine

University of London

Funded by Clinical Trials Unit, London School of Hygiene and Tropical Medicine



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My Contribution

I led the protocol development and amendments, national and international ethics submissions and amendments, local hospital site approvals (including Research & Development approval at each site and Research Passport updates at each site), data collection, data and database management, data cleaning, data analysis, interpretation and publication, of the CRASH-3 Intracranial Bleeding Mechanistic Study (IBMS).

I travelled to each of the 14 hospital sites (UK and Malaysia) that participated in the CRASH-3 IBMS. I accessed the clinical imaging system (Picture Archive and Communications System) at each site, identified the patient using the trial randomisation code and hospital number, and identified which scans were done pre-randomisation and/or post-randomisation (using data on the date and time of randomisation from the CRASH-3 trial Entry Form). I manually rated each of the scans (on site) from the 1,767 patients included in the CRASH-3 IBMS. Data collection took place over a period of three years (2016-2019), including at least 14 placements ranging from weeks to several months, depending on the number of patients recruited at each site. Due to the logistic difficulty of travelling to each of these sites for continued periods of data collection, these placements involved overnight stay at each of the towns or cities in which the hospitals were based (minus the London hospitals and Addenbrooke's Hospital in Cambridge, which were easier to visit as day trips from my address).

Although the data collection process was logistically challenging, a major advantage of having collected the data myself is that I understand the data and clinical management of TBI in a more meaningful way than if I were to only have access to the final dataset. My experiences at each of the hospital sites that I visited enhanced my understanding of the patient pathway that led to my final dataset, and this humanised every data point. I forged professional relationships with clinical staff including nurses and medical doctors, and used national and international placement opportunities to observe and discuss the clinical management of TBI patients with hospital staff; from the pre-hospital ambulatory service, the in-hospital emergency care, urgent neurosurgery post-trauma, the early treatment process in wards, to the rehabilitation process post-discharge. This enhanced my understanding of the complexity of TBI treatment and management. It also helped me to identify barriers in effectively conducting clinical research at specific sites, and therefore improved the local conduct of this and other clinical trials. I was able to answer questions relating to trial procedures and this enhanced practitioners' understanding of the motivations for any changes to trial procedures, and the global scope of their contribution. Incidentally, some of the data collected as part of my thesis served as an audit of the CRASH-3 trial data and led to raising and resolving data monitoring queries. My data collection experience improved my understanding of how research works in practice, and how its efficiency can be improved. This led me to appreciate the dynamic relationship between knowledge and practice.

Abstract

Background: The CRASH-3 trial hypothesized that Tranexamic Acid (TXA) could reduce intracranial bleeding and the risk of head injury death in patients with traumatic brain injury (TBI). Because “head injury death” includes death from intracranial bleeding, to simplify the trial procedures, the investigators did not collect data on the extent of intracranial bleeding in all trial patients. Furthermore, TXA may increase the occurrence of stroke, and this outcome was recorded in the trial outcome form, but cerebral infarction as seen on imaging was not. Additional information on the hypothesized mechanism of action of TXA in TBI could help explain the CRASH-3 trial results.

Research questions, aims and hypotheses: The CRASH-3 Intracranial Bleeding Mechanistic Study (IBMS) sought to investigate whether the mechanism of action of TXA in TBI could be assessed using routinely collected brain imaging. If so, the IBMS aimed to explore the potential effects of TXA on intracranial bleeding and infarction. Specifically, it was hypothesised that TXA could reduce intracranial bleeding and/or increase cerebral infarction.

Methods: The IBMS was nested within the CRASH-3 trial: a prospective, double-blind, parallel-arm, randomised trial. Patients eligible for the CRASH-3 trial, with a Glasgow Coma Scale (GCS) score of ≤ 12 or intracranial bleeding on pre-randomisation CT were eligible. Outcomes were examined on routinely collected brain scans done pre- and/or post-randomisation. The primary outcome is the volume of intra-parenchymal bleeding in patients randomised within three hours of injury. Secondary outcomes include new and progressive bleeding, post-neurosurgical bleeding, infarction, and a composite “poor outcome”. The primary outcome was analysed using a linear mixed model, and dichotomous outcomes using relative risks or hazard ratios.

Findings: The IBMS included 14% of the CRASH-3 trial patients ($n=1767/12,737$): 884 TXA, 883 placebo. Patients had a median baseline GCS of 7 (IQR 3–10). Only 46% of patients were scanned pre- and post-randomisation ($n=812/1767$) and 35% were scanned post- but not pre-randomisation ($n=614/1767$). A total of 21% of patients had evidence of neurosurgical haemorrhage evacuation on a post-randomisation scan. There was no evidence for a reduction in intra-parenchymal bleeding with TXA (1.09, 95% CI 0.81–1.45) or in intracranial bleeding in neurosurgical patients (0.79, 95% CI 0.57–1.11). There was no evidence for a reduction in the composite (RR=1.01, 95% CI 0.93–1.10) or increase in the hazard of infarction with TXA (HR=1.31, 95% CI 0.95–1.80). In patients scanned pre- and post-randomisation, there was no evidence that TXA reduces progressive bleeding (RR=0.92, 95% CI 0.74–1.13) and no clear evidence that TXA reduces new bleeding (RR=0.86, 95% CI 0.72–1.02).

Conclusions: Routine imaging cannot provide reliable information on the effects of TXA in TBI. The associated methodological flaws mean that the treatment effect estimates are not valid and precise. 1) The large proportion of missing post-randomisation scans could depend on whether a patient received TXA. 2) The inclusion of a large proportion of severely injured patients may dilute effect estimates towards the null. 3) The receipt of TXA may affect whether patients undergo neurosurgery, and this complicates the assessment of the effects of TXA using scans done post-randomisation and post-neurosurgery.

Implications for future research: If a research protocol mandated that scans were done at a set time-point post-randomisation, this would reduce the risk of bias from missing outcomes. If less severely injured patients were included, this would reduce the occurrence of neurosurgery and missing outcomes as a result of death.

Research Questions, Aim and Hypotheses

In this thesis, I sought to answer a number of research questions to inform the background, methods, analysis, and interpretation of this thesis. These questions have been detailed below, with a summary of the findings from various reviews that were done as part of this thesis to help answer these questions. These questions were explored by conducting reviews of the relevant literature and seeking expert opinion. I have listed these questions in the order they were encountered in the thesis. This is followed by more specific aims and hypotheses about how TXA might influence neuro-radiological outcomes after TBI.

Research question 1. Have there been, or are there any ongoing, double-blind randomised trials of anti-fibrinolytic drugs in patients with TBI?

- In 2016, I worked with Information Specialist (Deirdre Beecher) at the Cochrane Injuries Group to update a Systematic Review published in 2015 in this area.
- We searched several databases to identify all relevant completed, ongoing and pending randomised trials in this area (see Section 1.10 for more information).
- We identified three ongoing or pending randomised trials on the effects of TXA in TBI. I assessed the quality of these trials according to an Epidemiological Risk of Bias tool. Of the three trials, the CRASH-3 trial was the largest into the effects of TXA in TBI.
- I led the publication of this review, highlighting the uncertainty regarding the use of TXA in TBI (Thesis Research Paper 1).

Research question 2. What are the available brain imaging modalities and methods to examine intracranial bleeding and infarction?

- I performed a literature review and found that CT scanning is the most commonly used neuro-imaging modality done as part of routine in-hospital patient care and can identify larger intracranial bleeds in the acute stage of injury. Other imaging methods, such as MRI, are more sensitive and specific in identifying small and large bleeds and other pathologies (such as infarction) in the acute stage of injury. However, MRI and its specific sequences are not routinely used in all TBI patients or in all hospitals.
- I performed a literature review and found that automated and manual methods are available to estimate intracranial bleeding volume.
 - I found that automated methods result in less measurement error of intracranial bleeding volume than manual methods. However, automated methods were not used in this thesis because scan assessment happened at each participating hospital (as per advice from the Medical Research Ethics Committee) where the relevant software would need to be installed on clinical computers with access

to scans. Due to potential technical and other difficulties in doing this, I explored alternative methods of estimating haemorrhage volume.

- I identified a number of manual methods that have been used to estimate intracranial bleeding volume. One simple manual method (ABC/2) has been validated for estimating intracranial bleeding volume.

Research question 3. Is there a difference in bleeding volume estimates with the manual ABC/2 method compared to automated methods, and if so, what factors influence this discrepancy?

- I conducted a systematic literature review on the association between ABC/2 and automated methods for estimating haemorrhage volume. I found that the ABC/2 method has good agreement with automated methods, especially for bleeds that have spherical shapes, and so ABC/2 was chosen to estimate the haemorrhage volume for some bleed types in this thesis (see Section 2.24). Because SDH typically has a non-spherical shape, an alternative method was used to estimate SDH volume (see Section 2.25).

Research question 4. Why might patients not be routinely scanned before or after randomisation?

- This thesis found that TBI patients are routinely scanned on admission to hospital. This admission scan was done before randomisation, unless patients had a GCS of ≤ 12 , in which case the CRASH-3 trial procedure allowed randomisation before CT (to reduce time to randomisation).
- This thesis found that a large proportion of patients who are not scanned after randomisation are either mildly injured or severely injured at baseline (according to clinical signs such as GCS). Patients who died due to head injury are at greater risk of not being scanned after randomisation, compared to those who died of a different cause or survived.

Research question 5. What are some of the statistical approaches to estimate the effect of a treatment on a continuous outcome and how do they handle missing data?

- In this thesis, I considered three statistical approaches to examine the effect of TXA on intracranial bleeding.
 - First, I considered Analysis of Covariance (ANCOVA). In ANCOVA, the post-randomisation bleeding volume can be compared between treatment groups, and adjusted using the pre-randomisation bleeding volume. If there are baseline differences between treatment groups, ANCOVA is more efficient than the CHANGE method (comparing the change in volume from pre- to post- between treatment groups) and POST method (comparing the post- volumes between

groups, without considering pre- volumes). However, ANCOVA can only include patients who are scanned both pre- and post-randomisation.

- Next, I considered Analysis of Variance (ANOVA) where the post-randomisation bleeding volume is compared between treatment groups, and pre-randomisation bleeding volume is not included in the analysis. This approach can include all patients with post-randomisation scans, and so in this case may be less biased and more powerful than ANCOVA.
- Finally, I considered a Linear Mixed Model (LMM). In this analysis, the post-randomisation bleeding volume can be compared between treatment groups. If patients are only scanned pre-randomisation, this information is included the estimate of the pre-randomisation bleeding volume. If patients are only scanned post-randomisation, this information is included in the estimate of the post-randomisation bleeding volume. This model allows all patients to be included, even if they have missing pre- or missing post-randomisation scans, and so is less biased and more efficient than the first two options.

Research question 6. Can the potential effects of TXA on radiological outcomes be assessed using routinely collected brain imaging?

- This thesis found that the potential effects of TXA on intracranial bleeding and infarction cannot be reliably assessed using routinely collected imaging. This is mainly because a large proportion of patients are not scanned 24-48 hours after randomisation as part of their routine care. The reasons patients are not scanned can be affected by the missing values themselves and/or the trial treatment. This thesis found that estimates for the effects of TXA based on routinely collected data are at high risk of bias.

Research Aims. This study aims to examine the mechanism by which TXA might exert its effects in isolated TBI, specifically its effect (if any) on intracranial haemorrhage and infarction, and whether this varies by time from injury to randomisation.

- This thesis did not provide a reliable assessment of these aims.

Research Hypotheses. TXA could reduce intracranial bleeding and/or increase cerebral infarction in patients with TBI.

- This thesis did not provide sufficient information to confirm or refute these hypotheses.

Structure of PhD thesis

I have written a research paper style thesis that includes five chapters. I have included three research papers published in peer reviewed journals between 2016 and 2019. Sections of the published versions of the research papers are presented in the main text, with duplicate sections omitted or amended for clarity. Copies of the full research papers are included in the Appendices. The published research papers are presented in Chapters 1, 2 and 3. I have also included one manuscript submitted for publication consideration. This is included in Chapter 3.

Chapter 1 describes the occurrence of traumatic brain injury (TBI) and intracranial bleeding after TBI. Then, the processes by which blood clots (coagulation) and blood clots break down (fibrinolysis) will be described, with attention to these processes in patients with TBI. The potential effect of an anti-fibrinolytic drug called tranexamic acid (TXA) on intracranial bleeding expansion, infarction, and death, will be considered. Research Paper 1 (published in 2016) is included in Chapter 1 and considers the evidence for the use of TXA in TBI and highlights the uncertainty around its use in this context. This will lead to a discussion on the importance of examining the mechanism of action of TXA in TBI, which will lead to the rationale for the current study. Relevant sections of Research Paper 2 will be included in this chapter (discussion section of protocol, published in 2017).

Chapter 2 describes the methods for the current study (CRASH-3 Intracranial Bleeding Mechanistic Study, IMBS). This study is nested within a large randomised trial, which examined the effect of TXA on death and disability in patients with TBI (CRASH-3 trial). Research Paper 2 (protocol, published in 2017) will be included in this chapter. This includes the CRASH-3 IBMS trial design and registration, ethical approval, eligibility criteria, consent to participate, participating hospitals, randomisation procedure, primary and secondary outcomes and their measurement. The pilot study will be summarised and amendments that were made to the methods as a result. The data collection procedure, sample size and data management plan will be presented. Confidentiality of patient data and potential risks of participation will be considered. Research Paper 3 (statistical analysis plan, published in 2018) is included in this chapter. The plans for publication and dissemination will be presented.

Chapter 3 will start by describing the CRASH-3 IBMS population, including reference to a Consolidated Standard of Reporting Trials (CONSORT) diagram and baseline tables. I will consider the inter-rater reliability of intracranial bleeding occurrence at baseline. I will describe the baseline CT scan data, with attention to the occurrence of intracranial bleeding and other neuro-radiological features of TBI. Sections of Research Paper 4 are included in this chapter, which describes the baseline CT scan data in the context of the results of the CRASH-3 trial. Then I will explore the effect of TXA on intracranial bleeding and infarction (and whether this varies

by time to treatment) using data from baseline and follow-up scans. I will present the results from the primary and secondary analyses as per the pre-specified statistical analysis plan.

Chapter 4 will examine the occurrence of missing pre-randomisation and post-randomisation scans (i.e. baseline and follow-up scans). The potential reasons for missing scans will be explored, including any association between injury severity and missing scans. The potential impact of missing scans on treatment effect estimates will be considered.

Chapter 5 provides a critique of the CRASH-3 IBMS in the context of previous trials in this area, and considers the implications for research and practice. I consider the methodological challenges in using routinely collected brain imaging to provide valid and precise estimates of the effect of TXA on intracranial bleeding and infarction in TBI. Limitations include the large proportion of missing post-randomisation scans that could depend on whether a patient received TXA, null bias from baseline unsurvivability and misclassification of outcomes, and the possibility that TXA may enhance the appearance of bleeding on CT. Strengths include improved knowledge about the occurrence of intracranial bleeding in patients with TBI. This study also highlights the importance of baseline severity when examining the effect of TXA in TBI.

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TABLE OF ABBREVIATIONS

ANCOVA	Analysis of covariance
CI	Confidence interval
CONSORT	Consolidated standard of reporting trials
CRASH	Corticosteroid Randomisation after Significant Head Injury
CRASH-2	Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage
CRASH-2 IBS	CRASH-2 Intracranial Bleeding Study
CRASH-3	Clinical Randomisation of an Antifibrinolytic in Significant Head Injury
CRASH-3 IBMS	CRASH-3 Intracranial Bleeding Mechanistic Study
CRFs	Case Report Forms
CT	Computed tomography
CTU	Clinical Trials Unit
DMP	Data Management Plan
EDH	Epidural Haemorrhage
g	Gram
GCS	Glasgow Coma Scale
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
h	Hours
HR	Hazard ratio
ICC	Intra-class correlation
ICH-GCP	International Conference on Harmonisation Good Clinical Practice
IPH	Intra-parenchymal Haemorrhage
ISRCTN	International Standard Randomised Controlled Trials registry
IVH	Intra-ventricular Haemorrhage
IQR	Interquartile range
LSHTM	London School of Hygiene & Tropical Medicine
MAR	Missing at random
MCAR	Missing completely at random
MESH	Medical Subject Headings

MNAR	Missing not at random
ml	Millilitre
mm	Millimetre
mmHg	Millimetres of Mercury
msv	Millisievert
MHRA	Medicines and Healthcare Products Agency
MRI	Magnetic Resonance Imaging
NHS	National Health Service
OR	Odds Ratio
RR	Relative Risk
SAH	Subarachnoid Haemorrhage
SDH	Subdural Haemorrhage
TARN	Trauma Audit and Research Network
TBI	Traumatic Brain Injury
TPA	Tissue Plasminogen Activator
TXA	TXA
UK	United Kingdom

1 BACKGROUND

1.1 Traumatic brain injury occurrence

Traumatic brain injury (TBI) is defined as an alteration in brain function, or other evidence of intracranial pathology, caused by external mechanical force ^{1,2}. Worldwide over 60 million people suffer from TBI each year ³. This results in over 10 million deaths or hospitalisations each year ⁴. TBI is the leading cause of death and disability in young adults ⁵, particularly in low-income and middle-income countries where rates of road traffic crashes are increasing ⁶. Projections of global mortality and burden of disease suggest that road traffic crashes will be the third major cause of death and disability by 2030 ⁶. Falls are the leading cause of TBI in high-income countries ⁷. The population aged over 60 is predicted to double by 2050 ^{8,9} and with individuals remaining mobile and semi-independent to older ages, this places them at an increased risk of falls from frailty ^{2,10}. Indeed, the burden of TBI continues to rise in those aged over 65 ¹¹. Other causes of TBI include contact sports ⁹ and physical assault ¹². Males are more likely to die from TBI compared to females at all ages ¹¹, which may reflect differences in risk taking ¹³ or differential exposure to hazards in specific workplaces ¹⁴. The estimated cost of TBI to the world economy is US \$400 billion annually ¹⁰. Estimated costs are based on a host of consequences of TBI (described below), including direct and indirect medical costs.

The worldwide societal and economic burden of TBI may be reduced by preventative measures such as adherence to road safety legislation, improved road conditions and vehicle design, countermeasures such as seatbelt and helmet use, and improved hazard management in homes and workplaces ¹⁵⁻¹⁷. Yet the World Health Organization expects TBI to continue to be a major cause of death and disability ¹⁸. There is an urgent global need for safe and effective TBI treatment and rehabilitation to improve both life expectancy and quality of life ¹⁹. Patients who survive death from TBI are at risk of physical, psychological, cognitive and other neurological problems that can persist for months or years after injury ²⁰⁻²⁷. Severe TBI often results in motor impairment that persists for at least 3 years after the injury ²² and cognitive impairments are present for at least 6 months after injury ²³. Problems with memory following TBI significantly affect an individual's quality of life ²⁴. This enhances the associated financial burden of medical care, psychological therapy, lost wages and reduced productivity, which is pronounced in those of a lower socio-economic status ²⁸. To reduce the burden of this life threatening and potentially disabling condition, it is increasingly important to identify effective clinical care for TBI patients.

1.2 Cerebral blood circulation

Oxygenated blood is supplied to the brain by four major vessels: two carotid and two vertebral arteries ²⁹. The carotid arteries principally supply the anterior portion of the cerebrum with blood. The vertebral arteries supply the posterior part of the cerebrum, part of the cerebellum, and brainstem with blood. Deoxygenated blood is carried from the brain to the heart via two groups of valve-less veins which allow for drainage: the superficial cortical veins and the deep or central veins ²⁹. Post-traumatic intracranial bleeding results when intracranial vessels (arteries or veins) rupture on impact and blood escapes into the surrounding space. Non-contrast-enhanced CT imaging of the head is quick and easy to perform, and has high sensitivity for detecting acute intracranial bleeding that will need neurosurgical intervention ³⁰. Therefore, it is usually the first neuroimaging modality used in TBI across hospital emergency departments around the world ³¹.

1.3 Computed tomography (CT) imaging

A head CT scanner uses x-rays to form a representation of the skull and brain (see Figure 1).

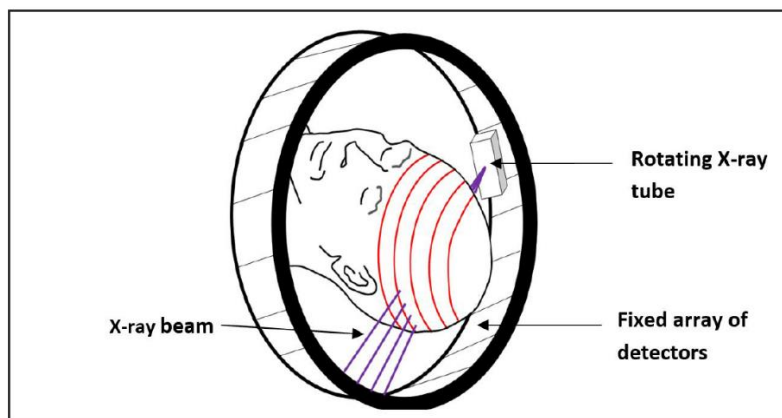


Figure 1. Helical scanning technique comprising rotating x-ray tube and fixed array of detectors. ^a

A patient lies in the CT scanner, a tunnel like machine, whilst the inside of the scanner rotates and takes x-rays of the head from different angles ³². These images are used to display cross-sections (slices) of the brain. Slice thickness typically ranges from 3-5mm in routine scanning, but this can vary depending on the level of detail required for interpretation ³². CT images are acquired in the axial plane (top to bottom of the brain). The axial data can be used to reconstruct images in other planes, including sagittal (separating the left and right of the brain) and coronal (separating the front and back of the brain).

^a Reproduced from Osborne et al (2016) ³²

The CT appearance of the skull and brain are based on density relative to water ³². The skull is the most dense part of the head and so absorbs the most x-rays; the skull has a bright white appearance on CT. Brain tissue is less dense than the skull and absorbs less x-rays, and has a grey appearance on CT. Cerebrospinal fluid flows through the brain's ventricles, and so the ventricles absorb few x-rays and have a black appearance on CT. Post-traumatic hyper-acute intracranial bleeding has not yet clotted and so it has the same density as blood flowing through cerebral vessels on non-contrast enhanced CT ³¹. Hyper-acute bleeding does not have a distinct appearance on CT. In the first few hours after injury, the blood has had opportunity to clot and so its appearance on CT appears as hyper-dense. In this acute bleeding phase, the clotted blood is more dense than brain tissue (and less dense than the skull) and so has a marked white appearance on CT ^{31, 32}.

1.4 Intracranial haemorrhage (bleeding) occurrence

TBI is associated with various neuropathological changes ³³. One of the most devastating is intracranial haemorrhage ^b expansion, which increases the risk of death and disability ³⁴. Larger intracranial bleeds, wherever located, are associated with an increased risk of death and disability compared to smaller bleeds ^{34, 35}. According to clinical measures of TBI severity, such as the Glasgow Coma Scale (GCS) ³⁶, patients with intracranial bleeding tend to have more severe TBI than patients without intracranial bleeding ³⁴. The GCS assesses impairments in consciousness indicated by eye, verbal and motor responses ^c. Each patient receives a total GCS score ranging from 3 to 15, with a lower score indicating reduced consciousness. GCS scores can be categorised as mild (13-15), moderate (9-12) or severe (3-8). The major advantage of the GCS is its simplicity and use as a standardized measure to compare outcomes between patients with different injury severities ³⁶. One caveat of GCS assessment is that it may overestimate injury severity in patients who are sedated, ventilated, paralysed or intoxicated ^{37 38}.

Several studies have used admission and/or repeat CT scans to describe the temporal course of intracranial bleeding progression in patients with TBI. Compared to patients with mild GCS, a greater proportion of patients with more severe GCS appear to show evidence of progressive bleeding (see Table 1).

^b The terms “bleeding” and “haemorrhage” are used interchangeably in this thesis.

^c The eye opening sub-scale score ranges from 1 to 4, with 1 indicating no response, 2 for response to pain, 3 for response to speech and 4 indicating spontaneous response. The verbal sub-scale score ranges from 1 to 5, with 1 indicating no response, 2 for incomprehensible sounds, 3 for the use of inappropriate words, 4 for confusion, and 5 for orientation to time, place and person. The motor sub-scale score ranges from 1 to 6, with 1 indicating no response, 2 for abnormal extension, 3 for abnormal flexion, 4 for flexion withdrawal from pain, 5 for movement to localised pain and 6 if the patient obeys commands.

Table 1. Intracranial haemorrhage (ICH) on admission and/or repeat head computed tomography (CT) scans) across a range of Glasgow Coma Scale (GCS) scores.

Study authors, publication date (n)	Baseline GCS range	Hours from injury to first CT, repeat CT	ICH on first CT	ICH on repeat CT
Albers et al., 2013 (n=3,088) ³⁹	14-15	6, N/A	5% (n=149)	N/A
Homnick et al., 2012 (n=341) ⁴⁰	13-15 (median 14.6 ± 0.7)	1, 48	All patients *	1%
Oertel et al., 2002 (n=142) ⁴¹	3-15 (median 8)	2, 24	All patients *	42%
Narayan et al., 2008 (n=69) ⁴²	4-14 (median 8)	6, 72 ≤3.5, 24 >3.5, 24	All patients (at least 2ml) *	51% 57% 28%

*by definition of inclusion criteria

One study in 3,088 patients with mild GCS found that 5% of patients showed evidence of intracranial haemorrhage on admission CT ³⁹. In patients with evidence of haemorrhage, 51% presented with intra-parenchymal haemorrhage (IPH), 26% with subarachnoid haemorrhage (SAH), 17% with subdural haemorrhage (SDH) and 6% with epidural haemorrhage (EDH). No patients with intracranial haemorrhage died or deteriorated neurologically within 24 hours of admission. Another study included 341 patients with a mild GCS and an admission head CT scan showing intracranial haemorrhage. Patients with at least two head CT scans done within 48 hours of injury were included. Only 1% of patients showed evidence of progressive haemorrhage 48 hours after admission (see Figure 2). The time that ICH stopped was determined by the time of the last head CT showing no progression of ICH and likely overestimated duration of ongoing haemorrhage. Therefore, in patients with mild GCS who present to hospital with intracranial haemorrhage, although this bleeding can continue for 24 hours or longer, most bleeds appear to stop progressing within a few hours of hospital admission ⁴⁰.

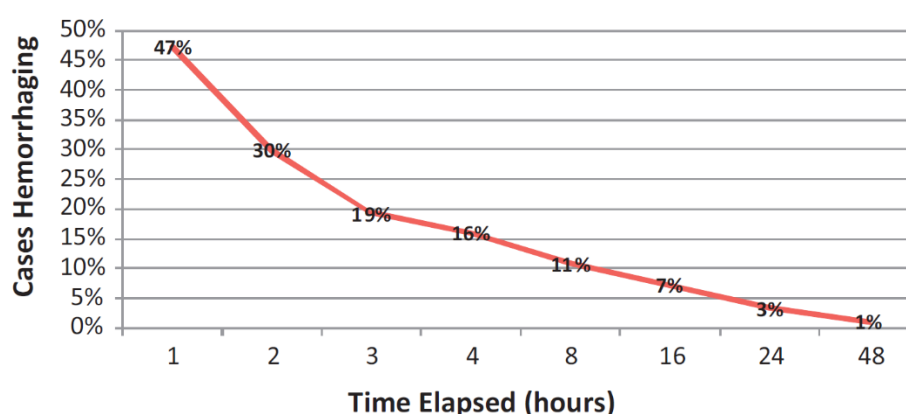


Figure 2. Temporal course of intracranial haemorrhage (ICH) progression from the time of Emergency Department presentation in patients with mild GCS. ^d

^d Figure reproduced from Homnick et al (2012) ⁴⁰.

Another study recruited 142 TBI patients across injury severities who had abnormalities on the admission CT scan ⁴¹. Intracranial haemorrhage progression was seen in 42% of patients between admission CT done 2 ± 1.6 hours after injury and repeat CT scanning done within 24 hours of injury. Furthermore, another study recruited 69 TBI patients except for the most and least severely injured, with a baseline CT scan done within 6 hours of injury that showed at least 2ml of intracranial haemorrhage, but no plan for neurosurgical haemorrhage evacuation within 24 hours of injury ⁴². A total of 51% of patients had evidence of progressive haemorrhage between admission and repeat CT done within 72 hours of injury ⁴².

Patients who were scanned earlier after injury (≤ 3.5 h vs. > 3.5 h) were more likely to have expanding haematomas on CT performed 24 hours after injury (57% vs. 28%) ⁴². If the initial CT scan was conducted more than 3.5 hours after injury, the percentage of patients with measurable changes in haematoma volume 24 hours after injury was reduced. In a subset of patients who had an intermediate scan (most of which were between 6 and 9 hours of injury), the mean volume change between the baseline and intermediate scan was 5.7ml, whereas the difference in mean volume between the intermediate scan and the 24 hour scan was 0.03ml ⁴². Thus, the maximal change in intracranial haemorrhage volume appeared to occur soon after injury.

1.5 Types of intracranial haemorrhage (bleeding)

TBI patients often present with multiple intracranial bleeds of different types ^{34, 43}. Intra-axial haemorrhage includes IPH (also referred to as intra-cerebral haemorrhage), which occurs in the brain tissue, and intra-ventricular haemorrhage (IVH), which occurs in the ventricles of the brain. Extra-axial haemorrhage (epidural, subdural, subarachnoid) occurs between the three membranes that surround the brain (dura mater, arachnoid mater and pia mater). EDH occurs between the skull and outer membrane of the central nervous system (dura mater). SDH occurs between the dura mater and middle membrane of the central nervous system (arachnoid mater). SAH occurs between the arachnoid mater and innermost membrane surrounding the central nervous system (pia mater). Figure 3 shows axial slices of CT scans with evidence of different types of intracranial haemorrhage.

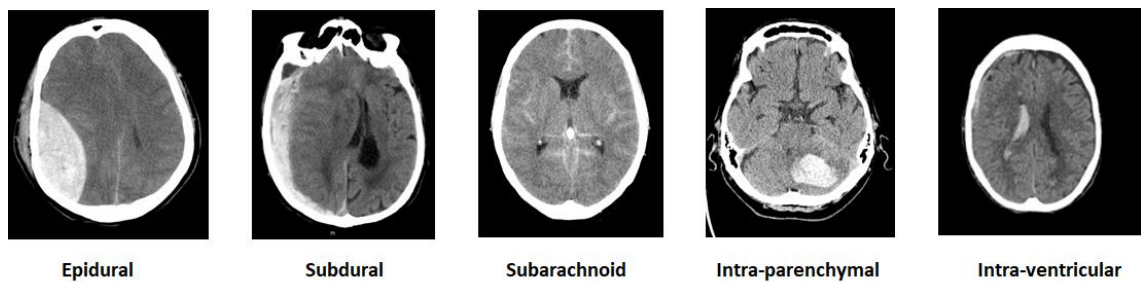


Figure 3. CT axial slices showing, from left: EDH, SDH, SAH, IPH, IVH. ^e

The Corticosteroid Randomisation after Significant Head Injury (CRASH) trial is the second largest randomised trial in TBI, among 10,008 patients across all injury severities ⁴³. In the CRASH trial, 56% of patients presented with at least one intracranial bleed ⁴³. Of 14,000 TBI patients in the Trauma Audit and Research Network (TARN), 30% of patients had SDH, whilst EDH, SAH and IPH each occurred in 22% of patients ³⁴. Of those with any intracranial bleed, 45% had one type, 16% had two types, 25% had three types and 14% had four types. The prevalence of these bleeds may be partly explained by the mechanism of the primary injury.

1.5.1 Subdural haemorrhage

High-speed road traffic crashes often result in rapid acceleration-deceleration forces that cause bridging veins to rupture between the cortical surface and sagittal sinus, causing acute SDH ⁴⁴. Because SDHs are typically venous bleeds (compared to EDHs, which are typically arterial), they are at lower pressure and so may not progress as quickly as EDH ⁴⁵. SDHs most commonly occur along the brain's convexity, but may also occur in the interhemispheric space or along the tentorium ^{46, 47}. Haemorrhage within the subdural space can travel freely and often covers the entire hemisphere ⁴⁴. But SDH is not bound by dural-calvarial attachments like EDH and therefore also has a potential to enlarge quickly. Indeed, SDH is associated with a larger increase in the risk of death than EDH ⁴⁸. In a study with 1,117 patients with TBI, the highest mortality was found in those with SDH and GCS 3-5 (74%), whilst patients with EDH and the same GCS had a mortality of 36% ⁴⁹. In an analysis of the effect of large SDH on mortality, the odds ratio halved after adjustment for variables including age (OR 3.36, 95% CI: 2.76 to 4.08) ³⁴. The association between large EDH and mortality remained virtually unchanged after the same adjustment (OR 1.85, 95% CI: 1.36 to 2.51) ³⁴.

SDH may be common in older patients because the brain may atrophy with age ⁵⁰, and this may result in the veins between the cortical surface and sagittal sinus becoming stretched, and as

^e The spherical white region on each scan shows the skull bone, the grey within shows the brain tissue and the off-white lesions of different shapes show the different intracranial haemorrhages Figure produced from images provided by <https://radiopaedia.org>

such, susceptible to rupture following head trauma ⁴⁴. Compared to younger patients, older patients with cerebral atrophy may accommodate more intracranial bleeding before their consciousness reduces ⁵¹. An analysis in 25,082 patients with isolated TBI in the TARN database suggested that for an equivalent severity of intracranial injury, older patients present with a higher GCS than younger patients (<65 years vs ≥ 65 years of age) ⁵¹. Injury severity may be obscured in older patients, which may partly explain why older patients with TBI have a worse prognosis than younger patients. The pre-injury use of anti-coagulants ⁵², pre-admission functional ability ⁵³, presence of co-morbidities such as hepatic disease, renal disease, cancer, and chronic steroid use ⁵⁴ also worsen prognosis after TBI in older adults ⁵⁵.

1.5.2 Epidural haemorrhage

Both traumatic and non-traumatic mechanisms can cause EDH ⁵⁶. The majority of traumatic EDHs are a result of motor vehicle collisions, physical assault or accidental falls ⁵⁶. The incidence is higher amongst adolescents and young adults ³⁴. EDHs can result from arterial or venous injury, but most result from arterial rupture of the middle meningeal artery ⁴⁵. Arterial EDHs can develop rapidly and are detected quickly as arterial blood flows at higher pressure than venous blood ⁵⁶. Patients with coagulopathy are at risk of EDH progression that requires surgery ⁵⁷.

A skull fracture is often present in patients with EDH ⁵⁶. Motorcycle crashes can cause skull fractures that injure the arteries or veins just under the skull (especially the meningeal vessel) and increase the risk of EDH ^{17 58}. After helmet laws were revised in Italy in 2000 such that helmets became compulsory for all motorcycle-moped-scooter drivers and their passengers, helmet use increased from less than 20% to over 96% ¹⁷. In a year, the number of patients who presented with EDH to a neurosurgical unit substantially reduced (42 vs 4), whilst the number of patients with SDH or diffuse injuries decreased to a lesser extent (18 vs 13) ¹⁷.

A study of 160 TBI patients with EDH found that EDHs enlarged by a mean diameter of 7mm in 23% of patients, between admission and 8 hours of injury ⁵⁹. In another study with 118 patients with EDH, 12% developed a delayed EDH after an initially negative CT scan, whilst 64% required immediate neurosurgical evacuation after admission ⁶⁰. Large EDHs often substantially increase intracranial pressure and require urgent neurosurgical decompressive evacuation. All acute EDHs (and SDHs) 10mm thick or more are considered for evacuation ⁴⁸. The neurosurgical prognosis following traumatic EDH is good for patients who receive rapid treatment. A study in 60 patients with EDH reported overall mortality of 25%, and 58% made a full recovery or had minimal neurological deficit ⁶¹. Faster neurosurgical intervention after coma onset (less than 2h vs more than 2h) was associated with less death (17% vs 65%) and better recovery (67% vs 13%). Similarly, a study in 82 patients who required neurosurgical evacuation

of SDH found that the risk of death reduced if evacuation occurred within 4 hours compared to beyond 4 hours of injury (30% vs 90%) ⁶².

1.5.3 Subarachnoid haemorrhage

SAH often occurs after arterial or venous injury, and typically distributes in the cerebral sulci overlying the brain. In the CRASH trial with 10,008 patients with head injury, 78% of patients had an admission head CT scan, and around a third of these patients presented with SAH ⁴³. In a study with 169 patients with TBI, of whom 69% had a GCS score of less than 9, the estimated prevalence of traumatic SAH was as high as 61% ⁶³. Lower estimates were reported in a study with 698 TBI patients where 15% of patients presented with isolated SAH on admission CT ⁶⁴. Compared to patients with other types of intracranial haemorrhage, patients with isolated SAH had lower injury severity scores (25.2 ± 11.5 vs. 18.2 ± 10.2 : $p < 0.0001$), higher emergency department GCS scores (10.5 ± 4.8 vs. 12.6 ± 3.9 : $p < 0.0001$), higher discharge GCS scores (14.3 ± 1.7 vs. 14.8 ± 0.9 : $p = 0.005$), shorter Intensive Care Unit stays (4.9 ± 6.4 vs. 3.1 ± 5.0 days: $p = 0.007$), lower mortality (14% vs. 4%: $p = 0.003$), and fewer head CT scans (3 ± 2 vs. 2 ± 1 : $p < 0.0001$) ⁶⁴. Patients with isolated SAH and GCS scores between 13 to 15 demonstrated low rates of clinical progression, and when progression did occur, it resolved without further intervention. Repeat CT scanning for patients with isolated traumatic SAH is therefore rarely indicated because these patients tend to have milder injuries than patients with other types of intracranial haemorrhage ^{64, 65}. Although SAH may occasionally clog the arachnoid villi with blood degradation products, reduce cerebrospinal fluid absorption and increase the risk of hydrocephalus, this is often transient ⁴⁴.

1.5.4 Intra-parenchymal haemorrhage

IPHS (cerebral contusions) also tend to occur with head motion from road-traffic crashes and are often localised to frontal and temporal lobes at the site of or opposite to the site of impact (“coup” and “contre-coup” pattern) ²⁶. IPHS in the frontal and temporal lobes are likely to grow in size ⁴¹ in a short period of time ⁶⁶. Whilst small IPHS that progress tend to be clinically silent and not require surgical decompression ⁶⁷, large IPHS in patients with low GCS are more likely to progress and often require surgical decompression ⁶⁸.

A number of studies have described the amount of intracranial haemorrhage expansion that occurs soon after injury. In one such study with 262 TBI patients with IPH, 43 IPHS (16%) expanded by more than 13ml within 24 hours of injury ⁶⁹. Compared to patients with mild GCS (13-15) or moderate GCS (9-12), patients with severe GCS (<9) were more likely to have IPHS that expanded by more than 13ml (0%, 11% and 26%, respectively). There were more

expanding IPHs in patients with IPH and associated haemorrhage compared to isolated IPH (17% vs 5%). Prognosis is worsened when IPH co-occurs with extra-axial bleeding ⁷⁰.

1.5.5 Intra-ventricular haemorrhage

IVH occurs in the brain's lateral, third or fourth ventricles where the cerebrospinal fluid ^f is produced, and typically occurs several hours after injury ⁴⁴. One study in 8,374 TBI patients with an admission CT scan, found that 118 patients (1%) showed evidence of IVH ⁷¹. Of those with IVH, 76% either had neurosurgical intervention or a Glasgow Outcome Scale score of 1 to 3 (i.e. severe disability, persistent vegetative state, or died). Although the estimated volume of IVH tends not to be as large as other types of haemorrhage, its occurrence is a poor prognostic sign, with expected mortality between 50% and 80% ⁷². The occurrence of IVH can indicate that the flow of cerebrospinal fluid through the ventricles is blocked (obstructive hydrocephalus), especially if the fourth ventricle collapses ⁷³. IPH and SAH commonly co-occur with IVH ⁷⁴. Approximately 70% of IVHs are secondary; they occur as an extension of an IPH or SAH into the ventricular system ⁷².

1.6 Intracranial haemorrhage expansion

Studies suggest that the risk of death and disability due to TBI may be reduced by preventing intracranial haemorrhage expansion ^{42, 75, 76}. But these studies are observational, and so the quality of this evidence is not robust. Furthermore, there is limited evidence on bleeding expansion, particularly according to bleed type, and whether expansion of different bleeds differentially affects the risk of death and disability.

One study of 142 TBI patients with a median GCS of 8 suggested that intracranial haemorrhage expansion varies according to haemorrhage type ⁴¹. Repeat CT scans done within 24 hours of injury suggested that IPH appeared to expand in 51% of patients, EDH in 22%, SAH in 17% and SDH in 11% of patients. But this study considered any expansion between first and second CT scans as evidence for expansion and did not measure the amount of expansion. The different eligibility criteria and definitions for expansion between studies make accurate estimation of expansion rates difficult. The decision for neurosurgical haemorrhage evacuation between first and second scans also complicates assessment of expansion rates. Furthermore, intracranial haemorrhage in its hyper-acute phase (before clotting) may not manifest on CT as its appearance is based on blood clot density ³¹. Therefore, intracranial haemorrhage may have occurred by the point of the first CT scan, but not be visible. Studies that suggest that the prevalence of new bleeding on a second CT scan is greater when the first CT scan is done

^f Cerebrospinal fluid cushions the brain and spinal cord.

sooner after injury ⁴² may not necessarily indicate that bleeding happens early, but that bleeding in its hyper-acute phase is not visible on a CT scan done very soon after injury ³¹. The absence of data on time from injury to scanning in many studies and the different times to scanning in studies that report these data limits understanding of the period over which expansion occurs or manifests on imaging. This makes it difficult to examine the effects of treatments aimed at reducing haemorrhage expansion; the effects of which may be modified or confounded by the time from injury to treatment.

1.7 Coagulation and fibrinolysis

Traumatic injury triggers two key processes: coagulation (the process by which blood clots) and fibrinolysis (the process by which blood clots break down). Coagulation involves aggregation and deposition of platelets at the point of injury ⁷⁷. After thrombin is activated, fibrin is produced and this interacts with the platelet plug to produce a clot that acts as a haemostatic seal at the point of damage ⁷⁸. Fibrinolysis involves breakdown of the fibrin mesh. Endothelial cells secrete tissue plasminogen activator (TPA), which converts plasminogen trapped within the clot into plasmin ⁷⁹. Plasmin attaches to fibrin and initiates clot breakdown.

The unique biochemical and cellular characteristics of the brain may make it prone to abnormal coagulation (coagulopathy) ⁸⁰. But there is no clear consensus on the definition of coagulopathy ⁸⁰. This has resulted in a wide range of estimates for the prevalence of coagulopathy in TBI patients, with some studies reporting prevalence of 10% and others of 97% ⁸¹. These estimates vary according to the type of laboratory test used to define coagulopathy, the timings of these tests, and the heterogeneity in injury severity ⁸². Decreased platelet counts, prolonged prothrombin time and partial thromboplastin time, and high levels of fibrinogen and fibrin degradation products (D Dimer) are observed in patients within the first 3 hours of TBI ⁸³. The highest D-dimer concentrations were found in the most severely injured patients ⁸⁴. One study in 61 head injury patients with a mean baseline GCS of 10 ± 4 reported that the 11 patients who died (6 of whom died due to head injury) had evidence of coagulopathy ⁸⁵.

A meta-analysis of 34 studies that reported the frequency of coagulopathy after TBI found that one third of patients with TBI have laboratory evidence of abnormal coagulation based on parameters such as fibrinogen, fibrin degradation products and anti-thrombin levels. The odds of mortality in patients with coagulopathy after TBI are nine times higher than in TBI patients without coagulopathy (OR 9.0, 95% CI 7.3–11.6); the odds ratios varied from 4 to 161 between studies. The odds of unfavourable outcome as measured by the Glasgow Outcome Scale (score of 1–3) are more than 30 times higher in TBI patients with coagulopathy (OR 36.3, 95% CI 18.7–70.5); the odds ratios varied from 16 to 58 between studies ⁸¹. Estimates for the prevalence

of coagulopathy in this analysis are imprecise, which may reflect differences in study size and varying definitions for coagulopathy. This would explain heterogeneity in clinical outcomes between studies.

Several studies suggest that TBI patients who have coagulopathy also have progressive intracranial haemorrhage. Specifically, coagulopathy is associated with an increased risk of progressive EDH (OR 0.36, 95% CI 0.15–0.85) ⁸⁶. But the association between coagulopathy and risk of haemorrhage may not be causative as some TBI patients with coagulopathy do not develop intracranial haemorrhage ⁸⁷.

Research Paper 1

The rest of this chapter includes Research Paper 1. The permission to reproduce this paper in this thesis is included in Appendix 1 and the full published version is included in Appendix 2. I have amended the published version of Research Paper 1 for clarity and presented this in the next section.

Title: Does tranexamic acid improve outcomes in traumatic brain injury?

Journal: British Medical Journal

Publication Date: 1 October 2016

Authors: Abda Mahmood, Ian Roberts, Haleema Shakur, Tim Harris, Antonio Belli
doi.org/10.1136/bmj.i4814



RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	LSH1512388	Title	Miss
First-Name(s)	Abda		
Surname/Family Name	Mahmood		
Thesis Title	Effect of tranexamic acid on intracranial haemorrhage and infarction in patients with traumatic brain injury: a randomised trial.		
Primary Supervisor	Haleema Shakur-Still & Ian Roberts (co-supervisors)		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	British Medical Journal (BMJ)		
When was the work published?	1 October 2016		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	N/A		
Have you retained the copyright for the work?*	No	Was the work subject to academic peer review?	Yes

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SECTION C – Prepared for publication, but not yet published


Where is the work intended to be published?	N/A
Please list the paper's authors in the intended authorship order:	N/A

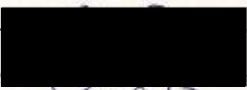
Stage of publication	Choose an item.
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SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I drafted the manuscript, including preparation of the tables and figures. I revised the manuscript with advice from Ian Roberts. Haleema Shakur-Still, Tim Harris and Antonio Belli critically read the manuscript and provided feedback for improvement. With input from the co-authors, I addressed the editorial and peer review comments prior to publication.
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SECTION E

Student Signature	
Date	9 Dec 2019

Supervisor Signature	
Date	9/Dec/2019

1.8 Tranexamic acid (TXA)

Tranexamic acid (TXA) reduces bleeding by inhibiting the enzymatic breakdown of fibrin blood clots. Plasmin binds to fibrin via lysine-binding sites and then splits fibrin into fibrin degradation products. TXA is a molecular analogue of lysine that inhibits fibrinolysis by reducing the binding of plasmin to fibrin (see Figure 4).

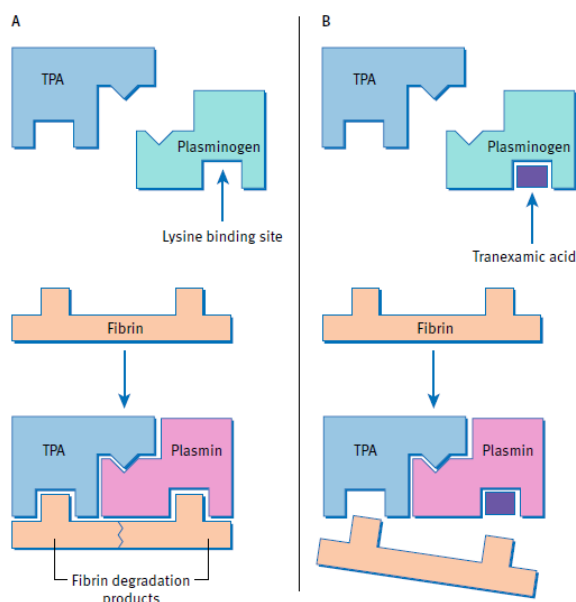


Figure 4. A: Normal fibrinolysis. **B:** Fibrinolysis inhibited by tranexamic acid. ^g

1.9 Effectiveness of TXA in reducing haemorrhage

TXA is used routinely in some cases of trauma and in surgery. For example, it reduces the need for blood transfusion in surgical patients^{88, 89}. A systematic review of 104 randomised trials of TXA in surgical patients found that it reduces the number of patients receiving a blood transfusion by one-third and halved the need for further surgery to control bleeding⁸⁸.

A systematic review of randomised trials of TXA following acute traumatic injury found that TXA reduces the risk of death due to bleeding by 15% (RR 0.85, 95% CI 0.76 to 0.96; $p = 0.0077$)⁹⁰. There is no apparent increase in the risk of vascular occlusive events with TXA following acute trauma (RR 0.69, 95% CI 0.44 to 1.07; $p=0.096$). Although three randomised trials were included in the review, the CRASH-2 trial provided 99% of the data into the effect of TXA in acute trauma. The CRASH-2 trial is a large, randomised, double-blind, placebo

^g The permission to reproduce Research Paper 1 in this thesis includes permission to reproduce this figure (see Appendix 1). Figure from Research Paper 1 (see Appendix 2).

controlled trial that explored the effects of TXA on death among adult trauma patients with, or at risk of, significant haemorrhage ⁹¹. The trial recruited 20,211 trauma patients with extra-cranial bleeding from 274 hospitals in 40 countries. Patients were randomly allocated to receive 1 gram (g) of TXA infused over 10 minutes, followed by an intravenous infusion of 1g over eight hours, or matching placebo (sodium chloride, 0.9%).

TXA treatment within an hour of injury reduced the risk of death caused by bleeding by about one third (RR 0.68; 95% CI 0.57 to 0.82; $p < 0.0001$). TXA treatment between one and three hours of injury reduced the risk of death caused by bleeding by about one fifth (RR 0.79; 95% CI 0.64 to 0.97; $p = 0.03$). There was no apparent benefit after three hours of injury, and TXA might even be harmful after this period (RR 1.44; 95% CI 1.12 to 1.84; $p = 0.004$).

1.10 TXA as a potential treatment in TBI

If TXA is effective after TBI, it should be most effective when given soon after injury, when intracranial bleeding is ongoing ⁴⁰. If early increased fibrinolysis exacerbates bleeding and increases the risk of death ⁸⁴, we would expect TXA to be most effective during this period. Furthermore, the potential anti-inflammatory effects of TXA may be important in reducing the extent of inflammation (oedema) around cerebral contusions ^{92, 93}. Neuro-inflammation is an important secondary injury mechanism after TBI that contributes to ongoing neurodegeneration and neurological impairment ⁹²⁻⁹⁴. Any anti-inflammatory effect of TXA would be particularly important for patients with severe isolated TBI who may have a shutdown in fibrinolysis ⁹⁵⁻⁹⁷.

However, there is also the potential for harm. In particular, TXA may increase the risk of cerebral thrombosis and ischaemia ⁹⁸. Cerebral ischaemia is an important secondary injury mechanism after TBI that worsens neurologic outcome and increases mortality ^{99, 100}. It can be precipitated by raised intracranial pressure, which can lead to cerebral hypo-perfusion ¹⁰¹⁻¹⁰⁴. In addition, thrombotic disseminated intravascular coagulation may increase the risk of cerebral microthrombi, which are often seen in the brains of TBI patients who die within 24 hours of injury ¹⁰⁵. By inhibiting fibrinolysis, TXA might increase the risk of cerebral ischaemia and thrombosis in TBI patients.

A 2015 systematic review of randomised trials of anti-fibrinolytic agents identified two relevant completed trials of TXA in TBI (see Table 2) ^{106, 107 h}.

^h The following databases were searched: the Cochrane Injuries Group's Specialised Register, The Cochrane Library, Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid OLDMEDLINE(R), Embase Classic+Embase (OvidSP), PubMed and clinical trials registries (28)

Table 2. Patients with intracranial haemorrhage, cerebral ischaemia, and mortality outcomes in two randomised trials of TXA in patients with traumatic brain injury. Values are numbers (percentages) unless stated otherwise.

Outcome	CRASH-2 Intracranial Bleeding Sub-study (2012) ¹⁰⁶			Yutthakasemsunt et al (2013) ¹⁰⁷		
	TXA	Placebo	Relative risk (95% CI)	TXA	Placebo	Relative risk (95% CI)
Intracranial haemorrhage	44 (36)	56 (44)	0.80 (0.59 to 1.09)	21 (18)	32 (27)	0.65 (0.40 to 1.05)
Focal ischaemic lesion / stroke	6 (5)	12 (9)	0.51 (0.20 to 1.32)	0	3 (3)	-
Deaths	14 (11)	24 (18)	0.60 (0.33 to 1.11)	12 (10)	17 (14)	0.69 (0.35 to 1.39)

Both trials were judged to be at low risk of bias across several domains (sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting) ⁱ. However, neither was large enough to answer the question definitively – the confidence intervals were wide and the P values statistically non-significant. The first trial (n=249) examined the effect of TXA in patients with extracranial bleeding but who also had TBI ¹⁰⁶. The second trial (n=229) examined the effect of TXA in patients with poly-trauma and TBI, or isolated TBI ¹⁰⁸. Both trials used information from pre- and post-randomisation CT scans to estimate the extent of bleeding and ischaemia. Both trials recruited patients who were within eight hours of injury but the numbers were not large enough to determine the balance of risks and benefits from TXA and whether this varies by time to treatment.

When the two randomised trials are combined in a meta-analysis, there appears to be a statistically significant reduction in intracranial haemorrhage (RR 0.75, 95% CI 0.58 to 0.98, p=0.03) and mortality (RR 0.63, 95% CI 0.40 to 0.99, p=0.05) with TXA. In one trial, focal ischaemic lesions occurred in 5% of TXA-treated patients and 9% of placebo-treated patients (RR 0.51, 95% CI 0.20 to 1.32; p=0.17) ¹⁰⁶. In the second trial, there were three strokes in the placebo group compared with none in the TXA group ¹⁰⁷. However, because the confidence intervals for intracranial haemorrhage, death and ischaemic lesion outcomes are so wide, the quality of this evidence is low. Furthermore, the patients in one of the trials had extracranial bleeding in addition to intracranial bleeding ¹⁰⁶. Because TXA reduces mortality in extracranial bleeding (CRASH-2), the mortality reduction seen in this trial could be from the extracranial injury rather than any effect on the brain injury itself. These trials do not reliably address the uncertainty regarding the effect of TXA on disability and thrombotic adverse effects including stroke.

ⁱ The quality of the evidence was rated as ‘high’, ‘moderate’, ‘low’ or ‘very low’ according to the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach. The GRADE approach considers: impact of the risk of bias of individual trials; precision of the pooled estimate; inconsistency or heterogeneity; indirectness of evidence; impact of selective reporting and publication bias on effect estimate. Risk of bias was assessed using The Cochrane Collaboration’s ‘Risk of bias’ tool.

In 2016, a review of trial registries identified three ongoing randomised trials of TXA versus placebo in patients with isolated TBI (see Table 3). These trials evaluated the effect of TXA on death, disability, vascular occlusive events, and other adverse events in TBI. These trials will inform whether TXA can be given to those with TBI.

Table 3. Randomised trials of TXA use in TBI.

Trial	Trial type	Status	Proposed sample size	No. of arms	Intervention	Comparison	Primary outcome	Secondary outcomes
Prehospital Administration of TXA for Moderate and Severe Traumatic Brain Injury (NCT02645552)	Double-blind, randomised trial	Pending recruitment	400 patients with moderate to severe TBI (GCS \leq 12)	2	<u>Arm 1:</u> 1g IV bolus of TXA over 10 minutes <u>Arm 2:</u> Placebo IV bolus over 10 minutes	Placebo (Sodium Chloride, 0.9%)	Neurological outcome (based on GOS-E) at six months post-injury	Vascular occlusive events (myocardial infarction, stroke, pulmonary embolism & deep vein thrombosis)
Prehospital TXA Use for Traumatic Brain Injury (NCT01990768)	Double-blind, randomised trial	Currently recruiting	1,002 patients with moderate to severe TBI (GCS \leq 12)	3	<u>Arm 1:</u> 1g IV bolus of TXA followed by 1g IV infusion of TXA over 8 hours. <u>Arm 2:</u> 2g IV bolus of TXA followed by placebo infused over 8 hours. <u>Arm 3:</u> Placebo IV bolus followed by placebo infused over 8 hours. *	Placebo (Sodium Chloride, 0.9%)	Neurological outcome (based on GOS-E) at six months post-injury	Volume of ICH, DRS, 28 day survival, neurosurgery, ventilator-free days, seizures, cerebral ischaemia, vascular occlusive events, alterations in fibrinolysis
Clinical Randomisation of an Antifibrinolytic in Significant Head Injury (CRASH-3) (NCT01402882)	Double-blind, randomised trial	Currently recruiting	10,000 patients with significant TBI (GCS \leq 12 or intracranial bleeding on CT scan)	2	<u>Arm 1:</u> 1g of IV bolus of TXA over 10 minutes followed by 1g IV infusion of TXA over 8 hours. <u>Arm 2:</u> Placebo IV bolus followed by placebo infused over 8 hours.	Placebo (Sodium Chloride, 0.9%)	Death in hospital within 28 days of randomisation	Vascular occlusive events, disability (based on DRS & POO), seizures, neurosurgery, days in intensive care, other adverse events

* IV bolus was administered in the pre-hospital setting and maintenance infusion was initiated on hospital arrival.

IV = intravenous. GCS = Glasgow Coma Scale. GOS-E = Extended Glasgow Outcome Scale. ICH = Intracranial Haemorrhage. DRS = Disability Rating Scale. POO = Patient Orientated Outcome measures.

In two of the trials (n=1402) patients were randomised within two hours of injury in the prehospital setting (NCT02645552, NCT01990768). To date, the CRASH-3 trial, with a sample size of approximately 13,000 patients, is the largest randomised trial into the effect of TXA in TBI ¹⁰⁹. In the CRASH-3 trial, patients were randomised in hospital and within eight hours of injury (NCT01402882) ¹⁰⁹.

Given the prevalence of TBI in older adults, a proportion of TBI patients enrolled in the CRASH-3 trial may receive anti-thrombotic treatments pre-admission, including anti-coagulant and anti-platelet medication ¹¹⁰. Anticoagulant therapy may increase the risk of intracerebral haemorrhage ¹¹¹ and so TXA could reduce haemorrhage expansion in these patients. This reduction may be greater in patients receiving specific anti-thrombotic treatments ¹¹². However, TBI patients who use anti-coagulant medication because of an underlying pro-thrombotic risk ¹¹³ may not benefit with TXA, especially since TBI patients may be at risk of developing intravascular micro-thrombosis ¹¹⁴. Therefore, the efficacy of TXA in TBI patients who used anti-thrombotic drugs pre-admission may be of clinical importance as these patients may be at greater risk of fatal bleeding or thrombosis.

The size of the CRASH-3 trial should ensure that TXA and placebo groups are balanced with regards to known and unknown confounders, such as the use of oral anticoagulant and antiplatelet medication, the concomitant degree of coagulopathy, and the use and timing of anti-thrombotic prophylaxis (e.g. low molecular weight heparin) ¹¹⁵. Therefore, it is unnecessary to standardise TXA and placebo groups for clinical management factors that may influence the extent of bleeding. Unless patients are randomised according to subgroup categories, any differences in the treatment effect may not be due to the factor defining the subgroup but some other factor associated with the subgroup ¹¹⁶. The CRASH-3 trial entry form does not measure all factors known to affect the extent of bleeding or thrombosis at baseline, and randomise patients on the basis of the primary intervention and these secondary factors. This would be logistically challenging and would result in a smaller trial. Instead, the entry form includes a small number of key patient characteristics to ensure a large and high-quality trial can be done where known (measured and unmeasured) and unknown confounders are balanced at baseline.

The results from the three more recent trials should provide clinicians with information about whether TXA is effective in reducing death and disability without increasing thrombotic events. These trials will also provide information about whether the effect of TXA varies by injury severity and time to treatment. Information on the effect of TXA administered within one hour, between one and three hours, and after three hours of injury may be more useful than the average effect of the treatment.

1.11 Mechanism of action of TXA in TBI

Although the CRASH-3 trial provides information on the effect of TXA on head injury death, it does not provide information on the mechanism by which TXA might exert its effects in TBI. An understanding of the mechanism of action of TXA and insight into factors that might affect this mechanism, is critical in the appropriate generalisation of trial results ¹¹⁷. If TXA reduces mortality by reducing intracranial haemorrhage as hypothesised, we may expect there to be less haemorrhage on head CT scans of TXA-treated patients. This information, along with the results of the main CRASH-3 trial, could inform the administration of TXA in TBI. If TBI patients who receive TXA soon after injury have less haemorrhage expansion compared to those who receive TXA later, then time between injury and treatment is a factor relevant to the mechanism of action which, with the results of the main CRASH-3 trial, should be considered when making treatment decisions. Furthermore, if TXA increases the risk of cerebral infarction, we may expect to see more infarcts in TXA-treated patients, particularly in those treated after a more prolonged period following injury ¹¹⁸. This information could be used to prevent adverse outcomes and ensure those receiving TXA are those most likely to benefit from it.

The CRASH-3 Intracranial Bleeding Mechanistic Sub-Study (IBMS) will include a sample of CRASH-3 trial patients. The effect of TXA on intracranial haemorrhage and infarction will be examined using routinely collected brain scans done pre-randomisation and post-randomisation. The knowledge gained from the CRASH-3 IBMS will add to the evidence base and could benefit the clinical management of patients with head injuries.

1.12 Aims

This study aims to examine the mechanism by which TXA might exerts its effects in isolated TBI, specifically its effect (if any) on intracranial haemorrhage and infarction, and whether this varies by time from injury to randomisation.

2 METHODS

This chapter includes sections of Research Paper 2 (study protocol) and Research Paper 3 (statistical analysis plan). The permission to reproduce Research Paper 2 in this thesis is confirmed in Appendix 3 and a copy of the full published version is included in Appendix 4. The permission to reproduce Research Paper 3 in this thesis is included in Appendix 5 and a copy of the full published version is included in Appendix 6. I amended and re-organised some sections of the published papers for clarity and have presented these in this chapter.

Research Paper 2

Title: 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 Intracranial Bleeding Mechanistic Sub-Study)

Journal: Trials

Publication Date: July 2017

Authors: Abda Mahmood, Ian Roberts, Haleema Shakur

DOI 10.1186/s13063-017-2073-

Research Paper 3

Title: A nested randomised trial of the effect of tranexamic acid on intracranial haemorrhage and infarction in traumatic brain injury (CRASH-3 intracranial bleeding mechanistic study): Statistical analysis plan

Journal: Wellcome Open Research

Publication Date: July 2019

Authors: Abda Mahmood, Ian Roberts, Haleema Shakur

doi.org/10.12688/wellcomeopenres.14731.3

Please note that the terms cerebral ischaemia and cerebral infarction in the paper titles refer to the same outcome. This was amended from ischaemia to infarction in order to avoid confusion with ischaemic changes associated with small vessel disease.

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	LSH1512388	Title	Miss
First Name(s)	Abda		
Surname/Family Name	Mahmood		
Thesis Title	Effect of tranexamic acid on intracranial haemorrhage and infarction in patients with traumatic brain injury: a randomised trial.		
Primary Supervisor	Haleema Shakur-Still & Ian Roberts (co-supervisors)		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Trials Journal		
When was the work published?	2017 July		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	N/A		
Have you retained the copyright for the work?*	No	Was the work subject to academic peer review?	Yes

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SECTION C – Prepared for publication, but not yet published


Where is the work intended to be published?	N/A
Please list the paper's authors in the intended authorship order:	N/A


Stage of publication	Choose an item.
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SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I reviewed the literature that informed the background, methods and discussion sections of this paper. I conducted a pilot test of the data collection forms at the Queen Elizabeth Hospital in Birmingham (UK), and this informed the methods section of this paper. I wrote the working procedures for data collection and data management (reviewed by data managers at the Clinical Trials Unit, London School of Hygiene and Tropical Medicine), and these informed the methods section of this paper. I drafted the manuscript, including preparation of the figures. I revised the manuscript with input from Ian Roberts and Haleema Shakur-Still. I addressed the editorial and peer review comments prior to publication, with input from my co-authors. All authors are responsible for the conception and design of the study.
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SECTION E

Student Signature	
Date	9 Dec 2019

Supervisor Signature	
Date	9/12/2019

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	LSH1512388	Title	Miss
First Name(s)	Abda		
Surname/Family Name	Mahmood		
Thesis Title	Effect of tranexamic acid on intracranial haemorrhage and infarction in patients with traumatic brain injury: a randomised trial.		
Primary Supervisor	Haleema Shakur-Still & Ian Roberts (co-supervisors)		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Wellcome Open Research		
When was the work published?	2019 June		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	N/A		
Have you retained the copyright for the work?*	No	Was the work subject to academic peer review?	Yes

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	N/A
Please list the paper's authors in the intended authorship order:	N/A

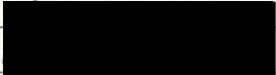
Stage of publication	Choose an item.
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SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)

I collected and cleaned the data for this trial, wrote the statistical code using Stata, and conducted analyses blind to treatment allocation. I drafted the manuscript (statistical analysis plan), with input from Medical Statisticians at the London School of Hygiene and Tropical Medicine. I revised the manuscript with feedback from Ian Roberts and Haleema Shakur-Still. I addressed the editorial and peer review comments prior to publication, with input from my co-authors.

SECTION E

Student Signature	
Date	9 Dec 2019

Supervisor Signature	
Date	9/12/19

2.1 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 CRASH-3 IBMS on 20 December 2016.

2.2 Trial design

The CRASH-3 IBMS is a mechanistic, prospective, randomised, placebo-controlled, parallel group, international, multi-centre, double-blind trial nested within the CRASH-3 trial (NCT01402882).

2.3 Eligibility criteria

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 (see Figure 5).

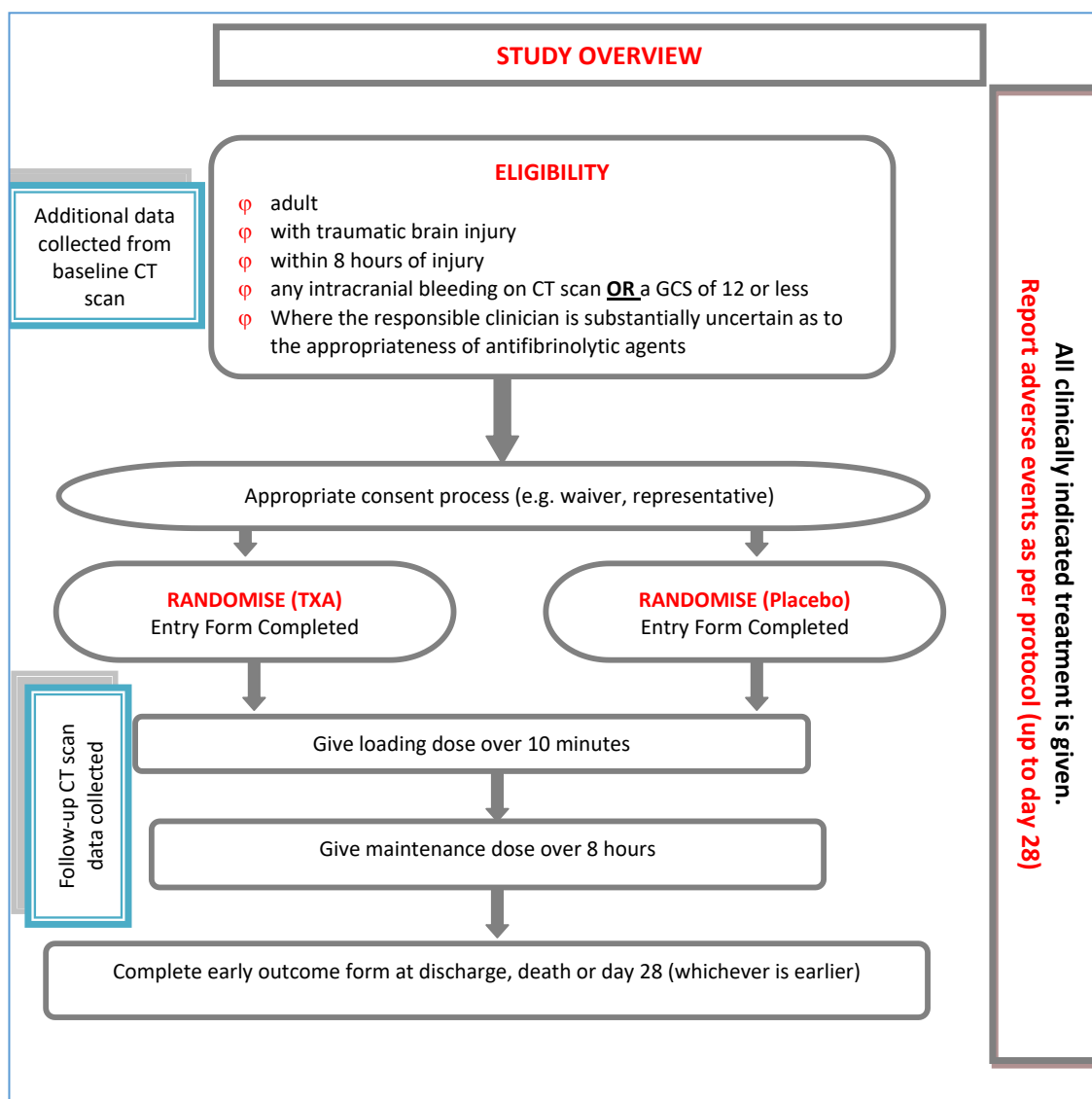


Figure 5. Flowchart: inclusion criteria for the CRASH-3 trial (blue boxes show additional procedure for the CRASH-3 IBMS).^j

^j Figure from Research Paper 2 (see Appendix 4).

2.4 Trial status

The first patient was enrolled in the CRASH-3 trial on 20 July 2012. Data collection for the CRASH-3 IBMS started in February 2016. The CRASH-3 trial completed recruitment on 31 January 2019. Routinely collected brain imaging data from patients included in the CRASH-3 IBMS was examined for the purpose of the IBMS and recorded in a web database before this date. A total of 1,767 CRASH-3 trial patients' scans were examined as part of the IBMS; these patients either had a pre-randomisation scan, a post-randomisation scan, or both pre-randomisation and post-randomisation scans.

2.5 Participating hospitals

The hospitals participating in the IBMS were selected based on the number of patients enrolled in the CRASH-3 trial, whether it was possible for the scan assessor (Abda Mahmood) to perform on-site examination of electronic brain imaging done as part of routine care at that site, and the willingness of the trial principal investigator at site to take part. These hospitals were selected between February 2016 and January 2019, as the CRASH-3 trial was ongoing. 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, London; University Hospital Coventry, Coventry; Salford Royal Hospital, Salford; 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 the names of all participating sites in the final results publication, including the number of patients included in the IBMS at each site. All regulatory and ethical approvals were in place before data for the IBMS were collected at each site.

2.6 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 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 local ethical approvals were gained from 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.

The CRASH-3 trial protocol section “CT scan study” clarified that a separate protocol for this study would be presented (Section 2, Trial Design, 2.1 Overview, Page 10) ¹¹⁹. The UK Medicines and Healthcare Products Agency (MHRA) confirmed that the CRASH-3 IBMS protocol did not alter the main CRASH-3 trial protocol, and so did not require submission to MHRA for approval.

2.7 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 ¹²⁰.

Section 24 of the declaration states that *“For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons”* ¹²⁰.

In the CRASH-3 trial, patients are unable to provide consent and so consent is sought from the patient’s relative or a legal representative ¹²¹. If the patient’s relative or a legal representative are not available, consent is sought from two clinicians, and the patient is randomised into the trial if these two clinicians agreed for the patient to be randomised ¹²¹. If the patient regains capacity, 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 and their participation in the trial discontinued. For patients who were included in the trial but did not regain capacity, written informed consent is sought from a relative or legal representative. The requirements of relevant local and national ethics committees are adhered to at all times. The CRASH-3 trial included consent to extract data from patient medical records. Collecting CT scan data for the CRASH-3 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 access CT scans, particularly for patients who have deceased or are disabled as a result of their injuries, where re-consent would be distressing and unwelcome. The London School of Hygiene and Tropical Medicine (LSHTM) and national Ethics Committees extended their

approvals to extract CT data from the CRASH-3 trial without further patient consent. Patients who withdrew from the main CRASH-3 trial were not included in the CRASH-3 IBMS.

2.8 Randomisation into the CRASH-3 trial

TBI patients eligible for inclusion into the CRASH-3 trial are randomly allocated to receive TXA or matching placebo (0.9% sodium chloride) and the trial treatment is started as soon as possible. Patients are randomised by selecting the lowest available numbered pack from a block of eight treatment packs. An independent statistician from Sealed Envelope (London, UK) prepared the randomisation codes using a computerised random number generator. These codes are shared with a certified clinical trial supply company so the treatment packs can be prepared in accord with the randomisation list.

There is no need to withhold any clinically indicated treatment in the CRASH-3 trial. TXA or placebo are provided as an additional treatment to the usual management of TBI. The 1g loading dose of the trial treatment is administered by intravenous injection immediately after randomisation in hospital. The 1g maintenance dose (by intravenous infusion) should start as soon as the loading dose is completed.

2.9 Adverse events in the CRASH-3 trial

Any untoward medical occurrence affecting a trial patient up to 28 days after randomisation will be reported in line with the CRASH-3 trial protocol. If the patient develops an adverse event during the treatment phase, the trial drug should be stopped. In this situation, the patient should be treated in line with local procedures and then followed up.

2.10 Unblinding in the CRASH-3 trial (before recruitment is complete)

The treatment allocation is double-blinded such that trial team members, outcome assessors and patients are unaware of whether a trial patient will receive TXA or placebo. In the CRASH-3 trial, if there are contraindications to TXA following randomisation, the trial treatment should be stopped and all standard clinical care provided. Unblinding is only necessary if the clinician believes that clinical management depends importantly upon knowledge of whether the patient received TXA or placebo. In this case, a 24 hour telephone service is available to confirm whether the patient received TXA or placebo.

It will not be necessary to unblind treatment allocation on the basis of data from the CRASH-3 IBMS, as these data are collected as part of routine patient care, and any clinical decisions made on the basis of clinically indicated imaging will be independent of the IBMS.

2.11 Monitoring

The independent Data Monitoring Committee monitor the unblinded results as the CRASH-3 trial is ongoing, and may recommend for the early termination of the trial if there is clear evidence for benefit or harm with TXA. The final decision for early termination lies with the Trial Steering Committee.

All data for the CRASH-3 trial will be subject to statistical monitoring and approximately 10% of data will be subject to on-site monitoring. Consent Forms will be monitored centrally by the Trial Coordinating Centre (where permission is given to do so). Investigators/institutions are required to provide direct access to source data/documents for trial-related monitoring, audits, ethics committee review and regulatory inspection. All trial-related and source documents must be kept for at least five years after the end of the trial. As all the CRASH-3 IBMS data will be collected directly from source data by the study lead (Abda Mahmood), additional monitoring will not be done for this data.

2.12 Potential risks

The effective radiation dose from a CT scan is about 2 millisievert (mSv) which is approximately the amount received from background radiation in eight months. Because CRASH-3 IBMS will use data from CT scans done as part of routine patient care, patients will not be exposed to extra radiation. There is no additional burden or risk to the patient as a result of their participation in the CRASH-3 IBMS. It is standard care for all patients with TBI and associated clinical signs to have a CT scan. Follow-up CT scans are often conducted for diagnostic purposes around 24 to 72 hours after the initial scan. Steps taken to minimise the risks associated with handling personal data will be detailed in the Confidentiality section.

2.13 Confidentiality

Only staff with authorised access to the scans, either as clinicians or research contract holders, will be able to retrieve and review them. Completed scan data forms will be uploaded onto a secure web database. Access to the database is only possible for authorised individuals, who have login accounts and passwords. The entry and outcome scan data forms will contain no patient identifiable data. Scans include the date and time of the scan and this information could potentially be used by anyone with access to the hospital radiology system to identify the patient. For this reason, scan data forms will only include the randomisation number, the time interval between the injury and the scan (pre-randomisation scan form) and the time interval between randomisation and the scan (post-randomisation scan form). As no personal data will be collected, the anonymity of each patient will be protected.

2.14 Sample size

We originally planned for the CRASH-3 IBMS to be conducted in 1,000 CRASH-3 trial patients. This sample size was based on the reduction in intracranial bleeding volume seen with TXA in the CRASH-2 Intracranial Bleeding Sub-study¹⁰⁶. We expected a 15% reduction in intracranial bleeding with TXA (24ml TXA, 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 patients to achieve 80% power to detect the expected treatment effect, which was reduced to 987 patients with adjustment ($1542 \times (1 - (0.6^2))$)¹²². The sample size estimates were reviewed and approved by Medical Statisticians at LSHTM.

The blinded data from 1,000 patients showed that because sites could randomise patients before a CT scan was done if the patient had a GCS score of 12 or less, pre-randomisation CT scans were often not done (26%), or done only minutes after randomisation (10% of patients were scanned between 1 and 30 minutes after randomisation). TXA may not have had sufficient opportunity to act and its effect on intracranial bleeding or infarction manifest on a scan done this quickly after randomisation. The inclusion of these scans would dilute any effect of TXA on intracranial bleeding and infarction towards the null. Increasing the sample size could reduce some of this null bias. Furthermore, given the less frequent occurrence of post-randomisation cerebral infarction compared to intracranial bleeding (7% vs 97%), increasing the sample size would allow for a more reliable examination of the effect of TXA on cerebral infarction.

The sample size was increased to include a maximum of 2,000 patients. This was the approximate maximum number of patients I could feasibly collect data from before the CRASH-3 trial completed recruitment. I did not expect 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.

Assuming that 47% of patients will be dropped (26% pre-randomisation, 21% post-randomisation) from a study with 2000 patients because they are not scanned pre- or post-randomisation, this leaves a study with 1060 patients who are scanned both pre- and post-randomisation. Using the same standard deviation (adjusted for baseline), correlation and baseline adjustment values as the original sample size calculation, there is 83% power to detect the expected treatment effect. Realistically, I expected around 1,700 patients could be included in the CRASH-3 IBMS. If we assume that around 47% of patients will be dropped from the analyses, this leaves a study with 901 patients scanned pre- 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.

2.15 Interim analyses

There are no interim analyses planned for the CRASH-3 IBMS because this is an exploratory study to help explain the CRASH-3 trial results; these analyses from a small sample of trial patients are unlikely to provide overwhelming evidence of benefit or harm with TXA. The findings from the CRASH-3 IBMS may inform the interpretation of the CRASH-3 trial results, but are unlikely to be used in isolation to support clinical decisions, especially before all data in the IBMS have been examined and before the CRASH-3 trial completes recruitment. The final analysis of the unblinded results will take place after CRASH-3 trial recruitment is complete, the data have been cleaned and the CRASH-3 trial database and CRASH-3 IBMS database have been locked as per the procedures detailed in the Data Management Plan (DMP) (version 1.0) (see Appendix 9).

2.16 Publication and dissemination plans

The results from this trial will be published in peer reviewed journals. Dissemination of results to patients will take place via the media, trial website (www.crash3@lshtm.ac.uk) and relevant patient organisations. All participating sites will be credited in key publications.

2.17 Funding

The CRASH-3 IBMS is fully funded by LSHTM (Grant reference EPAA6020). The design, management and interpretation of the CRASH-3 trial and IBMS are entirely independent of the manufacturers of TXA or the funders.

2.18 Indemnity

LSHTM accepts responsibility attached to its sponsorship of the CRASH-3 trial and IBMS and, as such, would be responsible for claims for any non-negligent harm suffered by anyone as a result of participating in the CRASH-3 trial and IBMS. The indemnity is renewed on an annual basis and LSHTM assures that it will continue renewal of the indemnity for the duration of this trial.

2.19 Sponsorship and trial management

The CRASH-3 trial and IBMS are sponsored by LSHTM and its responsibilities coordinated by the Clinical Trials Unit. The responsibilities of the Clinical Trials Unit are overseen by the Trial Management Group. The composition, roles and responsibilities of the Trial Management

Group, Protocol Committee, Independent Data Monitoring Committee, Trial Steering Committee and other responsible committees are detailed elsewhere ¹⁰⁹.

OUTCOMES

2.20 Primary outcome

The mean volume of IPH will be compared between trial arms in patients randomised within three hours of injury, adjusting for prognostic covariates.

In the original IMBS protocol ¹²³, we said the total volume of intracranial bleeding would be compared between treatment groups. Since publishing the protocol, we collected blinded data from 1700 trial patients, which suggest that any effect of TXA on intracranial bleeding expansion may only be reliably detected in IPH. These bleeds are less likely to be surgically evacuated compared to SDH and EDH, which are often larger and therefore substantially increase intracranial pressure and require urgent neurosurgical evacuation. Large SDHs and EDHs are easier to evacuate because they occur outside of the brain tissue, whereas IPHs 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 TXA on SDH and EDH expansion given that large bleeds are often evacuated before we can examine any effect of TXA on them. Including bleeds that may not be affected by TXA in the primary outcome would dilute any effect of TXA 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 IPHs 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 spontaneous intracerebral bleeding expansion with TXA ¹²⁴. Finally, IPHs are often spherical in shape, so there is less measurement error with the ABC/2 method of volume estimation compared to SDH and EDH, which have concave and convex shapes, respectively. For these reasons, the primary outcome will examine the effect of TXA on the total volume of IPH.

In the original IBMS protocol ¹²³, 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 TXA ¹²⁵. 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

^k Please note that the TICH-2 trial examined the effect of TXA on spontaneous intracerebral bleeding expansion, not post-traumatic intracerebral bleeding expansion.

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 TXA 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 TXA towards the null. Therefore, we will restrict the analysis of the primary outcome to three hours of injury.

2.21 Secondary outcomes

- (a) Frequency 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 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;¹
- (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), head injury 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.

¹ A 25% increase in haemorrhage volume between pre- and post-randomisation scans was used to define progressive haemorrhage in the two previous double-blind randomised trials of TXA on haemorrhage expansion in TBI^{106, 107}. The same definition was chosen in the CRASH-3 IBMS to ensure synthesis of findings across studies. But I note in Chapter 5 that this definition may be arbitrary with limited clinical value.

OUTCOME MEASUREMENT

2.22 Estimating haemorrhage volume on head CT

Patients often undergo one brain CT scan as part of routine medical care prior to randomisation into the CRASH-3 trial. After randomisation into the CRASH-3 trial, many patients are scanned again as part of routine medical care. In the IBMS, we will measure the volume of intracranial haemorrhage on pre-randomisation and post-randomisation CT scans. I conducted a systematic literature review of the methods and scales that have been used to estimate haemorrhage occurrence and volume on head CT. I have provided an overview of the methods, findings and conclusions of this review below.

Objectives. To identify a simple validated method to estimate intracranial haemorrhage volume on head CT scans.

Search methods. In March 2016, I searched PubMed, Embase and Medline online databases for publications written in English or translated into English.

Selection criteria. I searched for studies that used CT grading scales, classifications or categorisations of intracranial haemorrhage.

Search terms. To identify relevant studies, I used Medical Subject Headings (MESH) and searched the Titles and Abstracts of studies included in these databases using specific search terms. For intracranial haemorrhage, search terms included: Intracranial hemorrhage, traumatic [MeSH Terms], intracranial haemorrhage, intracranial hemorrhage, intracranial bleed*, intracranial clot*. For CT scans, search terms included: Tomography, X-Ray Computed [MeSH Terms], Computed tomogram*, CT scan*, CT head, head CT. For CT rating scales, search terms included: CT class*, CT grad*, CT scale*, CT categor*, grading scal*, classification scal*, classification grad*, classification system, scale*, grade*, classification*. I searched for studies that included at least one term from each of the three lists of terms i.e. studies that reported CT rating scales including intracranial haemorrhage.

Data collection. I performed the electronic searches in each database and reviewed the Titles and Abstracts of the articles to explore whether they provided relevant information on the review objectives (one rater, Abda Mahmood, Candidate).

Main results. I identified 12 relevant studies and have summarised these in Tables 4 and 5. Table 4 describes six established CT rating scales that include a categorisation of intra-cranial haemorrhage. Table 5 describes six further rating scales used for the characterisation of intra-cranial haemorrhage.

Table 4. Established CT rating scales that include examination of intra-cranial haemorrhage.

CT rating scale	Year published	Rating scale categories
Fisher scale ¹²⁶	1980	Groups 1-4: 1, no SAH/IVH; 2, diffuse thin (<1mm) SAH with no clots; 3, localised clots and/or layers of blood (>1mm in thickness) +/- ICH/IVH; 4, no or thin SAH + ICH/IVH
World Federation of Neurological Surgeons (WFNS) SAH grading ¹²⁷	1988	Grade 1-5: 1, GCS score of 15 without focal deficit 2, GCS score of 13/14 without focal deficit 3, GCS score of 13/14 with focal deficit 4, GCS score of 7-12 5, GCS score of 3-6
Marshall scale ¹²⁸	1991	Diffuse injury I-IV: I, (no visible IC pathology); II, cisterns present with midline shift (0-5mm) and/or lesion densities – no high or mixed-density lesion >25cm ³ may inc. bone fragments/foreign bodies; III, (swelling), cisterns compressed/absent with midline shift (0-5mm)/mixed density >25cm ³ ; IV, (shift), midline shift >5mm – no high/mixed density lesion>25cm ³ ; Evacuated mass lesion, any lesion surgically evacuated; Non-evacuated mass lesion – high/mixed density lesion >25cm ³ , not surgically evacuated
ABC/2 ¹²⁹	1996	A: greatest haemorrhage diameter by CT B: diameter 90 degrees to A C: approximate number of CT slices with haemorrhage multiplied by slice thickness <i>*highly correlated with computer-assisted planimetric image analysis (R²=0.96)</i>
Rotterdam ¹³⁰ *Modified Marshall scale	2005	Basal cisterns (0, normal; 1, compressed; 2, absent); Midline shift (0, no shift / <=5mm; 1, shift > 5mm); Epidural mass lesion (0, present; 1, absent); Interventricular blood or tSAH (0, absent; 1, present) <i>*final score is sum of scoring items + 1</i>
Modified Fisher scale ¹³¹	2006	Grade 0-4: 0, no SAH/IVH; 1, focal/diffuse, thin SAH, no IVH; 2, focal/diffuse, thin SAH, with IVH; 3, focal/diffuse, thick SAH, no IVH; 4, focal/diffuse, thick SAH, with IVH <i>*thin SAH (<1mm thick); thick SAH (>1mm depth)</i>

Table 5. Other CT measurement techniques including categorisation of intra-cranial haemorrhage.

Author(s)	Year published	n with [injury]	Measurement technique and/or findings
Peterson & Esperson ¹³²	1984	54 w/ EDH (artificial)	Volume estimate (0.5 x height x length x depth) moderately reliable. Midline shift and “vessel-free space” poor indicators of size.
Hijdra et al ¹³³	1990	182 w/ aneurysmal SAH	Blood in 10 basal cisterns and fissures in 4 ventricles graded: 0, none; 1, sedimentation in posterior; 2, partly filled; 3, completely filled. Sum score of IV blood was the total of the four scores and ranged from 0-12.
Greene et al ¹³⁴	1995	252 w/ traumatic SAH	In descending order of contribution to GOS at discharge: basal cistern effacement, tSAH thickness, cortical sulcal effacement, mass lesion(s), tSAH location. Midline shift non-sig. Grade 1-4: 1, (thin SAH, ≤ 5 mm); 2, (thick, 5mm); 3, (thick tSAH with mass lesion(s)); 4, (thick tSAH with mass lesions).
Claassen et al ¹³⁵	2001	301 w/ aneurysmal SAH	Lower grades, higher GCS and discharge GOS. Amount and location of SAH, IVH, and ICH quantified. Thick clot completely filling any cistern/fissure – best predictor of DCI. Blood in both lateral ventricles – best predictor of IVH. Additive and independent predictors. Grade 1-4: 1, no SAH/IVH; 2, minimal/thin SAH, no IVH in both lateral ventricles; 3, thick SAH, no IVH in both lateral ventricles; 4, thick SAH, IVH in both lateral ventricles.
Wardlaw et al ¹³⁶	2002	425 w/ TBI	7-point grading scale (normal, mild, moderate, or severe focal injury, mild, moderate, or severe diffuse injury)
Bhattathiri et al ¹³⁷	2003	43 w/ spontaneous ICH	Site and sides of involvement, scale present on scan itself, and length, breadth, height and depth of ICH, and midline shift. Correlation high for volume, depth and midline shift.

Conclusions. This review identified one method that focuses exclusively on estimating haemorrhage volume (i.e. ABC/2). This is a simple validated scale for measuring intracranial haemorrhage volume (ABC/2) and shows good agreement with the gold standard of computer-assisted volumetric analysis, which requires demarcation of the borders of haemorrhage ¹³⁸⁻¹⁴⁹.

2.23 Systematic literature review on association between ABC/2 and automated methods for estimating haemorrhage volume

The ABC/2 method is a quick and easy technique used to estimate the volume of intracranial haemorrhage ¹²⁹. This method assumes haematoma volume is approximately equal to an ellipsoid shape (i.e. three dimensional oval shape). For ease of assessment, the formula for calculating the volume of an ellipsoid [$\frac{4}{3} \times \pi \times (A/2) \times (B/2) \times (C/2)$] can be simplified to ABC/2 if we assume π is equal to 3. This method selects a representative slice near the centre of the haematoma on which the bleed is most visible. On this slice, two measurements are taken: (A) the maximal diameter; (B) width perpendicular to A. For the measurement of depth, the maximal number of slices on which the haematoma is visible is multiplied by slice thickness (C). These three measurements are multiplied and the sum divided by two (ABC/2) to provide the volume measurement in cm^3 (ml). One cubic centimetre is equivalent to one millilitre.

I conducted a systematic literature review on the association between ABC/2 and computer assisted methods of estimating intracranial haemorrhage volume. I have provided an overview of the rationale, methods, findings and conclusions from this review below.

Background. Automated methods provide a more accurate estimate of haemorrhage volume compared to manual methods because they can precisely trace the size and shape of a lesion. However, manual methods may be the only practical option in some settings, and so the degree of agreement between manual and automated methods is relevant for researchers and clinicians who may only have resources to use the manual method. If the manual method provides sufficiently similar estimates to the gold standard automated method, the decision to use one over the other could be based on logistic practicalities and preference.

Objectives. To explore the association and accuracy of the ABC/2 method of estimating haemorrhage volume compared to computer-assisted automated volumetric analyses.

Search methods. In March 2016, I searched PubMed, Embase and Medline online databases for publications written in English or translated into English.

Selection criteria. I searched for studies that compared the ABC/2 method of estimating haemorrhage volume against automated methods of estimating haemorrhage volume. Although this review was primarily concerned with the agreement between these two methods, it did not exclude studies that only reported correlations between these two methods.

Search terms. To identify relevant studies, I used MESH and searched the Titles and Abstracts of studies included in these databases using specific search terms. For the ABC/2 method, search terms included: ABC/2, ABC/2 method, ABC/2 technique, ABC/2 formula, ABC/2 equation, Tada formula. For computer assisted automated methods, search terms included: Image processing, computer assisted (MESH), Automated, semi-automated, semi automated, planimetr*, computer assisted, computer-assisted, volumetric analys*, software. I searched for studies that included one term from each of the two lists of terms i.e. studies that used both manual and automated methods.

Data collection. I performed the electronic searches in each database and reviewed the Titles and Abstracts of the articles to explore whether they provided relevant information on the review objectives (one rater, Abda Mahmood, Candidate). If the Abstracts did not provide the relevant information on the correlation and/or agreement between ABC/2 and automated methods, or did not provide information on how ABC/2 was used or what specific automated method was used, the Methods sections of the articles were reviewed for this information.

Main results. A total of 41 relevant studies were identified. Full texts were not available for 8 of these studies. A total of 16 studies provided haemorrhage volumes estimates (or other relevant statistics) using manual and automated methods. These findings are summarised in Table 6.

Conclusions. Of the 16 studies that provided relevant information on the review objective, most examined the association between manual and automated methods in traumatic or spontaneous intra-cerebral haemorrhage (i.e. IPH) (n=11) – one of these studies also estimated the volume of SDH using these methods. A smaller proportion of studies were in patients with EDH (n=2), infarction (n=2) or gliomas (n=1). Although the majority of studies provided average volume measurements for each method (n=11), they did not provide relevant statistics for agreement between the manual and automated methods. A total of 14 studies provided correlation coefficients, which are not reflective of agreement between methods, as two measures may correlate well but one may be substantially higher or lower than the other¹⁵⁰.

Table 6. Studies on the association between the ABC/2 method and automated methods for estimating volumes of intra-cranial bleeding, infarction or tumours.

Authors	Year	n	Type of haemorrhage	Computer assisted method	Mean haemorrhage volume *		Association
					ABC/2	Automated	
Gebel et al ¹³⁸	1998	298	Intra-parenchymal	Volumetric analysis (Propety software)	68.7 cm ³	63.3 cm ³	R=0.93 (slope 1.11)
		44	Subdural	Volumetric analysis (Propety software)	91.0 cm ³	82.4 cm ³	R=0.842
Wang et al ¹³⁹	2009	40	Intracerebral	Volumetric analysis	46.6 ml	33.8 ml	R=0.96
Sims et al ¹⁵¹	2009	50	Sub-acute stroke	Planimetry	-	-	R=0.74 (slope 1.00)
Kleinman et al ¹⁴⁰	2011	23	Intracerebral	Manual slice by slice segmentation	20 cm ³	27 cm ³	R ² =0.96
Maeda et al ¹⁴¹	2013	20	Intracerebral	Planimetry	12.8 cm ³	15.0 cm ³	R=0.98, p<0.001
Mirsky et al ¹⁵²	2013	25	Perinatal arterial ischemic stroke	Planimetry	46 cm ³	32 cm ³	R ² =0.84
Yang et al ¹⁴²	2013	147	Infra-tentorial	Computer assisted volumetric analysis (CAVA)	3.7 ml (median)	4.8 ml (median)	R: Cerebellar 0.98; Brainstem 0.98; Regular shape 0.97; Irregular shape: 0.98
Yan et al ¹⁴³	2013	344	Intracerebral parenchyma	Planimetry	-	-	R > 0.9
Xu et al ¹⁴⁴	2014	294	Intracerebral	Software 3D Slicer	58.4 cm ³	50.4 cm ³	t=10.01, p<0.01
Wang et al ¹⁴⁵	2014	106	Intracerebral	Software program using Matlab	38.7 ± 51.0 ml	27.8 ± 35.6 ml	R ² = 0.97 (p<0.001)
Webb et al ¹⁴⁶	2015	507 (4369 scans)	Intracerebral	Planimetry	15.2 cm ³	12.7 cm ³	R ² =0.93 (specialized reading centre); R ² =0.87 (local site)
Saefudin et al ¹⁵³	2016	68	Haemorrhagic stroke	Multi-slice	Slice thickness	21.76 ml	R=0.79
Hu et al ¹⁴⁷	2016	35	Epidural	Planimetry			R=0.99, p<0.05
Yan et al ¹⁴⁸	2016	53	Traumatic epidural	Planimetry	25.19 ± 30.13 ml	31.72 ± 39.24 ml	R ² =0.99 (slope 0.65)
Screenivasen et al ¹⁵⁴	2016	40	Glioma tumours (irregular shape)	ROI based manual image segmentation using Image J software	44.23 cm ³ (mean); 26.36 cm ³ (median)	40.42 cm ³	R ² =0.83
Khan et al ¹⁴⁹	2016	135	Spontaneous intracerebral	Planimetry using Analyze software	-	-	ABC/2 underestimates planimetry: mean difference = 7.3ml

*unless indicated otherwise

Compared to the manual ABC/2 method, computer-assisted automated volumetric analyses precisely trace the size and shape of a lesion, and so provide more accurate estimates of haemorrhage volume in irregularly shaped or multi-lobular lesions^{129, 143, 145-149, 152, 155-159}. It is unclear whether the ABC/2 method overestimates^{139, 144, 145, 147, 152, 155-158} or underestimates^{141, 159} haemorrhage volume compared to computer-assisted methods, and whether adjusting for the depth of the lesion underestimates or overestimates haemorrhage volume^{160 148}. Furthermore, the data collection process is less labour intensive and time consuming when using automated methods in a large number of patients as haemorrhage volume can be automatically computed rather than manually estimated. Recent studies have confirmed good agreement between ABC/2 and computer assisted automated methods in intra-cerebral haemorrhage¹⁴⁶.

Although the ABC/2 method is a less specific measure of haemorrhage volume than computer assisted volumetric methods, and overestimation due to false positives would dilute the effect of the treatment towards the null, its low sensitivity and underestimation due to false negatives would not impact the effect of the treatment on haemorrhage. Furthermore, the more accurate method of estimating haemorrhage would require for the software (e.g. OsiriX MD) for conducting automated or semi-automated volume estimation to be installed on a clinical computer at each hospital site, and this may prove logistically challenging. It would cost approximately £7,660 in total for OsiriX MD to be installed at 15 hospital sites¹⁶¹. Because it is unknown how long it will take for this software to be approved for installation for research purposes and installed on clinical computers at each hospital site, we judge that this method may only be possible in a smaller number of patients given the time constraints and limited budget of a clinical trial. Alternatively, the ABC/2 method can be done using clinical imaging software PACs that will already be in place at each site. Although a more accurate method in a small trial would result in less measurement error, a less accurate method in a larger trial would result in less random error. We believe that the ABC/2 method is sufficiently accurate and so we chose to use this method in a larger trial. Furthermore, the assessor rating the scans will be blind to treatment allocation and so any bias from measurement error should be balanced between treatment groups.

2.24 Estimating IPH, IVH and EDH volume using ABC/2

Volume estimation of intracranial haemorrhage is aided by the characterisation of haematomas. The final shape of a haematoma is influenced by its location. IPH and EDH tend to have regular shapes that are clearly definable in every dimension (i.e. their length, width and depth can be measured on a CT scan). The ABC/2 method assumes the haemorrhage has an ellipsoid shape, and has been validated in IPH¹³⁸ and EDH^{147, 148}. We will estimate the volume of IPH and EDH using the ABC/2 method.

In the original protocol, I said that the ABC/2 method had been validated in IVH. Since, I learnt that I made an error when interpreting the results of one research study. In this study, patients had both IPH and IVH, and the ABC/2 method was validated in IPH but not IVH¹⁴⁶. Despite this, the volume of IVH has been estimated using the ABC/2 method in the CRASH-3 IBMS. I will consider the implications of this error when interpreting the results.

2.25 Estimating SDH volume using maximum width

SDH are crescent shaped as they follow the pattern of the brain's convexity. The exact limits of SDH are not clearly definable in any dimension. This type of haemorrhage can theoretically occupy the entire subdural space. Given that the ABC/2 method assumes the haemorrhage has an ellipsoid shape, it would not provide an accurate volume estimation of SDH. Indeed, there have been reports of underestimation in SDH volume when using an adapted version of the ABC/2 method compared with computer assisted volumetric analysis^{141, 159}.

Some researchers and clinicians propose that the volume of SDH would be more accurately estimated using a formula which takes the difference between two spheres (divided by 8) to represent the subdural space that a SDH occupies (see Appendix 10). This method has been tested at the Neurosurgical Trauma Unit at the Queen Elizabeth Hospital in Birmingham (UK) and could provide more clinically relevant estimates of SDH volume than the ABC/2 method¹⁶². Although this method overestimates SDH volume, the investigators expect that this would be less than the error from the ABC/2 method. The key measurement in determining the clinical significance of a SDH is its width (i.e. the B measurement when using the ABC/2 method)⁴⁸. In the CRASH-3 IBMS, we will measure the maximum width of a subdural bleed, and compute its volume using the aforementioned formula (see Appendix 10).

2.26 Total haemorrhage volume

The total haemorrhage volume on each scan will be calculated by totalling the volumes of IPH, IVH, EDH and SDH.

2.27 Measurement of SAH

SAHs occur in the area between the arachnoid membrane and the innermost membrane surrounding the brain (pia mater). The shape of the subarachnoid space resembles a spider's web and so haemorrhage in the subarachnoid space cannot be clearly measured in any dimension. Although there are a number of CT grading scales that include the characterisation of SAH^{126, 131},

they are criticised for being subjective and not comprehensive enough to serve as a primary grading scale for this type of haemorrhage ¹⁶³. For example, the Fisher scale and its modified version do not consider SAH in isolation but in combination with IVH ¹³¹.

In the CRASH-3 IBMS, the size of SAH will be characterized as small, medium or large. Each bleed will then be described as focal (localised to a specific location), multiple (not localised but not widespread) or diffuse (widespread). This method is also subjective and may have low sensitivity and specificity, therefore misclassification would bias the treatment effect towards the null value. But we hope that by using this method in a large trial, the bias from measurement error would be offset by a reduction in random error.

2.28 Petechial haemorrhage

Petechial haemorrhage manifests as a very small hyper-intensity on a CT scan. CT scans and accompanying radiology reports will be examined to indicate whether petechial haemorrhage is present.

2.29 Cerebral infarction

Cerebral infarction (or ischaemic stroke) is due to the compromise of blood and oxygen flow through either large or small arteries supplying the brain parenchyma. Thrombotic occlusion of intracranial vessels produce wedge-shaped cortical infarctions.

Cerebral infarction would reliably manifest on a CT scan done at least 48 hours after randomisation ¹⁶⁴. However, given that clinical scans are done for diagnostic purposes, it is not possible to carry out scans at set time-points post-randomisation. Brain imaging techniques including Magnetic Resonance Imaging (MRI) diffusion weighted imaging have higher sensitivity and specificity compared to CT in the early diagnosis of infarction, and are often clinically warranted when there is a suspected stroke. Therefore, the assessor will examine all available brain scans done within 28 days of randomisation and accompanying radiology reports for evidence of infarction, and record the time from randomisation to detection.

Furthermore, given that CT imaging is the first and most common neuroimaging examination performed for emergency assessment of suspected acute haemorrhage and stroke around the world ^{165, 166}, the majority of scans included in the CRASH-3 IBMS will be CT scans. Therefore, it is important to clarify how we will capture this endpoint when only CT scans are available. Cerebral infarction manifests as wedge-shaped low attenuation on a CT scan. Given that oedema also manifests as low attenuation on CT, the radiology reports that accompany CT scans should indicate whether the low attenuation is representative of oedema or infarction. Brain imaging reports often refer to cerebral infarction by the affected vascular territory (e.g. anterior cerebral

artery, middle cerebral artery, posterior cerebral artery, lacunar, cerebellar, brainstem). The assessor will examine all available brain imaging to assess whether oedema or infarction can be excluded given the appearance of earlier scans. For example, some patients have oedematous haemorrhagic lesions which on CT manifests as high density haemorrhage surrounded by low density oedema. In later scans, the haemorrhage may resolve but the oedema may remain. If only considered alone, the later CT scan may have the appearance of infarction but could be representative of residual oedema. We will attempt to minimise such errors by comparing the appearance of cerebral infarction/oedema between consecutive scans, and consider the accompanying scan reports for radiological opinion. If the available scans and accompanying reports are unable to confirm the presence of an infarct, we would seek further radiological and clinical opinion.

2.30 Mass effect and other CT endpoints

Space-occupying intracranial lesions can displace brain tissue. The shift of midline structures past the centre line of the brain will be measured in millimetres (mm). We will also record whether mass effect has caused ventricular effacement and sulcal effacement.

All scans will be rated according to the Marshall classification; the most extensively used CT classification scale in TBI ¹²⁸. Three main characteristics define the Marshall classification: presence of mass lesion, degree of compression of perimesencephalic cisterns and degree of midline shift. See Appendix 11 for a flowchart developed for the purpose of this study to aid Marshall classification ratings.

DATA COLLECTION, MANAGEMENT AND INTEGRITY

2.31 Data collection procedure

The CRASH-3 trial database will be used to prepare a list of all patients with either a GCS score of 12 or less or a pre-randomisation CT scan at participating sub-study hospitals. The list will include unique randomisation (box and pack) numbers, date and time of randomisation, and time between injury and randomisation into the CRASH-3 trial. The randomisation numbers will be used at the participating site to identify the patient using their hospital number. The outcome assessor (with training in brain imaging assessment) will hold a letter of access at the participating hospital and use the patient hospital number to retrieve and assess pre- and post-randomisation scans from the hospital electronic imaging system (usually PACs). The outcome assessor will complete the entry and outcome forms at each site using the relevant scans and accompanying radiology reports. All data are collected by the same outcome assessor who is blind to treatment allocation.^m

If the patient does not have a pre-randomisation scan, only the post-randomisation scan form is completed. If the patient does not have a post-randomisation scan, only the pre-randomisation scan form is completed. We record whether pre- and/or post-randomisation scans are available so we can examine missing data by trial arm.

In most cases, the post-randomisation scan is the first scan done after randomisation, which is normally within 72 hours of randomisation. But ongoing clinical management and the decision to randomise without the baseline CT scan means that some patients are scanned within minutes after randomisation. TXA would not have had sufficient opportunity to effect haemorrhage or infarction in such a way that would manifest on a scan this soon after randomisation. Therefore, for patients scanned within minutes of randomisation, we measure all the outcomes of interest on the next available post-randomisation scan, which is normally closer to 72 hours of randomisation. All available brain imaging (not only CT) is examined for evidence of cerebral infarction.

The time stamped on the scans will be used to calculate the following time intervals: 1) the time between injury and the pre-randomisation CT scan; 2) the time between randomisation into the trial and the post-randomisation scan. If a patient has undergone neurosurgery following their injury and this is evident on any of the rated scans, information on the date and time of neurosurgery will be collected using prospective reports including patient anaesthetic charts. The outcome data is collected for all patients included in the CRASH-3 IBMS (unless consent was withdrawn) irrespective of whether the trial treatment was received (i.e. on an intention to treat

^m As confirmed in the *My Contributions* section of this thesis (page 5), all scans rated as part of the CRASH-3 IBMS were rated by one outcome assessor, Abda Mahmood (Candidate).

basis). The outcome data are directly uploaded into an electronic database developed for the purpose of this trial and accessed at each site. See Appendix 9 for the complete data collection working procedure.

2.32 Data management and integrity

All trial data are managed in accord with the IBMS DMP (see Appendix 9) which is stored in the Trial Master File. The DMP working procedures are produced in conjunction with LSHTM policies and procedures, the Clinical Trials Unit and trial specific working procedures, and regulatory requirements. The web database was built to comply with International Conference on Harmonisation Good Clinical Practice guidelines (ICH-GCP) Guidelines, United Kingdom Clinical Trials Regulations, and the Data Protection Act ¹⁶⁷. The database uses MySQL for data storage and Hypertext Preprocessor (PHP) 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. 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 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, United States of America].

SCAN ASSESSOR TRAINING & PILOT TEST OF DATA COLLECTION FORMS

Scan assessor training

I studied the anatomy and function of the human brain whilst completing a BSc (Honours) in Applied Psychology (accredited by the British Psychological Society) and MSc in Psychological Research (2008-2012). As part of a Research Assistant post at the Department of Psychiatry (Warneford Hospital, University of Oxford) and Centre for Functional MRI (now Wellcome Centre for Integrative Neuroimaging, John Radcliffe Hospital, University of Oxford), I completed a short course in theory and practice of functional and structural brain imaging (2015).

For the purpose of data collection for my PhD project, I received one-to-one training in CT scan assessment of key intracranial pathologies seen after TBI (2016). During this training, I pilot tested the data collection forms in 90 patients at the first site (Queen Elizabeth Hospital, Birmingham), as per the above method and under the supervision of a Clinical Research Fellow and Neurosurgical Registrar at this site (Dr David Davies). I assessed scans from these patients using the data collection forms from the CRASH-2 Intracranial Bleeding Study ¹⁰⁶. I accessed and examined all scans electronically on PACs at the hospital site. I examined all scans in the axial format, in conjunction with their accompanying radiology reports.

Pilot test of data collection forms

I was trained to identify different types of haemorrhage (IPH, IVH, SDH, EDH, SAH) using their distinctive shapes and typical locations. I estimated their volumes using the ABC/2 method (IPH, IVH, EDH), where possible. I identified different types of mass effect (sulcal effacement, ventricular effacement, midline shift) by first comparing the symmetry of the cerebral hemispheres. If patients showed evidence of midline shift, I estimated the degree of shift in mm, by using the PACs ruler to mark where the midline should be and measure how far it had deviated from this location. I also practised identifying peri-haemorrhagic oedema, which often manifests as low attenuation surrounding high attenuation on CT, and used consecutive scans to confirm if low attenuation was indicative of residual oedema when haemorrhage resolved but oedema remained. I was trained to identify signs of cerebral infarction, which if seen on CT, often manifests as wedge-shaped low attenuation. I was also trained to identify the occurrence of neurosurgical haemorrhage evacuation, and if relevant, the type of neurosurgery evident on the scan (e.g. craniotomy, craniectomy). All scans were interpreted in conjunction with their accompanying radiology reports. These reports were used to confirm whether patients presented with the outcomes of interest. I found that radiology reports were written in different degrees of

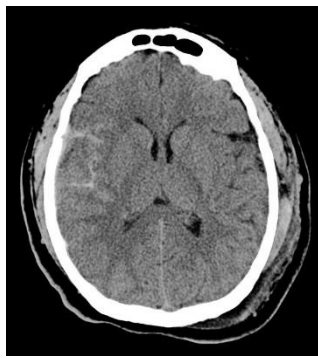
detail, and in some cases, comments were brief – confirming there was no interval change compared to a previous scan. In these cases, I would use the report from the previous referenced scan to examine whether the outcomes of interest were seen on the next scan. Discrepancies between the reports and what appeared visible on the scan were discussed with Dr Davies and confirmed during the training placement.

As a result of this training placement, the CRASH-2 Intracranial Bleeding Study forms were amended for the purpose of the CRASH-3 IBMS. This included using the Marshall Classification (a validated TBI rating scale with prognostic value)¹²⁸, and excluding a separate field for the compression of basal cisterns as basal cistern effacement is included in Diffuse Injury III (swelling) of the Marshall Classification.

SAH assessment

The specified categories for SAH (small, medium, large; focal, multiple, diffuse) were included in the CRASH-3 IBMS for the reasons detailed in the *Outcome Measurement: Measurement of SAH* section 2.27 above.

The Common Data Elements for Radiological Imaging of Patients with SAH were proposed in 2019 to facilitate standardization and aggregation of imaging data in patients with SAH¹⁶⁸. Because these guidelines were developed after I started data collection for the IBMS in 2016, I was not able to consult these in advance of protocol development. These guidelines note that the imaging modality (e.g. CT) and type (e.g. non-contrast CT) are *core elements* that must be reported in imaging studies of SAH. These guidelines also propose *supplemental* elements which are highly recommended for specific diseases and therapeutic areas, supplemental elements that are commonly collected but whose relevance depends on study design or type of research, and *exploratory* elements which are reasonable to use but require further validation. Many of the recommended supplemental elements (i.e. presence of SAH, IVH, SDH, midline shift) were recorded in the IBMS. However, the measurement of the size and spread of SAH in the IBMS does not readily compare with the SAH definitions in the Common Data Elements (i.e. Fisher grade, Hijdra scale). Furthermore, the IBMS did not record whether SAH was secondary to ruptured intracranial aneurysms (although I suspect these would be included in the Large size classification in the IBMS). Therefore, the size and spread measures of SAH in the IBMS could be considered *exploratory* Common Data Elements¹⁶⁸. Figure 6 shows example images of the size (small, medium, large) and spread (focal, multiple, diffuse) ratings of SAH in the IBMS.



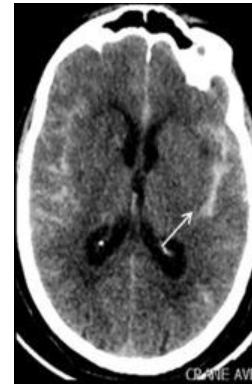
Small, Focal / Multiple



Medium, Focal / Multiple



Medium, Multiple



Medium, Diffuse ⁿ



Large Multiple / Diffuse ^o Large, Diffuse ^p

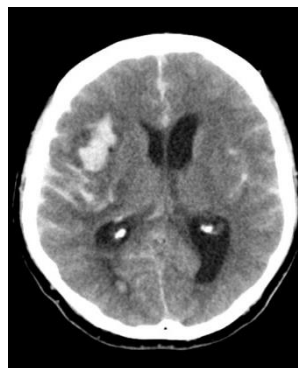


Figure 6. Examples of the size and spread of SAH on non-contrast CT as measured in the CRASH-3 IBMS.

Note that the Large SAHs seen in this Figure are secondary to aneurysms.

ⁿ Image from Edjlali et al (2015). ¹⁶⁹

^o Image from Lang (2016) ¹⁷⁰

^p All other images in Figure 6 are from Murphy et al (2020) ¹⁷¹

EDH, IPH and IVH assessment using ABC/2 method

Scan examination included using the ABC/2 method to estimate the volume of EDH, IPH and IVH (as detailed in Section 2.23). This method selects a representative slice of the haemorrhage on which the haemorrhage is most visible. On this slice, two measurements are taken to estimate the size of the surface area of the bleed: A (maximum length); B (width perpendicular to maximum length). These measurements were done using the ruler tool on PACs. For an estimate of the depth of the bleed, a third measurement C is taken (number of slices on which the bleed is clearly visible multiplied by thickness of each slice). When these three measurements are multiplied and the sum divided by 2 (ABC/2), this provides the approximate volume of that bleed in cm^3 (i.e. ml), assuming the bleed is an approximately spherical shape. This method has been validated in IPH and EDH and shows good agreement with automated volumetric analysis. The ABC/2 method has not been validated in IVH, but was used to estimate IVH volume in the IBMS (as confirmed in Section 2.23). Figure 7 shows an example of the A, B and C measurements of an IPH rated on axial slices. For example, if an IPH had a maximal length of 33 mm (A) with a perpendicular width of 20 mm (B), and this bleed was visible on 5 slices of 5mm thickness each - providing a C estimate of 25mm, the approximate volume of this bleed would be 7.5ml (i.e. $30\text{mm} \times 20\text{mm} \times 25\text{mm} / 2 = 7,500 \text{ mm}^3 / 1000 = 7.5\text{cm}^3$).

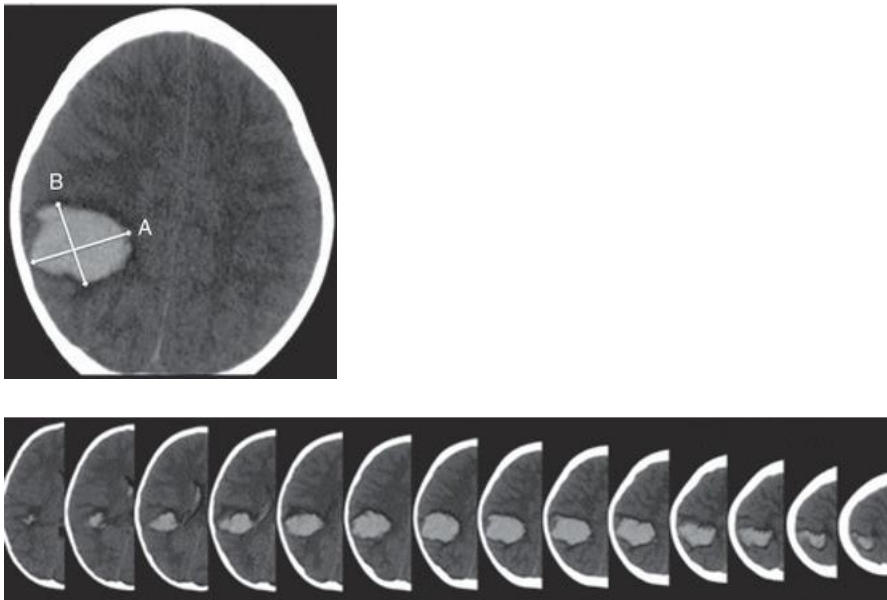


Figure 7. ABC/2 method for estimation of Intra-parenchymal haemorrhage (IPH): maximum length (A), perpendicular width (B), number of slices (in this case 14 slices) multiplied by thickness of each slice (C).^q

^q Reproduced from Kleinman et al (2011) ¹⁴⁰

Not all haemorrhages have a neat spherical shape and so the ABC/2 method is subject to measurement error. Figure 8 shows example A and B measurements for IPH and EDH in patients included in the CRASH-3 IBMS. Please note that these pictures were taken with permission of the PIs at the relevant sites and do not contain any patient identifiable information. The different images on which these bleeds were visible (for the measurements of C) were not available for the purpose of this illustration, but were used to estimate the volume of these haemorrhages. Images showing how IVH volume was estimated were not available for the purpose of this illustration. For IVH, the same measurements were taken: longest length (A), width perpendicular to the length (B); the number of slices multiplied by slice thickness (C).

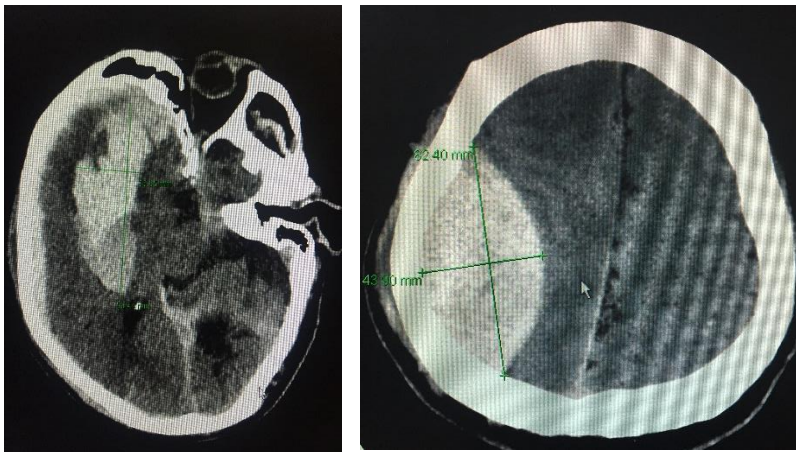


Figure 8. Left: Example IPH volume estimation using ABC/2 method: A (99.44mm) and B (35.65mm). Right: Example EDH volume estimation using ABC/2 method: A (82.40mm) and B (43.90mm).

SDH assessment

The more precise method for the estimation of SDH volume was preferred over the ABC/2 method, for the reasons detailed above (*Outcome Measurement: Estimating SDH volume using maximum width*). The volume of SDH was estimated using the maximum diameter of the subdural bleed (as detailed in Section 2.24). The axial slice on which the SDH diameter was largest was chosen as the representative slice. For this slice, the maximal diameter of the SDH was recorded. Figure 9 shows examples of the SDH slices chosen to estimate the SDH diameter in four patients.

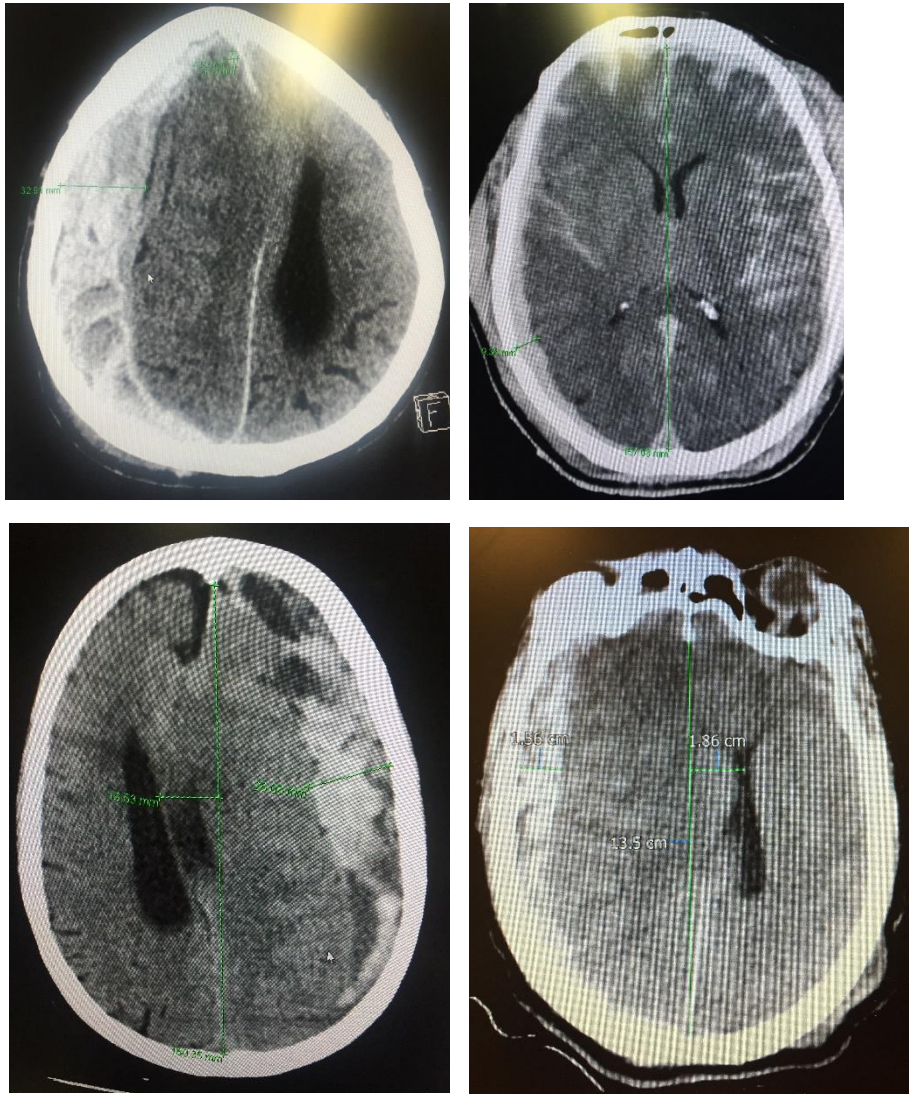


Figure 9. Examples of the slices chosen to estimate SDH diameter in four CRASH-3 IBMS patients with SDH. Top left: 32.91mm; Top right: 9.33mm; Bottom left: 26.08mm; Bottom right: 15.6mm.

The SDH maximal diameter value was substituted into the below formula to calculate the approximate volume of the SDH. This formula takes the difference between two spheres and divides this by 8 to represent the subdural space the SDH occupies $((4/3 \pi r^3 - 4/3 \pi r^3) / 8)$. The division by 8 is because the measurement is for unilateral SDH (divide by 2), SDH is typically thicker at the centre and thinner at the sides (divide by 2) and is bound by superior-inferior and anterior-posterior cerebral axes (divide by 4). The standard longitudinal diameter (temporal – temporal) is used to estimate the radius (i.e. 137mm diameter / 6.85mm radius)¹⁷². For example, for a SDH with a diameter of 9.33mm (i.e. 0.933cm), the approximate volume is 60ml:

$$[4/3 \pi (6.85)^3 - 4/3 \pi (6.85-r)^3] / 8$$

$$4/3\pi(6.85)^3 - 4/3\pi(6.85 - \mathbf{0.933})^3$$

$$1346.36 - 867.75 = 478.61$$

$$478.61 / 8 = 59.83 \text{ cm}^3 \text{ (i.e. 60ml)}$$

Patient anonymity

In order to ensure that no patient identifiable information was recorded on the data collection forms, we decided not to record the time of the CT scan. On the pre-randomisation form, we recorded the number of hours and minutes between injury and CT scan. On the post-randomisation form, we record the number of hours and minutes between randomisation and CT scan. If needed in future, this information could be used to calculate the timing of the CT scan using the CRASH-3 trial data on the date and time of randomisation, the number of hours from injury to randomisation, and the CRASH-3 IBMS data on the time from injury to the pre-randomisation scan.

See Appendix 12 for the final pre- and post-randomisation outcome forms.

PILOT STUDY

Data were collected from the first site as per the finalised pre-randomisation and post-randomisation scan forms. Blinded data were reviewed following data collection at this site. A summary of the findings follow.

2.33 Summary

From the CRASH-3 trial database, a total of 212 patients were identified as eligible for the CRASH-3 IBMS at the first site. These patients were randomised into the CRASH-3 trial between February 2013 and July 2016. All patients were scanned before randomisation but the scans for one patient were unavailable for reading for technical reasons. Patients were scanned within a mean of two hours of injury (SD=0.9). A total of 161 patients (76%) had a post-randomisation scan and 49 (23%) did not have one done. A total of 19 patients (9%) died before the post-randomisation scan. Patients were rescanned within a mean of 58 hours (SD=52.5) after randomisation (excluding eight patients who were rescanned more than 10 days after randomisation). All patients had CT evidence of intracranial haemorrhage. On the pre-randomisation scan, 74% of patients had at least one SDH, 71% had SAH, 55% had IPH, 11% had IVH, 7% had petechial haemorrhage and 5% had EDH. A total of 14 patients (7%) had evidence of a focal ischaemic lesion (acute or historic) on the pre-randomisation scan. A total of 27 patients (13%) had neurosurgical evacuation before the post-randomisation scan.

2.34 Amendment to eligibility criteria to reduce missing post-randomisation scans ^r

Of the 49 patients without a post-randomisation scan, 27% had a GCS score of 3 and 41% had a GCS score of 14 or 15 (see Figure 10).

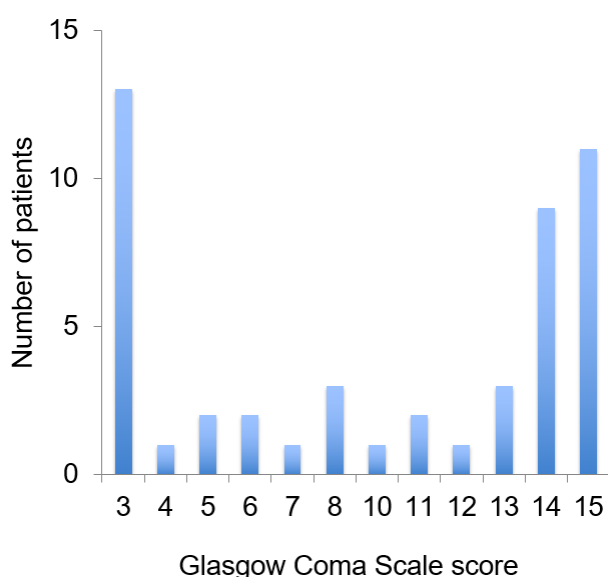


Figure 10. Occurrence of missing post-randomisation scans by GCS score.

Examination of the occurrence of missing post-randomisation scans according to GCS score suggested that the majority of missing scans were from patients with less severe injuries. The pathologies of interest, intracranial haemorrhage expansion and cerebral infarction, predominantly occur in the more severely injured ⁶⁹. So we revised the eligibility criteria from the first site onwards to only include patients with a GCS score of 12 or less.

Although the revision in eligibility criteria ($GCS \leq 12$) reduced the amount of missing data from patients with mild injuries, a substantial proportion of missing data is from patients with severe injuries. Furthermore, the occurrence of missing data could relate to the trial treatment (e.g. TXA could reduce intracranial bleeding and so a second scan is not clinically indicated, TXA could increase infarction and so a second scan is clinically indicated). Therefore, in the analysis plan, there is particular attention to exploring the potential reasons for missing data, as missing data can result in biased treatment effect estimates.

Examination of GCS scores from three subsequent UK sites in which the CRASH-3 IBMS was to be conducted indicated that a total of 403 patients had a GCS score of 12 or less (Site 2: $n=220$; Site 3: $n=112$; Site 4: $n=71$). We initially planned to conduct the CRASH-3 IBMS in the

^r The decision to amend the eligibility criteria to include patients with a GCS of ≤ 12 was made after the first round of data collection at the first site. The original protocol, in which part of the eligibility was determined by whether patients has a GCS of ≤ 12 or CT with intracranial bleeding, did not change in response to this decision. This is because patients with a GCS ≤ 12 are included in the population of eligible patients as per the original protocol.

UK only, due to ease of access to electronic imaging and the number of patients recruited into the CRASH-3 trial. However, because a large proportion of patients have milder injuries, this amendment to the procedure meant that international sites were approached to meet the planned sample size.

2.35 Simple exploratory analyses

Simple exploratory analyses were performed on the data from Site 1 to examine whether the data captured expected associations. SDH is the most common type of intracranial haemorrhage, and three simple analyses were performed using SDH size.

SDH was dichotomized as small or large according to whether the maximal width of SDH (cumulative if a patient had more than one SDH) was $<6\text{mm}$ or $\geq 6\text{mm}$, respectively. According to the formula for estimating SDH haemorrhage volume (see Appendix 10), a SDH of 6mm maximal diameter would have a volume of approximately 25ml. A non-evacuated bleed of 25ml or more has the worst grading in the Marshall Classification, and so for the purpose of this analysis, a SDH with a diameter of 6mm or more was considered large.^s

Pre-randomisation haemorrhage size and head injury death

I would expect patients who died due to head injury to have more intracranial bleeding on their pre-randomisation scan compared to patients who died from a different cause or survived. This can be examined using the size of SDH seen pre-randomisation and information about the cause of death from the CRASH-3 trial outcome form. Patients with larger SDHs ($\geq 6\text{mm}$ vs $<6\text{mm}$) were at greater risk of head injury death (see Table 7). Specifically, patients with a larger SDH were at more than three times the risk of head injury death ($\text{RR}=3.32$, $\text{CI } 1.79\text{--}6.12$, $p=0.0001$).

Table 7. Number (%) of patients with SDH on the pre-randomisation scan by death.

SDH width	Head injury death	Non head injury death / alive	Total
$\geq 6\text{mm}$	23 (31.5%)	50 (68.5%)	73
$<6\text{mm}$	13 (9.5%)	124 (90.5%)	137
Total	36	174	210

^s After conducting these analyses, I noted that there had been an error in my calculation. A SDH of 3.5mm diameter would have an estimated volume of 25ml and a SDH of 6mm diameter would have an estimated volume of 40ml. Therefore, some of the patients in the $<6\text{mm}$ group may have bleeds greater than 25ml. I did not amend this section to dichotomize bleeds according to whether they were more or less than 3.5mm in maximal diameter because the 6mm distinction was what I believed distinguished bleeds of less than or more than 25ml when conducting these analyses on the pilot data.

Pre-randomisation haemorrhage size and neurosurgery

Given that larger bleeds are associated with a greater risk of death and disability, I would expect patients with large bleeds are at greater risk of neurosurgical haemorrhage evacuation. Indeed, the risk of undergoing neurosurgery after randomisation is more than four times greater in patients with a larger SDH on the pre-randomisation scan (RR=4.64, CI 2.06–10.48, p=0.0002) (see Table 8).

Table 8. Number (%) of patients with SDH on the pre-randomisation scan by the propensity to have neurosurgery before the post-randomisation scan.

SDH width	Neurosurgery	No neurosurgery	Total
≥ 6mm	20 (25%)	60 (75%)	80
0–6mm	7 (5.4%)	123 (94.6%)	130
Total	27	183	210

Pre-randomisation haemorrhage size and pre-randomisation midline shift

I would expect larger bleeds to cause more shift of the midline structures. As expected, as the size of SDH increases, the degree of midline shift also increases ($r = 0.77$, $p < 0.05$) (see Figure 11).

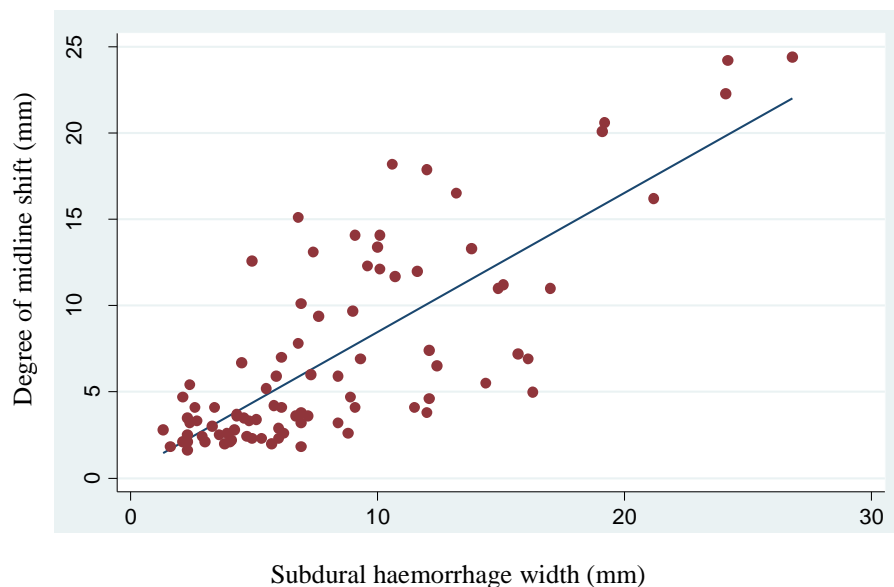


Figure 11. Correlation between size of SDH and degree of midline shift.

STATISTICAL ANALYSIS PLAN

2.36 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, they will not be included in the CRASH-3 IBMS.

2.37 Baseline characteristics

We will report baseline characteristics, including, age, sex, GCS, pupil reaction, systolic blood pressure, mean (and SD) number of hours from injury to pre-randomisation scan, mean (and SD) haemorrhage volume (or median and interquartile range), 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.

2.38 Inter-rater reliability

The inter-rater reliability of pre-randomisation haemorrhage occurrence, as estimated in the CRASH-3 IBMS, will be assessed using relevant Entry Form data from the CRASH-3 trial. This will examine consistency among ratings between the CRASH-3 IBMS data collector and clinical staff who completed the CRASH-3 trial Entry Form.

2.39 Primary analysis: initial plan

In the original protocol, we planned to use analysis of covariance (ANCOVA) to compare the mean volume of intracranial bleeding seen after randomisation between treatment groups, adjusting for prognostic variables measured pre-randomisation: bleeding volume, time from injury to CT scan, GCS, age and systolic blood pressure. We expect 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). A linear regression analysis using the blinded imaging data from 1,000 patients indicated that the selected covariates are predictive of post-randomisation bleeding volume ($p < 0.05$).

We planned to adjust the primary analysis using these covariates and the stratification factor (treatment site) ¹⁷³. Baseline adjustment eliminates conditional bias arising from a chance difference in covariates between treatment groups, and increases precision in the treatment effect estimate by factoring out the covariance between baseline factors and post-randomisation bleeding volumes ¹⁷⁴. We planned to present ratios and 95% confidence intervals to examine the relative effect of TXA (versus placebo) on mean bleeding volume.

However, blinded imaging data from 1,000 patients suggested that only 50% of patients were scanned both before and after randomisation, and only these would be retained in complete-case ANCOVA analyses. A 50% reduction in power as a result of missing scans would outweigh the 30% increase in power from baseline adjustment (adjusted analysis requires 1000 patients, unadjusted analysis requires approximately 1500 patients; see sample size section) ¹⁷⁵.

Furthermore, 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.

To retain a larger sample size, we could choose not to adjust the primary analysis using the pre-randomisation bleeding volume, but at the expense of losing any power gained from adjusting for pre-randomisation bleeding. An alternative approach is to use a linear mixed model, which without missing data, provides identical treatment effect estimates (and near identical standard errors) as the more standard ANCOVA analysis (see Appendix 13). Compared to ANCOVA, 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 efficiency ¹⁷⁶.

2.40 Primary analysis: revised plan ^t

Linear mixed model ¹⁷⁶ will be used to compare the mean change in IPH volume from pre- to post-randomisation between treatment groups. This 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.

The same covariates (time from injury to CT scan, GCS, age, systolic blood pressure, site) will be included in the analysis. The main effect of site (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= ≈1750), we expect any loss in efficiency from this method (compared to the random centre effects method) to be minimal. The linear mixed model described above will include an interaction between each covariate and whether bleeding volume was measured before and/or after randomisation.

The blinded data indicates that pre-randomisation and post-randomisation bleeding volumes are positively skewed. 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% 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 TXA.

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 TXA 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.

^t This revision followed peer review of the Statistical Analysis Plan ¹⁷⁷. The first version was submitted to Wellcome Open Research for publication consideration on 13 August 2018. One peer reviewer submitted a referee report on 17 September 2018 (approved) and another reviewed submitted a report on 18 October 2018 (approved with reservations). In response to the second reviewer's reservations (see Appendix 6), a revised analysis plan was submitted on 8 January 2019. A third reviewer submitted a referee report on 21 May 2019 (approved). The Statistical Analysis Plan was approved for publication on 6 June 2019. All versions and reviewer reports are publicly available at <https://wellcomeopenresearch.org/articles/3-99>.

2.41 Secondary analyses

Composite poor outcome, progressive haemorrhage, new haemorrhage, haemorrhagic oedematous lesions and mass effect: We will express the effect of TXA 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 TXA on the degree of midline shift (measured in millimetres) using a basic linear mixed model, with pre-randomisation midline shift included as an outcome. We will extend this model to include covariates: time from injury to scan, GCS, age and systolic blood pressure.

Cerebral infarction: We will express the effect of TXA 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 TXA received soon after injury reduces intracranial haemorrhage, a patient who received TXA 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, TXA 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 TXA may have less blood on a post-randomisation and post-neurosurgery scan compared to patients who receive placebo. We will express the effect of TXA 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 a variable 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 TXA 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.

2.42 Subgroup analyses

Time from injury to randomisation: Most intracranial bleeding occurs within hours of injury ^{40, 41, 125, 178}. Subgroup analyses will examine whether the effect of TXA 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 ¹²⁵, we expect TXA 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 (TXA, placebo) and time to randomisation (≤ 1 hour, 1–3 hours, >3 –8 hours) to examine whether the effect of TXA 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 TXA in those treated after 3 hours of injury compared to those treated within 3 hours of injury ⁹⁸. We will use relative risks and 95% confidence intervals estimated using generalised linear models to examine whether the effect of TXA 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 TXA on cerebral infarction within time strata. In a separate report, we will examine whether TXA 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) ¹⁷⁹.

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.

2.43 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 scans and baseline data for patients included in the analysis to help identify any selective missingness of outcomes by treatment arm ¹⁸⁰. 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 effect ¹⁸¹.

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) ¹⁸¹. 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 effect ¹⁸².

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) ¹⁸¹.

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 MNAR. 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 TXA reduces intracranial haemorrhage expansion and the risk of death, patients who receive TXA may be more likely to be scanned post-randomisation compared to those who receive placebo. On the other hand, if TXA 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.

Best-worst and worst-best sensitivity analyses

A simple approach to explore the impact of missing outcomes on treatment effect estimates are “best-worst” and “worst-best” scenarios ¹⁸³.

For dichotomous outcomes, the best-worst scenario assumes that everyone with missing data in the treatment group had a good outcome (e.g. infarction absent) and everyone with missing data in the placebo group had a bad outcome (e.g. infarction present). The worst-best scenario assumes that everyone with missing data in the treatment group had the bad outcome and everyone with missing data in the placebo group had the good outcome. If these methods do not give different results, then the impact of missing data on the effect estimate for this outcome may be negligible. But if there is a difference, it can provide a range of uncertainty due to missing data, and any conclusions regarding the effect of TXA on a given dichotomous outcome can be interpreted in the context of this uncertainty ¹⁸³.

For continuous outcomes, a ‘beneficial outcome’ might be the group mean plus 2 standard deviations of the group mean, and a ‘harmful outcome’ might be the group mean minus 2 standard deviations of the group mean ¹⁸³. This represents a possible range of uncertainty given 95% of the observed data (if normally distributed).

2.44 Between-centre effects

There is no clear evidence for the hypothesis that between-centre differences in unfavourable outcome affect the chance of demonstrating a treatment effect in randomised trials of TBI ¹⁸⁴. This study estimated the between-centre differences beyond the random variation that may result from some centres that only treat a small number of patients. Given this evidence and that we have no biologically plausible reason to expect any variation in a treatment effect between centres, we do not anticipate to find centre effects in the CRASH-3 IBMS. Furthermore, the majority of hospitals included in the CRASH-3 IBMS are in the UK. The homogeneity in patient characteristics and care facilities is further reason not to expect a between-centre difference in treatment effect. Nonetheless, the main effect of site will be included in the analyses.

3 RESULTS

3.1 Description of study population

A total of 1767 CRASH-3 trial patients were identified as eligible for the CRASH-3 IBMS. The CONSORT diagram describes the flow of patients by treatment group (see Figure 12). A total of 884 patients (50%) were randomly allocated to the TXA group and 883 patients (50%) to the placebo group. CRASH-3 trial entry and outcome data were collected for all patients in the IBMS, who were recruited across 14 hospitals in the UK and Malaysia, between February 2013 and January 2019. Patients were recruited across 10 hospitals in the UK (n=1146; 65%) and 4 hospitals in Malaysia (n=621; 35%). Routinely collected imaging data were examined for the purpose of the IBMS between February 2016 and January 2019.

A total of 80% of patients in the IBMS were male (n=1413) and 20% were female (n=354). Patients had a median age of 45 years (IQR 29 to 63), median systolic blood pressure of 136 millimetres of Mercury (mmHg) (IQR 120 to 155), and median GCS score of 7 (IQR 3 to 10). The CRASH-3 trial entry data indicated that 65% (n=1143) of patients in the IBMS presented with a severe GCS (3-8), 30% (n=532) with a moderate GCS (9-12) and 5% (n=92) with a mild GCS (13-15). A total of 13% (n=232) of patients presented with bilateral un-reactive pupils, 11% (n=202) with unilateral reactive pupils and 73% (n=1289) with bilateral reactive pupils. Pupil reaction could not be assessed in 2% (n=43) of patients and was unknown in one patient. Most patients in the IBMS were randomised into the CRASH-3 trial within 3 hours of injury (76%, n=1350); the rest were randomised between 3 and 8 hours of injury (23%; n=415), minus two patients who were randomised between 9 and 10 hours of injury (0.1%). All patients were included in the analyses even if they did not adhere to the CRASH-3 trial protocol and receive their allocated treatment, as per the intention-to-treat principle. This approach preserves the prognostic balance afforded by randomization, thereby minimizing any risk of bias from comparing groups that differ in prognostic variables¹⁸⁵. See Table 9 for the pre-randomisation demographic and clinical characteristics of all patients in the IBMS.

A total of 65% of patients (n=1147) had a pre-randomisation (baseline) CT scan done within a median of 2 hours after injury (IQR 1h to 2h). The pre-randomisation scans for 13 patients were unavailable for reading for technical reasons (5 TXA group, 8 placebo group). Of those with a pre-randomisation scan, 72% (n=829) presented with SAH, 64% (n=732) with SDH, 62% (n=709) with IPH, 19% (n=215) with EDH, 16% (n=184) with IVH, and 6% (n=71) with petechial haemorrhage. A total of 15% of patients (n=177) presented with haemorrhagic oedematous lesions, 1% (n=13) with acute cerebral infarction, 44% (n=503) with midline shift, 53% (n=609) with sulcal effacement and 40% (n=456) with ventricular effacement. The most

common Marshall Classification rating was Diffuse Injury II (46%, n=533), followed by non-evacuated mass lesions (43%, n=487). Diffuse Injuries I, III and IV were each rated for 5% or fewer patients^u. See Table 10 for a summary of pre-randomisation CT scan characteristics stratified by treatment group. TXA and placebo groups appear to be approximately balanced for all observed demographic and clinical characteristics.

Discrepancies between the CRASH-3 trial time since injury data and timestamp of the first CT scan meant that it was not possible to confirm whether five patients in the IBMS were scanned pre-randomisation (0.3%). A total of 46% of patients were scanned pre-randomisation and post-randomisation (n=812/1767). A total of 35% of patients were scanned post-randomisation but not pre-randomisation (n=614/1767). A total of 81% of patients were scanned post-randomisation (n=1431/1767). The post-randomisation scans were done within a median of 23 hours after injury (IQR 8h to 48h) and 21 hours (IQR 5h to 46h) after randomisation.

^u Marshall Classification: Diffuse Injury I (no intracranial pathology); Diffuse Injury II (midline shift 0-5mm, basal cistern present, no high/mixed density lesion >25cm³); Diffuse Injury III (midline shift 0-5mm, basal cisterns compressed/effaced, no high/mixed density lesion >25cm³); Diffuse Injury IV (midline shift >5mm, no high/mixed density lesion >25cm³); Evacuated mass lesion (any lesion evacuated surgically); Non-evacuated mass lesion (high/mixed density lesion >25cm³, not surgically evacuated).

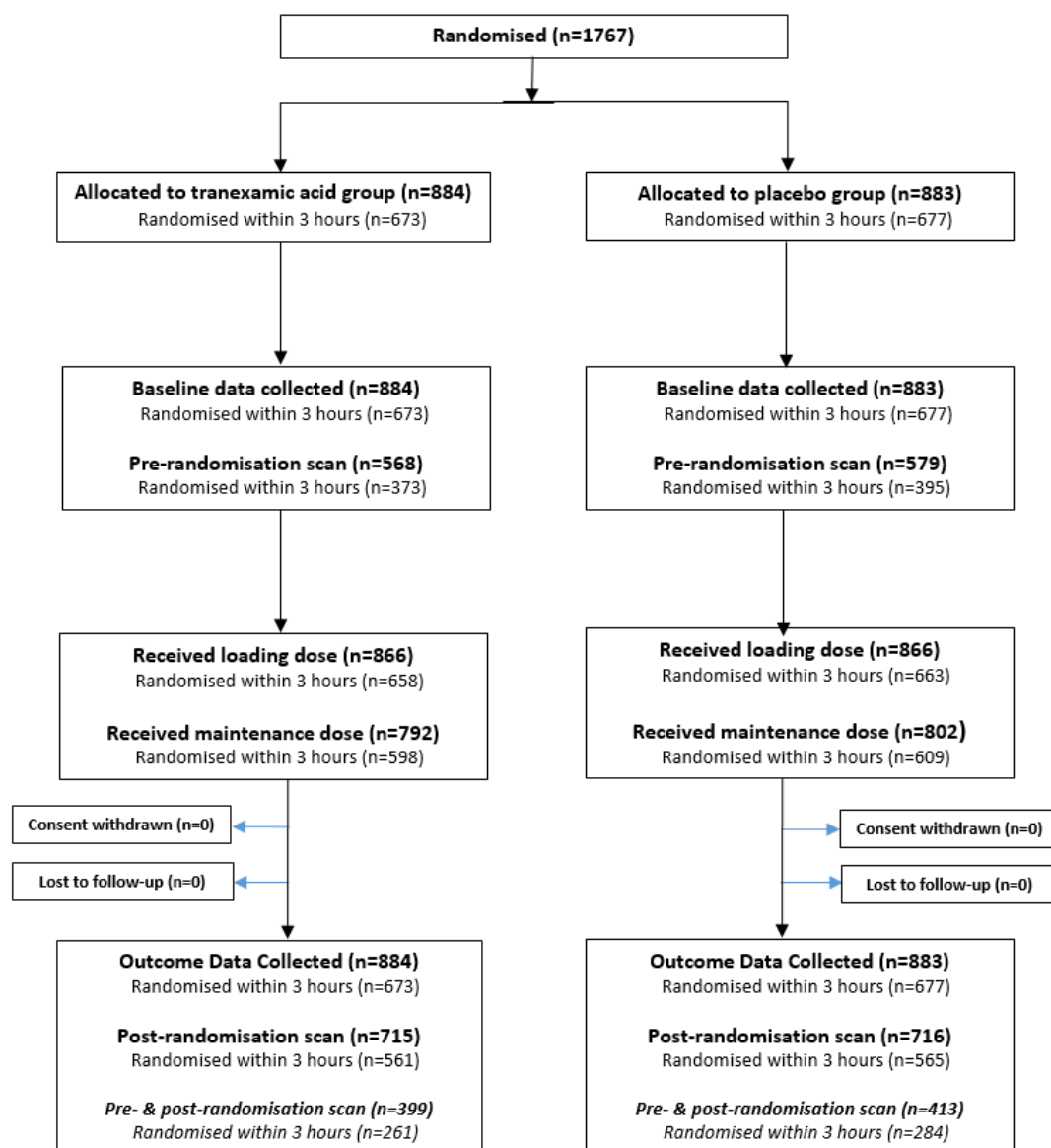


Figure 12. CONSORT diagram on flow of patients in the CRASH-3 IBMS.

Table 9. Baseline demographic and clinical characteristics.

	All patients (n=1767)	TXA group (n=884)	Placebo group (n=883)
Sex			
Male	1413 (80%)	701 (79%)	712 (81%)
Female	354 (20%)	183 (21%)	171 (19%)
Age			
Median (IQR) age in years	45 (29 - 63)	45 (29 - 64)	45 (29 - 63)
Glasgow coma score (GCS)			
Mild (13-15)	92 (5%)	47 (5%)	45 (5%)
Moderate (9-12)	532 (30%)	264 (30%)	268 (30%)
Severe (3-8)	1143 (65%)	573 (65%)	570 (65%)
Median (IQR) GCS	7 (3 - 10)	7 (3 - 10)	7 (3 - 10)
Pupil reaction			
Both react	1289 (73%)	637 (72%)	652 (74%)
One reacts	202 (11%)	97 (11%)	105 (12%)
None react	232 (13%)	124 (14%)	108 (12%)
Unable to assess	43 (2%)	25 (3%)	18 (2%)
Unknown	1 (<1%)	1 (<1%)	0 (0%)
Systolic blood pressure			
< 90	27 (2%)	14 (2%)	13 (1%)
90 – 119	370 (21%)	194 (22%)	176 (20%)
≥ 120	1362 (77%)	672 (76%)	690 (78%)
Unknown	8 (<1%)	4 (<1%)	4 (<1%)
Median (IQR) systolic blood pressure	136 (120 - 155)	136 (120 - 156)	136 (121 - 154)
Hours since injury			
≤1	166 (9%)	77 (9%)	89 (10%)
>1 to ≤3	1184 (67%)	596 (67%)	588 (67%)
>3	417 (24%)	211 (24%)	206 (23%)
Pre-randomisation CT Scan			
Yes	1147 (65%)	568 (64%)	579 (66%)
No	615 (35%)	313 (35%)	302 (34%)
Unknown	5 (<1%)	3 (<1%)	2 (<1%)
Median (IQR) hours from injury to scan	1.8 (1.4 – 2.4)	1.8 (1.5 – 2.4)	1.8 (1.4 – 2.3)

Data are n (%) of participants, unless otherwise indicated.

Table 10. Baseline computed tomography characteristics.

	All patients (n=1147)	TXA group (n=568)	Placebo group (n=579)
Intracranial bleeding			
Intra-parenchymal	709 (62%)	371 (65%)	338 (58%)
<i>Mean (median) vol, ml</i>	4 (1)	5 (1)	4 (1)
Intra-ventricular	184 (16%)	97 (17%)	87 (15%)
<i>Mean (median) vol, ml</i>	2 (<1)	2 (1)	3 (<1)
Subdural	732 (64%)	355 (63%)	377 (65%)
<i>Mean (median) vol, ml</i>	53 (46)	56 (49)	51 (43)
Epidural	215 (19%)	109 (19%)	106 (18%)
<i>Mean (median) vol, ml</i>	19 (6)	20 (6)	18 (6)
Any measurable intracranial bleeding	1024 (89%)	512 (90%)	512 (88%)
<i>Mean (median) vol, ml</i>	46 (37)	47 (39)	45 (35)
Subarachnoid	829 (72%)	414 (73%)	415 (72%)
Petechial	71 (6%)	30 (5%)	41 (7%)
Oedema			
Oedematous lesions	177 (15%)	95 (17%)	82 (14%)
Infarction			
Acute cerebral infarction	13 (1%)	3 (1%)	10 (2%)
Mass effect			
Midline shift	503 (44%)	250 (44%)	253 (44%)
<i>Mean (median) degree of shift (mm)</i>	8 (6)	8 (6)	8 (6)
Sulcal effacement	609 (53%)	318 (56%)	291 (50%)
Ventricular effacement	456 (40%)	224 (39%)	232 (40%)
Marshall classification			
Diffuse injury I	25 (2%)	12 (2%)	13 (2%)
Diffuse injury II	533 (46%)	245 (43%)	288 (50%)
Diffuse injury III	60 (5%)	37 (7%)	23 (4%)
Diffuse injury IV	30 (3%)	16 (3%)	14 (2%)
Non-evacuated mass lesion	487 (43%)	253 (45%)	234 (40%)
Unknown	12 (1%)	5 (1%)	7 (1%)

Data are n (%) of participants, unless otherwise indicated.

3.2 Inter-rater reliability of pre-randomisation haemorrhage occurrence

All data in the CRASH-3 IBMS were collected by one assessor. The CRASH-3 trial entry forms were completed by clinical staff in participating hospitals, and included a question on the types of intracranial bleeding seen on pre-randomisation CT scans. This information can be used to examine the extent to which the CRASH-3 IBMS assessor and the CRASH-3 trial entry form assessors recorded the same type of bleed at baseline for the same patient (i.e. inter-rater reliability).

The Kappa-statistic indicates the magnitude of inter-rater agreement for dichotomous (yes/no) ratings. This calculation is based on the difference between the observed agreement and agreement expected by chance alone. Kappa is standardized to lie on a scale of -1 to 1 where 1 is perfect agreement, 0 is agreement expected by chance, and negative values indicate agreement less than chance. Agreement is considered perfect when the Kappa value is between 0.81 and 0.99, substantial between 0.61 and 0.80, moderate between 0.41 and 0.6, fair between 0.21 and 0.40, and slight between 0.01 and 0.20 ¹⁸⁶.

The ratings for EDH occurrence agreed between raters in 89% of patients (kappa = 0.57, moderate), IVH in 88% of patients (kappa = 0.50, moderate), SAH in 77% of patients (kappa = 0.50, moderate), SDH in 74% of patients (kappa = 0.43, moderate), and for IPH in 65% of patients (kappa = 0.33, fair). The kappa-statistic had a probability of less than 0.0001 for all bleed types, which suggests that the hypothesis that bleed occurrence ratings were randomly assigned can be rejected.

Other than the prevalence of SDH where the CRASH-3 trial entry form rating is greater than the IBMS rating (67% vs 64%), the prevalence of each bleed is greater according to the IBMS rating: SAH (59% vs 72%); IPH (42% vs 62%); EDH (13% vs 19%); IVH (9% vs 16%). A discrepancy between ratings may be expected given that the IBMS assessor collected the data by assessing scans in conjunction with their accompanying radiology reports that are often written post-randomisation, whilst randomisation into the CRASH-3 trial should have been based on information known pre-randomisation. The CRASH-3 trial entry forms were often completed using verbal report from radiologists or other clinical staff whilst patients were having their pre-randomisation CT scan done, and so the most visible or most clinically relevant bleed(s) may have been recorded on the entry form. This would plausibly explain discrepancies in pre-randomisation bleed occurrence ratings between the IBMS assessor and clinical staff who completed the trial entry forms.

3.3 Intra-rater reliability

During a training placement in March to April 2016 at the Queen Elizabeth Hospital in Birmingham, I examined the scans for 90 patients to explore whether the CRASH-3 IBMS was feasible. At the time of this assessment, the scans for 7 patients could not be read for technical reasons. I did not examine the scans for all the outcomes included in the final data collection forms as these had not yet been developed. The priority of the training placement was to explore whether scans were routinely done before and after randomisation and the extent to which post-randomisation scans may be missing. This was also an opportunity to practise using the ABC/2 method of measuring haemorrhage volume, and so if a patient presented with multiple haemorrhages, I estimated the volume of what appeared to be the largest haemorrhage(s). I estimated the volume of large IPHs using the ABC/2 method (as discussed in Section 2.24) and SDH using the maximum diameter (as discussed in Section 2.25). I also rated scans according to the Marshall Classification (see Appendix 11). The training placement (Reading 1) and the final data collection for these patients (Reading 2) occurred on separate occasions. The scan assessment during Reading 2 was done blind from the assessment during Reading 1.

In this section, I will assess the degree of agreement between Readings 1 and 2 of the same patient's scan by the same assessor (i.e. the intra-rater reliability). The intra-rater reliability of dichotomous and ordinal outcomes will be assessed using the Kappa statistic, and continuous outcomes (bleed volume) using Intra-Class Correlations (ICCs).

Intracranial haemorrhage (pre-randomisation scan)

A discrepancy between haemorrhage occurrence and volume ratings between Readings 1 and 2 should be expected. Reading 1 involved estimating the volume of the largest bleeds seen on the scan and information about the occurrence of other bleeds was extracted from available radiology reports. Reading 2 involved recording the occurrence and volume of all bleeds (irrespective of size), where possible, using scans and their accompanying radiology reports.

During Reading 1 compared to Reading 2, fewer patients were recorded as having IPH (30% vs 53%), SDH (28% vs 66%), IVH (4% vs 7%) and SAH (14% vs 66%). During Reading 1, EDH was referred to as extra-axial haemorrhage (as it is in some radiology reports) and because extra-axial haemorrhage could be EDH, SDH or SAH, I was unable to retrospectively confirm which patients had EDH for the purpose of this analysis. During Reading 2, a total of 3 patients (4%) were recorded as having EDH.

My ratings for IPH occurrence agreed in 65% of patients ($\kappa = 0.32$, fair) and the hypothesis that they were randomly assigned can be rejected ($p=0.0006$). My ratings for SDH occurrence agreed in 61% of patients ($\kappa = 0.33$, fair) and the hypothesis that they were randomly assigned can be rejected ($p<0.0001$). My ratings for IVH occurrence agreed in 94% of patients

(kappa = 0.42, moderate) and the hypothesis that they were randomly assigned can be rejected ($p < 0.0001$). My ratings for SAH occurrence agreed in 48% of patients (kappa = 0.16, slight) and the hypothesis that they were randomly assigned can be rejected ($p = 0.0038$). Please note that because the volume of SAH was not estimated, SAH occurrence was not recorded in a standardized way during Reading 1. For the purpose of this analysis, I examined the comments of the available sections of radiology reports (recorded as notes during the training placement) for 21/82 patients for confirmation of the presence of SAH. This would explain the larger discrepancy between Readings 1 and 2 for SAH compared to other types of haemorrhage.

ICCs were used to examine the reliability of bleeding volume estimates between Readings 1 and 2¹⁸⁷. The ICC usually has a value between 0 and 1, with higher values indicating stronger reliability¹⁸⁸. ICC values less than 0.5 are considered poor, between 0.5 and 0.75 moderate, between >0.75 and 0.9 good, and greater than 0.9 excellent¹⁸⁹. However, whether a given ICC value indicates sufficient reliability should depend on the intended use of the method¹⁸⁸.

The mean of the total bleeding volume (sum of all bleeds) was lower for Reading 1 compared to Reading 2 (18.0ml (SD=31.8ml) vs 31.1ml (35.4ml)). The estimated ICC between individual readings for each patient is 0.70 (95% CI 0.58 – 0.80), indicating moderate reliability. The ICC between mean readings for each patient is 0.83 (95% CI 0.73 – 0.89), indicating good reliability. There is evidence to reject the null hypothesis that neither ICC is zero: $F(81, 82) = 5.74$, $p < 0.0001$.

The mean of the total IPH volume was higher for Reading 1 compared to Reading 2 (5.1ml (SD=19.6ml) vs 3.7ml (SD=15.7ml)). The estimated ICC between individual IPH volume readings for each patient is 0.64 (95% CI 0.49 – 0.75), indicating moderate reliability. The ICC between mean readings for each patient is 0.78 (95% CI 0.66 – 0.86), indicating good reliability. There is evidence to reject the null hypothesis that neither ICC is zero: $F(81, 82) = 4.57$, $p < 0.0001$.

The mean of the total SDH volume was lower for Reading 1 compared to Reading 2 (12.9ml (SD=26.0ml) vs 25.4ml (SD=27.5ml)). The estimated ICC between individual SDH volume readings for each patient is 0.59 (95% CI 0.43 – 0.72), indicating moderate reliability. The ICC between mean readings for each patient is 0.74 (95% CI 0.60 – 0.83), indicating moderate reliability. There is evidence to reject the null hypothesis that neither ICC is zero: $F(81, 82) = 3.89$, $p < 0.0001$.

Marshall Classification

The Marshall Classification rating was missing for 1/83 patients whose pre-randomisation scans were read during Reading 1. Of the remaining 82 patients, the Marshall Classification was scored as Diffuse Injury I in 3 patients (4%), Diffuse Injury II in 53 patients (65%), Diffuse Injury III in 2 patients (2%), Diffuse Injury IV in 3 patients (4%), Evacuated mass lesion in 0 patients (0%), and Non-evacuated mass lesion in 21 patients (26%). During reading 2, the Marshall Classification was rated as Diffuse Injury I in 1 patient (1%), Diffuse Injury II in 48 patients (59%), Diffuse Injury III in 2 patients (2%), Diffuse Injury IV in 1 patient (1%), Evacuated mass lesion in 0 patients (0%) and Non-evacuated mass lesion in 30 patients (37%). My pre-randomisation Marshall Classification ratings agreed in 79% of patients ($\kappa = 0.61$, substantial) and the hypothesis that these ratings were randomly assigned can be rejected ($p < 0.0001$).

A third of patients whose scans were assessed during Reading 1 were not scanned post-randomisation ($n = 28/83$). In patients scanned post-randomisation, not all scans were retrievable during Reading 1 (largely due to technical difficulties and archiving) but were during Reading 2. This left 39 patients whose post-randomisation scans were rated using the Marshall Classification during both Readings 1 and 2. No patients' scans were rated as Diffuse Injury I or III during either reading. In both readings, Diffuse Injury II was rated in 21 patients (54%), Diffuse Injury IV in 1 patient (3%), and Non-evacuated mass lesion in 8 patients (21%). A total of 8 patients (21%) were recorded as having an Evacuated mass lesion during Reading 1 and 9 patients (23%) during Reading 2. My post-randomisation Marshall Classification ratings agreed in 95% of patients ($\kappa = 0.92$, perfect) and the hypothesis that these ratings were randomly assigned can be rejected ($p < 0.0001$).

Research Paper 4

Sections 3.3 to Section 3.6 of this chapter are from Research Paper 4. This paper was submitted for publication consideration in October 2019, and is currently undergoing revision. I have acquired permission to reproduce this manuscript in this thesis (see Appendix 7) and the full submitted manuscript is included in Appendix 8.

Title: TXA in traumatic brain injury: an explanatory study nested within the CRASH-3 trial.

Journal: European Journal of Trauma and Emergency Surgery

Authors: Mahmood A, Needham K, Shakur-Still H, Davies D, Belli A, Jamaluddin S F, [...], Roberts, I.

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	LSH1512388	Title	Miss
First Name(s)	Abda		
Surname/Family Name	Mahmood		
Thesis Title	Effect of tranexamic acid on intracranial haemorrhage and infarction in patients with traumatic brain injury: a randomised trial.		
Primary Supervisor	Haleema Shakur-Still & Ian Roberts (co-supervisors)		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	N/A		
When was the work published?	N/A		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	N/A		
Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	Choose an item.

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	European Journal of Trauma and Emergency Medicine
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Stage of publication	Undergoing revision

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	<p>I led the CRASH-3 Intracranial Bleeding Mechanistic Study. This includes the protocol development, national and local ethical approvals, and publication of the protocol and analysis plan.</p> <p>I collected the data presented in the submitted manuscript. I cleaned and analysed the data, and this analysis was checked by second author, Kelly Needham. I drafted the first version of the manuscript. I worked with Ian Roberts to revise the manuscript. The manuscript was further revised with input from the co-authors. I led the submission of the manuscript. The journal has responded with a request for major revisions (they would prefer for us to present the analysis of the treatment effect in this paper). The manuscript included in my thesis is the original submission. I will lead the revision and re-submission process (re-submission due 7 January 2020).</p>
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SECTION E

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Date	9 Dec 2019
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Date	12/9/2019.

3.4 Intracranial haemorrhage seen pre-randomisation, by GCS score and pupil reaction

Figure 13 shows the type and frequency of intracranial haemorrhage on pre-randomisation CT scans according to pre-randomisation GCS. A total of 61% of patients with a pre-randomisation CT scan presented with more than one type of haemorrhage. With the exception of EDH, which was more prevalent in patients with mild to moderate GCS, all other haemorrhage types were more common in patients with a severe GCS. SDH had a larger median volume of 46ml (IQR 27ml to 71ml) compared to EDH with 6ml (IQR 2ml to 20ml), IPH with 1ml (IQR 0·2ml to 3ml), and IVH with a median volume of 0·4ml (IQR 0·1ml to 2ml).

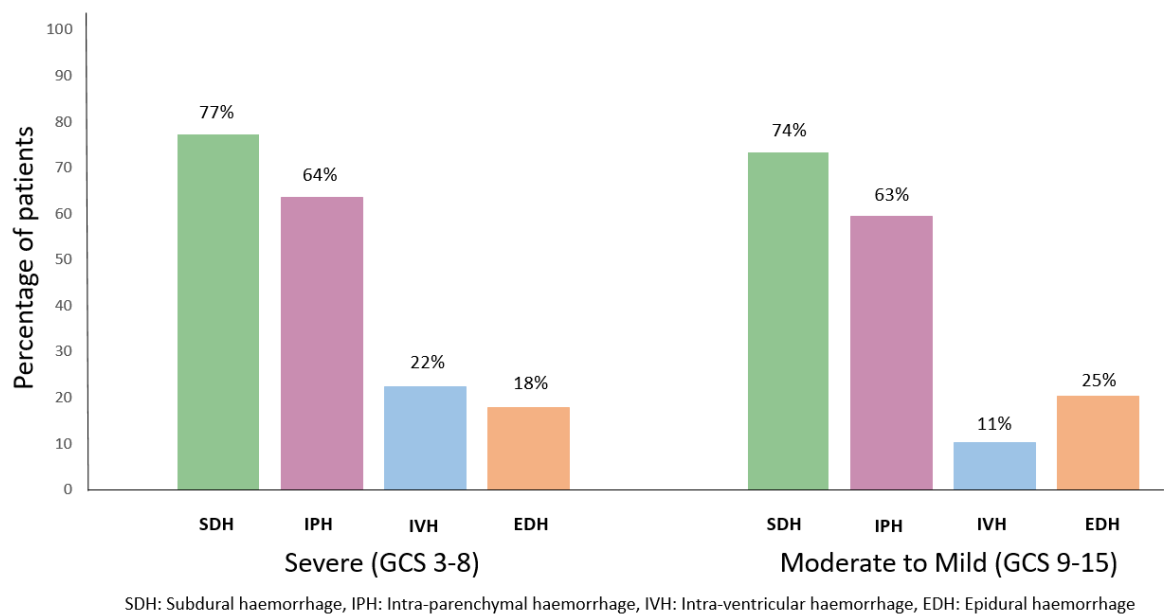


Figure 13. Pre-randomisation prevalence and type of intracranial bleeding by Glasgow Coma Score (GCS).

Figure 14 shows the volume distribution of intracranial haemorrhage on pre-randomisation CT scans by pupil reactions and GCS. The median volumes of 64ml (IQR 26ml to 108ml) in patients with no reactive pupils and 48ml (IQR 3ml to 93ml) in patients with one reactive pupil were larger than 26ml (IQR 1ml to 55ml) in patients with two reactive pupils. The median volumes of 37ml (IQR 3ml to 75ml) in patients with a severe GCS were greater than 28ml (IQR 1ml to 53ml) for moderate GCS and 18ml (IQR 0·2ml to 41ml) in mild GCS. But there is substantial overlap in haemorrhage volumes between pupil reaction groups and GCS groups.

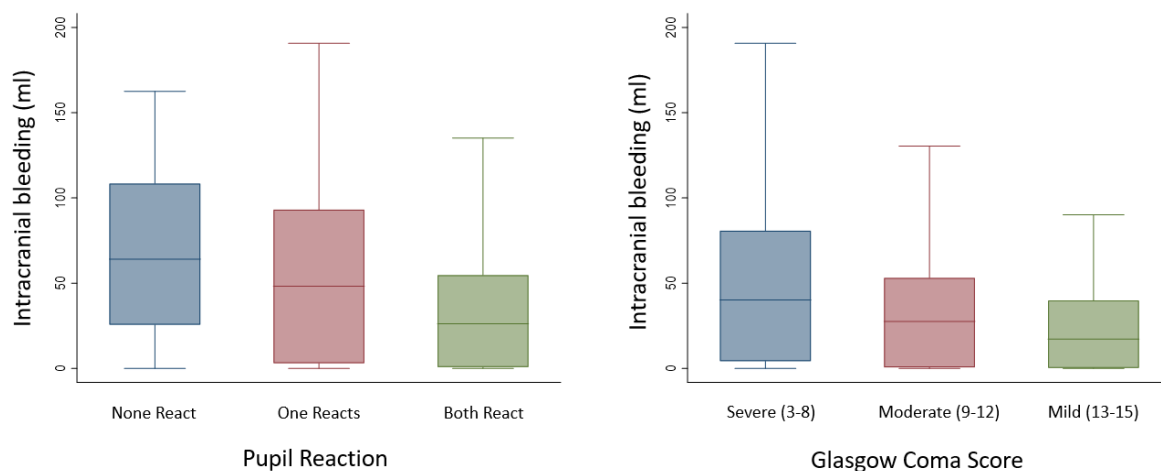


Figure 14. Pre-randomisation intracranial bleeding volume distribution.

Data on the time of injury (from the CRASH-3 trial entry form) and time of CT scan (from the CRASH-3 IBMS) were used to estimate the time-adjusted volume of intracranial haemorrhage. Table 11 shows the time-adjusted volume of haemorrhage by pupil reaction, GCS score, and type of haemorrhage. The time-adjusted volume of haemorrhage was largest in those with un-reactive pupils and in those with severe GCS. SDH was more rapid than EDH, IPH, and IVH.

Table 11. Baseline intracranial bleeding volume (adjusted for time from injury to baseline scan).

	Median (lower quartile, upper quartile) millilitres / hour
All patients (n=1,135)	16 (1, 36)
Pupil reaction	
None react (n=141)	32 (14, 55)
One react (n=94)	21 (2, 47)
Both react (n=867)	13 (0.5, 31)
Glasgow coma scale (GCS) score *	
Severe (n=388)	20 (2, 41)
Moderate (n=331)	13 (0.3, 29)
Mild (n=91)	8 (0.1, 20)
<i>Bilateral un-reactive pupils or GCS 3 * (n=131)</i>	28 (10, 54)
Type of intracranial bleeding	
Subdural (n=732)	25 (13, 42)
Epidural (n=215)	4 (1, 10)
Intra-parenchymal (n=709)	0.4 (0.1, 2)
Intra-ventricular (n=184)	0.3 (0.1, 1)

*Glasgow Coma Scale (GCS) score assessed before intubation / sedation (n=814 / 1,135) (72%)

But the bleeding rate may not be constant. A non-linear association was found between time and bleeding volume (see Figure 15). The majority of expansion occurred in the first 1 to 1.5 hours after injury. Patients with a severe GCS seemed to bleed more and faster than patients with moderate to mild GCS.

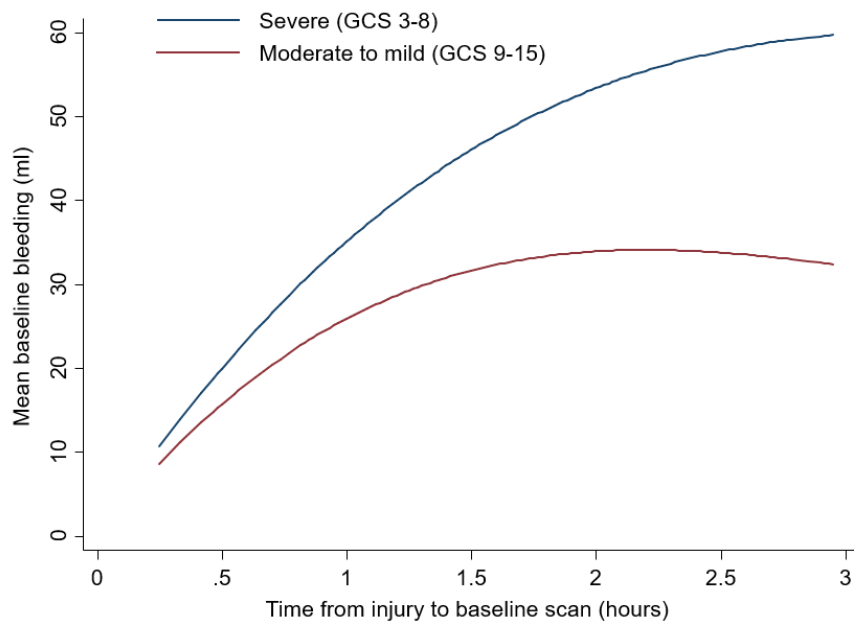


Figure 15. Association between time from injury to baseline scan and intracranial bleeding on baseline scan.

3.5 Signs of intracranial pressure on pre-randomisation CT

Compared to patients with mild to moderate GCS, the prevalence of sulcal effacement was greater in those with severe GCS (44% vs 59%; $n=190/433$ vs $n=417/702$), as was ventricular effacement (30% vs 47%; $n=128/433$ vs $328/702$), and midline shift (39% vs 48%; $n=169/433$ vs. $337/702$). Patients with a severe GCS and midline shift had a median shift of 7.4mm (IQR 4.1mm to 14.1mm) whilst those with moderate to mild GCS had a median shift of 4.3mm (IQR 2.8mm to 7.1mm).

3.6 Intracranial haemorrhage seen post-randomisation but not pre-randomisation

Seventy one percent ($n=812$) of patients with a pre-randomisation CT scan had a second or third clinically indicated CT scan. Over a third of these patients ($n=318$) had a bleed on a subsequent scan that was not seen on the first scan. Patients who had their first CT scan soon after injury were more likely to have a new bleed on a subsequent scan. The prevalence of new bleeds among those scanned ≤ 1.5 hours, >1.5 to 3 hours, >3 to 8 hours after injury was 46%, 38%, 31%, respectively. For every 1 hour increase from injury to the baseline scan, the risk of new bleeding on a further scan decreased by 12% (RR=0.88 [95% CI 0.80 – 0.96], $p=0.0047$) (adjusted for baseline GCS score, pupil reaction, and time from injury to follow-up scan). The sooner the first scan was done after injury, the greater the opportunity for a new bleed to manifest on a further scan.

3.7 Pre-randomisation intracranial haemorrhage and pressure, un-reactive pupils, and head injury death

An increase in the volume of intracranial bleeding (ml) was associated with an increase in the amount (mm) of midline shift (beta coefficient 0.10 [95% CI 0.09-0.10], $p<0.0001$) (see Figure 16). An increase in midline shift (mm) was associated with an increase in the risk of having one or more un-reactive pupils (RR 1.08 [95% CI 1.07-1.10], $p<0.0001$) (see Figure 17). Of those with pre-randomisation scans available for rating, 247 patients subsequently died from head injury. The median time-adjusted volume of intracranial bleeding among patients who died from head injury is 37ml/h (IQR 18ml/h to 58ml/h) and in those who did not die of head injury^v is 11ml/h (IQR 0.3ml/h to 28ml/h). Patients who died of head injury within 24 hours of injury had a higher median time-adjusted bleeding volume of 51ml/h (IQR 28ml/h to 73ml/h), than those who died within 48-72 hours of injury with 39ml/h (IQR 19ml/h to 56ml/h), and beyond 72 hours of injury with 28ml/h (IQR 14ml/h to 52ml/h).

^v This includes those who survived or died of another cause.

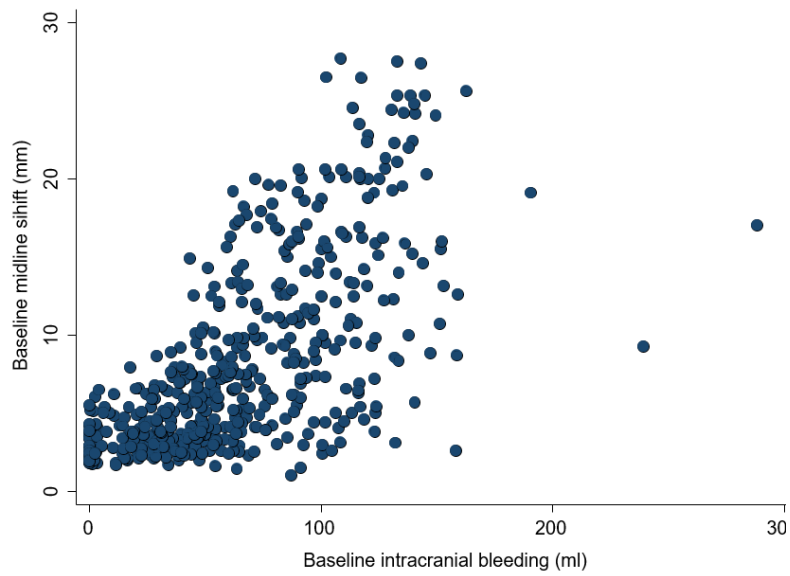


Figure 16. Association between baseline intracranial bleeding (ml) and baseline midline shift (mm).

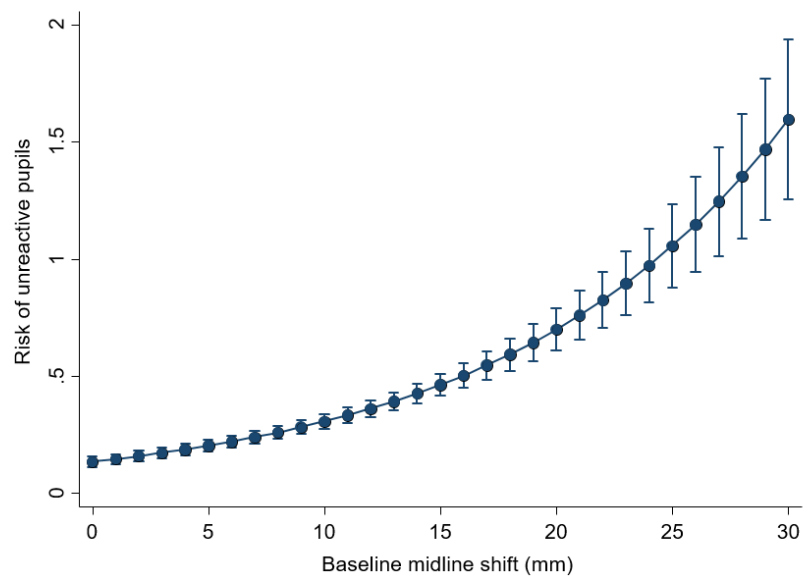


Figure 17. Association between baseline midline shift (mm) and baseline pupil reaction.

3.8 Effect of TXA on intracranial haemorrhage

As indicated in the statistical analysis plan in the methods chapter, all patients can be included in the analyses on the effect of TXA on intracranial haemorrhage volume, even if they were not scanned pre-randomisation and post-randomisation.

Appendix 14 shows that haemorrhage volumes were positively skewed (left-skew), and that these skewed data can be transformed into a more normal distribution using log transformation. This transformation may make any patterns in the data more interpretable. A linear mixed model was used to examine the effect of TXA (versus placebo) on log-transformed haemorrhage volumes. This analysis included the duration between injury to the pre-randomisation scan, age, GCS score, systolic blood pressure, and participating hospital site. Because haemorrhage volumes were log-transformed, the anti-log of the treatment effect estimate and its corresponding 95% confidence intervals (CIs) are presented in Table 12 to aid interpretation. See Table 12 for the proportional effect of TXA on intracranial haemorrhage. The values provide an estimate of the relative increase or decrease in haemorrhage volume with TXA (i.e. the treatment effect).

3.8.1 Primary analysis: effect of TXA on IPH

There is no evidence for a reduction in IPH with TXA compared to placebo: 1.06, 95% CI (0.84 – 1.35), $p=0.620$. The confidence intervals are wide and so the treatment effect estimate is compatible with a decrease or increase in IPH with TXA. There is no evidence for a reduction in IPH with TXA in patients randomised within 3 hours of injury (1.09, 95% CI (0.81 – 1.45), $p=0.570$) or after 3 hours of injury (0.95, 95% CI (0.63 – 1.43), $p=0.789$).

Sensitivity analysis: Because a change in haemorrhage volume between pre-randomisation and post-randomisation scans could be due to the effect of TXA or neurosurgical haemorrhage evacuation, patients who underwent neurosurgical haemorrhage evacuation by the first post-randomisation scan were removed from the primary analysis. There was no evidence for a reduction in IPH with TXA compared to placebo: 1.11, 95% CI (0.73 – 1.67), $p=0.629$.

3.8.2 Secondary analysis: effect of TXA on SDH, EDH and IVH

There is no evidence for a reduction in SDH (0.96, 95% CI (0.88 – 1.05), $p=0.405$) or EDH (0.84, 95% CI (0.52 – 1.37), $p=0.483$) with TXA compared to placebo. There is no evidence for a reduction in SDH or EDH in those randomised within or after three hours of injury (see Table 12).

There is no clear evidence for a reduction or increase in IVH (1.46, 95% CI (0.98 – 2.19), $p=0.063$) with TXA compared to placebo. There is no evidence for a reduction or increase in IVH with TXA in those randomised within three hours of injury (1.24, 95% CI (0.75 – 2.05), $p=0.399$) and no clear evidence for a reduction or increase in IVH in those randomised after three hours of injury (2.10, 95% CI (0.94 – 4.66), $p=0.069$). In most cases, the point estimates are imprecise.

Sensitivity analysis: In sensitivity analyses, patients who underwent neurosurgical haemorrhage evacuation by the first post-randomisation scan were excluded. There is no evidence for a reduction in SDH (1.02, 95% CI (0.93 – 1.12), $p=0.630$) or EDH (0.95, 95% CI (0.62 – 1.44), $p=0.803$) with TXA. There is no evidence for a reduction in SDH with TXA in those randomised within 3 hours of injury (1.03, 95% CI (0.91 – 1.15), $p=0.679$) or after 3 hours of injury (1.00, 95% CI (0.85 – 1.17), $p=0.961$). There is no evidence for a reduction in EDH with TXA in those randomised within 3 hours of injury (1.27, 95% CI (0.63 – 2.52), $p=0.504$) or after 3 hours of injury (0.67, 95% CI (0.38 – 1.18), $p=0.167$).

3.8.3 Secondary analysis: effect of TXA on post-neurosurgical haemorrhage

A total of 21% of patients underwent neurosurgical haemorrhage evacuation ($n=363/1767$). Of these, 31% ($n=111$) had a craniotomy (portion of skull replaced immediately after evacuation) and 69% ($n=252$) had a craniectomy (portion of skull not immediately replaced after evacuation).

In patients scanned pre-randomisation and post-randomisation, 24% of patients underwent neurosurgical haemorrhage evacuation between pre-randomisation and post-randomisation scans ($n=192/812$). A further 7% of patients who were scanned pre-randomisation showed evidence of neurosurgical haemorrhage evacuation on a further post-randomisation scan ($n=54/812$). In patients not scanned pre-randomisation but who had their first scan post-randomisation, 19% showed evidence of neurosurgical haemorrhage evacuation ($n=117/614$).

There was no evidence for a reduction in any intracranial haemorrhage with TXA in patients who underwent neurosurgical haemorrhage evacuation (0.79, 95% CI (0.57 – 1.11), $p=0.182$). There was no evidence for a reduction in IPH with TXA in patients who underwent neurosurgical haemorrhage evacuation (1.11, 95% CI (0.73 – 1.67), $p=0.629$).

3.8.4 Secondary analysis: effect of TXA on SAH

The effect of TXA on SAH was examined using relative risks (RRs) and 95% CIs. A total of 64% of patients presented with SAH in the TXA group (n=458/715) and 61% in the placebo group (n=440/716). Among all patients, there was no evidence for a reduction in SAH with TXA: RR=1.02, 95% CI (0.99 – 1.05), p=0.309. There was no evidence for a reduction in SAH in patients randomised within 3 hours (65% vs 60%; RR=1.03, 95% CI (0.99 – 1.06), p=0.148) or after 3 hours of injury (62% vs 66%; RR=0.98, 95% CI (0.92 – 1.05), p=0.558).

The effect of TXA on the size (large vs small) and spread (diffuse vs focal) of SAH was examined. In patients with SAH, there were less patients with large SAH in the TXA group compared to placebo group (7% vs 10%). But there was no clear evidence for a reduction in the size of SAH with TXA: RR=0.67, 95% CI (0.43 – 1.05), p=0.079. In patients with SAH, there were more patients with diffuse SAH in the TXA group compared to placebo group (18% vs 16%). But there was no evidence for an reduction in the spread of SAH with TXA: RR=1.11, 95% CI (0.59 – 2.06), p=0.746.

Table 12. Effect of TXA on intracranial bleeding.

	Proportional effect of TXA (95% CI)					
	≤3h since injury	p value (two-tailed)	>3h since injury	p value (two-tailed)	All patients	p value (two-tailed)
All patients						
Intra-parenchymal	1.09 (0.81 – 1.45)	0.570	0.95 (0.63 – 1.43)	0.789	1.06 (0.84 – 1.35)	0.620
<i>Excl. neurosurgery patients</i>	0.99 (0.71 – 1.37)	0.936	0.96 (0.62 – 1.48)	0.863	1.03 (0.79 – 1.35)	0.804
Intra-ventricular	1.24 (0.75 – 2.05)	0.399	2.10 (0.94 – 4.66)	0.069	1.46 (0.98 – 2.19)	0.063
Subdural	0.96 (0.87 – 1.07)	0.475	0.95 (0.82 – 1.10)	0.498	0.96 (0.88 – 1.05)	0.405
Epidural	1.07 (0.55 – 2.11)	0.834	0.57 (0.29 – 1.12)	0.102	0.84 (0.52 – 1.37)	0.483
Neurosurgery patients only						
Intra-parenchymal	1.58 (1.00 – 2.48)	0.049	0.50 (0.19 – 1.30)	0.153	1.11 (0.73 – 1.67)	0.629
Any intracranial bleeding	0.94 (0.62 – 1.42)	0.756	0.37 (0.19 – 0.72)	0.003	0.79 (0.57 – 1.11)	0.182

3.9 Secondary analysis: effect of TXA on cerebral infarction

The occurrence of cerebral infarction is defined as any patient who presents with acute infarction on any post-randomisation brain imaging scan done within 28 days of randomisation. This excludes patients who presented with the same infarction on a pre-randomisation scan. A total of 11% of patients (n=159/1431) presented with acute infarction post-randomisation, and this was not known to be present pre-randomisation.

Relative risk of cerebral infarction

A total of 12% of patients presented with infarction in the TXA group (n=89/715) and 10% in the placebo group (n=70/716). There is no clear evidence that TXA increases the risk of cerebral infarction: RR=1.27, 95% CI (0.95-1.71), p=0.109.

In those randomised within 3 hours of injury, 12% presented with infarction in the TXA group (n=70/561) and 10% in the placebo group (n=59/565). There is no evidence that TXA increases the risk of infarction in patients randomised within 3 hours of injury: RR=1.19, 95% CI (0.86 – 1.66), p=0.285. In those randomised after 3 hours of injury, 12% of patients presented with infarction in the TXA group (n=19/154) and 7% in the placebo group (n=11/151). There is no clear evidence that TXA increases the risk of infarction in those randomised after 3 hours of injury: RR=1.69, 95% CI (0.83 – 3.44), p=0.145.

The prevalence of infarction was greater amongst those randomised within three hours of injury (n=159/1126; 14%) compared to more than three hours of injury (n=30/305; 10%). Because patients were not randomised into the CRASH-3 trial on the basis of the duration between their injury and randomisation, subgroups of time since injury may be confounded, in this case by baseline severity. Therefore, the same analyses reported above were adjusted using factors indicative of severity and measured pre-randomisation. After adjusting for GCS score, pupil reaction, systolic blood pressure, age, and participating hospital site, there is no evidence that TXA increases the risk of infarction: RR=1.26, 95% CI (0.94 – 1.68), p=0.126. In those randomised within 3 hours of injury, there is no evidence that TXA increases the risk of infarction: RR=1.16, 95% CI (0.84 – 1.61), p=0.372. There is no clear evidence that TXA increases the risk of infarction in those randomised after 3 hours of injury: RR=1.91, 95% CI (0.99 – 3.68), p=0.052. Because this group is even smaller than the group of patients randomised within 3 hours of injury (n=305 vs. n=1126), the confidence intervals are wide and so the effect estimate is imprecise.

Hazard of infarction

Because TXA may increase the occurrence of cerebral infarction after a certain period after randomisation, a Cox proportional hazards model (which provides a rate) may be more appropriate (than a RR) for the analysis of TXA on infarction. The RR is the ratio of the risk of the outcome in the treated group divided by the risk of the same outcome in the comparison group, at a defined endpoint (e.g. end of study follow-up period). The HR is the ratio of the hazard of the outcome in the treated group divided by the hazard of same outcome in the comparison group. The hazard is the probability that if the outcome has not already occurred, it will occur in the next time interval, divided by the length of that interval ¹⁹⁰.

The hazard of cerebral infarction in the TXA group is 1.14 and the hazard in the placebo group is 0.88: HR=1.31, 95% CI (0.95 – 1.80), p=0.100. Among all patients, at any particular time after randomisation, there is no evidence for an increase in the hazard of infarction between treatment groups. Among those randomised within 3 hours of injury, the hazard of cerebral infarction in the TXA group is 1.12 and the hazard in the placebo group is 0.89: HR=1.26, 95% CI (0.88 – 1.79), p=0.203. Among those randomised after 3 hours of injury, the hazard of cerebral infarction in the TXA group is 1.25 and the hazard in the placebo group is 0.79: HR=1.58, 95% CI (0.74 – 3.34), p=0.235. In patients randomised within 3 hours of injury, or after 3 hours of injury, there is no evidence for an increase in the hazard of cerebral infarction at any particular time after randomisation.

The above analyses on the hazard of infarction in TXA and placebo groups were repeated after adjusting for baseline GCS score, pupil reaction, systolic blood pressure, age, and participating hospital site. There is no evidence that TXA increases the hazard of infarction in those randomised within 3 hours of injury: adjusted HR=1.21, 95% CI (0.85 – 1.73), p=0.297. There is no evidence that TXA increases the hazard of infarction in those randomised after 3 hours of injury: adjusted HR=1.68, 95% CI (0.78 – 3.59), p=0.185. Among all patients, at any particular time after randomisation, there is no evidence that TXA increases the hazard of cerebral infarction: adjusted HR=1.28, 95% CI (0.93 – 1.76), p=0.133.

These analyses were not adjusted using the time from injury to the pre-randomisation scan because not all patients scanned post-randomisation were scanned pre-randomisation. Adjusting for baseline covariates would reduce the sample size to the number of patients who have outcomes for all variables that have been used for adjustment (i.e. complete cases). Including the time from injury to

the pre-randomisation scan as a covariate in these analyses would have reduced the sample size by 43%. Any power gained from adjustment would be less than the large loss in power from dropping patients without a pre-randomisation scan ¹⁷⁵.

Survival analysis

Because it is not known when exactly a patient will have suffered infarction, it is not possible to examine any difference between treatment groups in the time duration between randomisation and occurrence of infarction. However, it is possible to use survival analysis to examine any difference between treatment groups in the time duration between randomisation and the time of the scan on which infarction was first seen (see Figure 18).

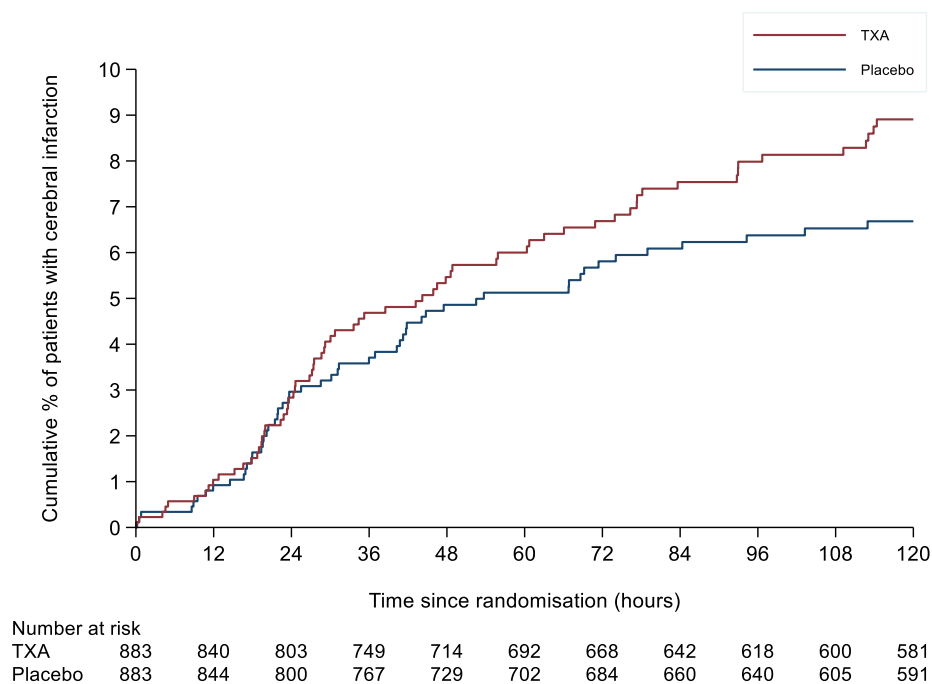


Figure 18. Time to cerebral infarct detection in tranexamic acid or placebo treated patients.

Figure 18 presents the cumulative proportion of patients who show evidence of infarction by time since randomisation ¹⁹¹. The numbers at risk along the x-axis show the number of patients at risk of infarction and still in follow-up in each treatment group at the specified time-points. If a patient shows evidence of infarction, dies or is discharged within 28 days of randomisation, they exit the study at that time point and are not included in the numbers at risk for following time-points.

The median time to the scan showing infarction is 47 hours (IQR 23–113) after randomisation in the TXA group and 41 hours (IQR 20–113) after randomisation in the placebo group. Because the data to the right of the survival graph is where there is least information and greatest uncertainty, the survival plot has not been extended to the end of the follow-up period (but all events are retained in analyses) ¹⁹¹. More than 75% of patients who presented with infarction did so within 120 hours of randomisation, and so the x-axis of Figure 18 was cut here.

The log-rank test for equality of survival curves tests the null hypothesis that there is no difference between treatment groups in the probability of the outcome at any time point after randomisation ¹⁹². The log-rank test suggests that there is no evidence for a difference in the occurrence of infarction between TXA and placebo groups: Log-rank = 2.73, $p=0.099$. The Cox proportional hazards model provides an estimate of the size of the difference between treatment groups. There is no evidence for a difference between treatment groups in the time duration between randomisation and the scan on which infarction was seen: HR=1.31, 95% CI (0.95 – 1.80), $p=0.10$. There is no evidence for a difference between treatment groups in patients treated within 3 hours of injury (HR=1.26, (95% CI 0.88 – 1.79), $p=0.20$) or after 3 hours of injury (HR=1.58, 95% CI 0.74 – 3.34), $p=0.24$).

Because infarction may result as a complication of neurosurgical intervention and not the effect of TXA, patients who underwent neurosurgery were excluded in a sensitivity analysis and the survival curves re-estimated. In the remaining non-neurosurgery patients, 70 presented with infarction (44 TXA, 26 placebo). The log-rank test suggests that there is some evidence for a difference in the occurrence of infarction between TXA and placebo groups in these non-neurosurgery patients: Log-rank = 4.55, $p=0.033$. The Cox proportional hazards model provides an estimate of the size of the difference between treatment groups: HR=1.68, 95% CI (1.03 – 2.73), $p=0.036$. However, this sensitivity analysis was based on a post-randomisation exclusion (occurrence of neurosurgery) and so should be interpreted carefully, especially in the context of the risk of bias from using post-randomisation scans done for clinical purposes.

3.10 Secondary analysis: effect of TXA on composite “poor” outcome

The composite “poor” outcome includes patients with progressive haemorrhage, new haemorrhage, infarction (not known to be present pre-randomisation), neurosurgery, or head injury death. A total of 33% of all patients had at least one of these outcomes ($n=586$), 13% had two ($n=236$), 6% had three ($n=105$), 2% had four ($n=30$) and 0.2% met the criteria for all 5 outcomes within the

composite (n=4). Patients with more than one outcome within the composite were only included in the analysis once.

A total of 55% of patients in the TXA group (n=483/884) met the definition for inclusion in the composite outcome and 54% in the placebo group (n=478/883). The effect of TXA on the composite outcome was evaluated using RRs and 95% CIs. There is no evidence for a reduction in the occurrence of the composite outcome with TXA: RR=1.01, 95% CI (0.93 – 1.10), p=0.832. There is no evidence for a treatment effect in those randomised within three hours of injury (54% vs 54%; RR=0.99 (95% CI 0.90-1.10), p=0.920) or after three hours of injury (58% vs 55%; RR=1.05 (95% CI 0.89 – 1.25), p=0.542).

3.11 Secondary analysis: effect of TXA on oedematous lesions ^w

In patients scanned post-randomisation, the effect of TXA on oedematous lesions (i.e. haemorrhagic lesions surrounded by oedema or residual oedema following haemorrhage resolution) was evaluated using RRs and 95% CIs. A total of 41% of patients presented with oedematous lesions in the TXA group (n=288/709) and 39% in the placebo group (n=278/712). There is no evidence that TXA reduces the risk of oedematous lesions: RR=1.01, 95% CI (0.98 – 1.05), p=0.544. There is no evidence that TXA reduces the risk of oedematous lesions in those randomised within 3 hours of injury (38% vs 36%): RR=1.01, 95% CI (0.97 – 1.05), p=0.583. There is no evidence that TXA reduces the risk of oedematous lesions in those randomised after 3 hours of injury (50% vs 49%): RR=1.01, 95% CI (0.94 – 1.09), p=0.818.

3.12 Secondary outcomes in patients scanned pre-randomisation and post-randomisation

In the 46% of patients who were scanned pre-randomisation and post-randomisation (n=812/1767), the pre-randomisation scan was done within a median of 2 hours after injury (IQR 1h to 2h) and the post-randomisation scan was done within a median of 35 hours after injury (IQR 19h to 77h) and 29h after randomisation (IQR 15h to 70h). Baseline demographic and clinical characteristics for this group of patients are similar to the overall IBMS population (see Table 13). But the proportion of patients with bilateral unreactive pupils is greater in the overall IBMS population than in those with both pre-randomisation and post-randomisation scans (13% vs. 8%), and the proportion of patients

^w Estimating the amount of peri-lesional oedema using the simple manual tools available in the CRASH-3 IBMS would have resulted in a large amount of measurement error and so this outcome was dichotomized. Alternative automated imaging methods and/or cerebral micro-dialysis would provide a more accurate assessment of the effects of TXA on neuro-inflammation after TBI.

with severe GCS is greater in the overall population compared to those with both pre-randomisation and post-randomisation scans (65% vs. 62%).

Table 13. Baseline demographic and characteristics in patients scanned before and after randomisation.

	All patients (n=812)	TXA group (n=399)	Placebo group (n=413)
Sex			
Male	663 (82%)	319 (80%)	344 (83%)
Female	149 (18%)	80 (20%)	69 (17%)
Age			
Median (IQR) age in years	44 (29 - 62)	45 (29 - 62)	43 (28 - 61)
Glasgow coma score (GCS)			
Mild (13-15)	64 (8%)	32 (8%)	32 (8%)
Moderate (9-12)	242 (30%)	115 (29%)	127 (31%)
Severe (3-8)	506 (62%)	252 (63%)	254 (62%)
Median (IQR) GCS	7 (3 - 10)	7 (3 - 10)	7 (3 - 11)
Pupil reaction			
Both react	652 (80%)	318 (80%)	334 (81%)
One reacts	68 (8%)	35 (9%)	33 (8%)
None react	66 (8%)	32 (8%)	34 (8%)
Unable to assess	25 (3%)	13 (3%)	12 (3%)
Unknown	1 (<1%)	1 (<1%)	-
Systolic blood pressure			
< 90	7 (1%)	2 (1%)	5 (1%)
90 – 119	185 (23%)	94 (24%)	91 (22%)
≥ 120	618 (76%)	302 (76%)	316 (77%)
Unknown	2 (<1%)	1 (<1%)	1 (<1%)
Median (IQR) systolic blood pressure	133 (120 - 153)	133 (120 - 153)	134 (120 - 152)
Hours since injury			
≤1	15 (2%)	6 (2%)	9 (2%)
>1 to ≤3	530 (65%)	255 (64%)	275 (67%)
>3	267 (33%)	138 (35%)	129 (31%)
Pre-randomisation CT Scan			
Yes	812 (100%)	399 (100%)	413 (100%)
Median (IQR) hours from injury to scan	1.8 (1.5 – 2.3)	1.8 (1.5 – 2.4)	1.8 (1.4 – 2.3)

Data are n (%) of participants, unless otherwise indicated.

3.13 Secondary analysis: effect of TXA on new haemorrhage

A total of 39% of patients (n=318/812) presented with a new haemorrhage (seen post- but not pre-randomisation): IPH was the most common type of new haemorrhage (n=58%), followed by IVH (n=28%), SDH (17%), EDH (6%) and SAH (6%). A total of 15% of patients with new haemorrhage presented with more than one type of new haemorrhage. In those with a new IPH, more patients had a severe GCS (3-8) at baseline compared to moderate to mild GCS (66% vs 34%). The same pattern was seen in those with a new IVH (69% vs 31%), new SDH (62% vs 38%), new EDH (75% vs 25%) and new SAH (55% vs 45%).

In those with a severe GCS (3-8) at baseline (n=506/812), 24% went on to have a new IPH (n=122), 12% had a new IVH, 7% had a new SDH (n=33), 3% had a new EDH (n=15) and 2% had a new SAH (n=11). In those with bilateral unreactive pupils at baseline (n=66/811), 30% had a new IPH (n=20), 14% had a new IVH (n=9), 8% had a new SDH (n=5), 2% had a new EDH (n=1) and 2% had a new SAH (n=1). In those with unilateral unreactive pupils at baseline (n=68/811), 24% had a new IPH (n=16), 13% had a new IVH (n=9), 9% had a new SDH (n=6), 3% had a new EDH (n=2) and 12% had a new SAH (n=8).

The effect of TXA on new haemorrhage was examined using RRs and 95% CIs. A total of 36% of patients in the TXA group (n=144/319) had evidence of new haemorrhage post-randomisation and 42% in the placebo group (n=174/413). There is no clear evidence for a reduction in new haemorrhage with TXA: RR=0.86, 95% CI (0.72 – 1.02), p=0.079. But when patients with bilateral unreactive pupils at baseline are excluded, there is some evidence for a reduction in new haemorrhage with TXA (35% vs 42%): RR=0.83, 95% CI (0.69 – 1.00), p=0.048. When patients with unilateral or bilateral unreactive pupils at baseline are excluded, there is some evidence for a 20% reduction in new haemorrhage with TXA (33% vs 40%): RR=0.80, 95% CI (0.66 – 0.98), p=0.033.

There is no clear evidence for a reduction in new haemorrhage with TXA in those treated within 3 hours of injury (41% vs 45%; RR=0.91, 95% CI (0.75 – 1.10), p=0.343) or after 3 hours of injury (26% vs 35%; RR=0.75 (0.52 – 1.08), p=0.121). After the analyses are adjusted for GCS score, pupil reaction, systolic blood pressure, site, age, and time from injury to the pre-randomisation scan, there is no evidence for a treatment effect in those randomised within 3 hours of injury (41% vs 45%; RR=0.89, 95% CI (0.73 – 1.08), p=0.224). There is some evidence for a treatment effect in those randomised after 3 hours of injury (26% vs 35%; RR=0.69, 95% CI (0.48 – 0.99), p=0.044).

Adjustment does not provide clear evidence for a treatment effect in all patients (36% vs 42%; RR=0.85 (0.72 – 1.01), p=0.069) but some evidence when excluding those with unilateral or bilateral unreactive pupils at baseline (33% vs 40%; RR=0.80, 95% (0.66 – 0.98), p=0.030).

All point estimates are less than 1 and so in the direction of a reduction in new haemorrhage with TXA, but imprecise (see Table 14).

3.14 Secondary analysis: effect of TXA on progressive haemorrhage

The effect of TXA on progressive haemorrhage was examined using RRs and 95% CIs. A total of 29% of patients had evidence of progressive haemorrhage in the TXA group (n=115/399) and 31% in the placebo group (n=130/413). There is no clear evidence for a reduction in progressive haemorrhage with TXA: RR=0.92, 95% CI (0.74 – 1.13), p=0.411. There is no clear evidence for a treatment effect in those randomised within 3 hours of injury (29% vs 31%; RR=0.94, 95% CI (0.73 – 1.22), p=0.636) or after 3 hours of injury (28% vs 33%; RR=0.87, 95% CI (0.60 – 1.25), p=0.447). There is no clear evidence for a reduction in progressive haemorrhage with TXA after excluding patients with bilateral unreactive pupils at baseline (29% vs 32%; RR=0.88, 95% CI (0.71 – 1.10), p=0.256), and unilateral or bilateral unreactive pupils at baseline (28% vs 32%; RR=0.86, 95% CI (0.69 – 1.09), p=0.216). Adjustment for GCS score, pupil reaction, systolic blood pressure, site, age, and time from injury to the pre-randomisation scan, does not affect the treatment effect estimates when excluding patients with bilateral unreactive pupils: RR=0.89, 95% CI (0.71 – 1.10), p=0.283; or when excluding patients with unilateral or bilateral unreactive pupils: RR=0.87, 95% CI (0.69 – 1.10), p=0.242).

3.15 Secondary analysis: effect of TXA on new and progressive haemorrhage in non-neurosurgery patients

The appearance of new intra-cranial haemorrhage on post-randomisation CT may reflect a complication of neurosurgery and not the effect of TXA. Therefore, the effect of TXA on new and progressive haemorrhage was re-examined after excluding patients who underwent neurosurgical haemorrhage evacuation. These sensitivity analyses provided no evidence that TXA reduces the occurrence of new and progressive haemorrhage in patients who did not undergo neurosurgical haemorrhage evacuation (see Table 14). However, the decision for neurosurgery can happen after randomisation and so could be affected by the receipt of TXA. If TXA reduces bleeding and the need for neurosurgery, then by excluding neurosurgery patients, these analyses may include a larger proportion of TXA treated patients. Therefore, these outcomes should be interpreted with caution.

Table 14. Effect of TXA on new and progressive haemorrhage.

	TXA group	Placebo group	RR (95% CI)	p value (two-tailed)
New bleeds (unadjusted)				
≤3 hours since injury	108 / 261 (41%)	129 / 284 (45%)	0.91 (0.75 – 1.10)	0.343
>3 hours since injury	36 / 138 (26%)	45 / 129 (35%)	0.75 (0.52 – 1.08)	0.121
All patients	144 / 399 (36%)	174 / 413 (42%)	0.86 (0.72 – 1.02)	0.079
<i>Exclude unreactive pupils (both)</i>	127 / 367 (35%)	158 / 379 (42%)	0.83 (0.69 – 1.00)	0.048
<i>Exclude unreactive pupils (one/both)</i>	108 / 332 (33%)	140 / 346 (40%)	0.80 (0.66 – 0.98)	0.033
<i>Exclude neurosurgery patients</i>	81 / 276 (29%)	101 / 290 (35%)	0.84 (0.66 – 1.07)	0.165
New bleeds (adjusted for GCS, pupil reaction, systolic blood pressure, site, age, and time from injury to pre-randomisation scan)				
≤3 hours since injury	108 / 261 (41%)	129 / 284 (45%)	0.89 (0.73 – 1.08)	0.224
>3 hours since injury	36 / 128 (26%)	45 / 129 (35%)	0.69 (0.48 – 0.99)	0.044
All patients	144 / 399 (36%)	174 / 413 (42%)	0.85 (0.72 – 1.01)	0.069
<i>Exclude unreactive pupils (both)</i>	127 / 367 (35%)	158 / 379 (42%)	0.83 (0.70 – 1.00)	0.052
<i>Exclude unreactive pupils (one/both)</i>	108 / 332 (33%)	140 / 346 (40%)	0.80 (0.66 – 0.98)	0.030
<i>Exclude neurosurgery patients</i>	81 / 276 (29%)	101 / 290 (35%)	0.80 (0.63 – 1.02)	0.069
Progressive bleeds (unadjusted)				
≤3 hours since injury	76 / 261 (29%)	88 / 284 (31%)	0.94 (0.73 – 1.22)	0.636
>3 hours since injury	39 / 138 (28%)	42 / 129 (33%)	0.87 (0.60 – 1.25)	0.447
All patients	115 / 399 (29%)	130 / 413 (31%)	0.92 (0.74 – 1.13)	0.411
<i>Exclude unreactive pupils (both)</i>	105 / 367 (29%)	123 / 379 (32%)	0.88 (0.71 – 1.10)	0.256
<i>Exclude unreactive pupils (one/both)</i>	92 / 332 (28%)	111 / 346 (32%)	0.86 (0.69 – 1.09)	0.216
<i>Exclude neurosurgery patients</i>	91 / 276 (33%)	98 / 290 (34%)	0.98 (0.77 – 1.23)	0.836
Progressive bleeds (adjusted for GCS, pupil reaction, systolic blood pressure, site, age, and time from injury to pre-randomisation scan)				
≤3 hours since injury	76 / 261 (29%)	88 / 284 (31%)	0.92 (0.72 – 1.19)	0.533
>3 hours since injury	39 / 138 (28%)	42 / 129 (33%)	0.86 (0.58 – 1.28)	0.457
All patients	115 / 399 (29%)	130 / 413 (31%)	0.91 (0.74 – 1.13)	0.409
<i>Exclude unreactive pupils (both)</i>	105 / 367 (29%)	123 / 379 (32%)	0.89 (0.71 – 1.10)	0.283
<i>Exclude unreactive pupils (one/both)</i>	92 / 332 (28%)	111 / 346 (32%)	0.87 (0.69 – 1.10)	0.242
<i>Exclude neurosurgery patients</i>	91 / 276 (33%)	98 / 290 (34%)	0.97 (0.76 – 1.22)	0.770

4 MISSING PRE-RANDOMISATION OR POST-RANDOMISATION SCANS

This section will explore the occurrence of missing scans, which are scans not done pre-randomisation or post-randomisation. If scans were done pre-randomisation and post-randomisation in all patients, this would mean that baseline adjustment were possible in all patients and outcomes could be examined in all patients (improving statistical power and reducing bias). However, because all data in the IBMS are from routinely collected brain imaging, not all patients require or have the opportunity to have scans done pre-randomisation and post-randomisation into the CRASH-3 trial. If scans were mandated in the study protocol, this would reduce the occurrence of missing scans in less severely injured patients who would otherwise not require a clinical scan, but there would still be missing scans in those who die before the opportunity for a post-randomisation scan. In this chapter, I consider whether the occurrence of missing scans is related to the CRASH-3 trial treatment, and if so, the extent to which this may bias the treatment effect estimates.

4.1 Examination of pre-randomisation scan missingness by injury severity

Part of the eligibility criteria for randomisation into the CRASH-3 trial was that patients must have a GCS score of ≤ 12 or evidence of intracranial bleeding on a pre-randomisation CT scan. Because the eligibility criteria for the IBMS was amended to only include patients with a GCS ≤ 12 (to reduce missing scans from mildly injured patients), many patients in the IBMS did not have a pre-randomisation CT scan done. Specifically, 35% of patients in the IBMS did not have a pre-randomisation scan done (n=615/1767).

In those with missing pre-randomisation scans, 71% had a severe GCS (n=434/615) and 29% had a moderate GCS (n=181/615). There were no missing pre-randomisation scans in those with a mild GCS (n=0/92). In addition, in those with missing pre-randomisation scans, 15% had bilateral unreactive pupils (n=91/615), 17% had unilateral unreactive pupils (n=105/615), and 67% have bilateral reactive pupils (n=409/615). Pupil reaction could not be assessed in 2% of patients with missing pre-randomisation scans (n=10/615). Most patients without pre-randomisation scans were randomised within 3 hours of injury (n=580; 94%) compared to more than 3 hours of injury (n=35; 6%).

Table 15 presents the baseline clinical presentations and occurrence of head injury death in patients with a pre-randomisation scan compared to patients without a pre-randomisation scan.

Table 15. Baseline clinical presentation and head injury death in patients with a pre-randomisation scan compared to patients without a pre-randomisation scan.

	Patients <u>with</u> pre-randomisation scan (n=1147/1767)	Patients <u>without</u> pre-randomisation scan (n=615/1767)
Glasgow Coma Score (GCS)		
Mild (13-15)	92 (8%)	0
Moderate (GCS 9-12)	348 (30%)	181 (29%)
Severe (GCS 3-8)	707 (62%)	434 (71%)
GCS 3	397 (35%)	181 (29%)
Pupil reaction		
Both react	877 (76%)	409 (67%)
One reacts	95 (8%)	105 (17%)
None react	141 (12%)	91 (15%)
Unable to assess	33 (3%)	10 (2%)
Time from injury to randomisation		
<=3 hours	768 (67%)	580 (94%)
>3 hours	379 (33%)	35 (6%)
Head injury death	250 (22%)	156 (25%)

Compared to patients with a pre-randomisation scan, a larger proportion of patients without a pre-randomisation scan have a GCS score of 3-8 (62% vs 71%), unilateral unreactive pupils (8% vs 17%) and bilateral unreactive pupils (12% vs 15%). Pupil reaction could not be assessed in a similar proportion of patients with or without a pre-randomisation scan (3% vs 2%). A larger proportion of patients who did not have a pre-randomisation scan were randomised within 3 hours of injury (67% vs 94%). Furthermore, a larger proportion of patients without a pre-randomisation scan subsequently died from head injury (22% vs 25%).

Missing data from scans not done before randomisation reduces the precision of treatment effect estimates because it is not possible to adjust for between patient variability at baseline, in terms of intracranial bleeding and other neuropathologies seen on CT. This reduces statistical power to observe a treatment effect if it exists, but it does not introduce bias as these scans are done before randomisation and therefore cannot be affected by TXA. The occurrence of missing pre-randomisation scans is approximately balanced between treatment groups (36% TXA group, 34% placebo group) and there is no evidence that TXA increases the risk of not having a pre-randomisation scan done: RR=1.04, 95% CI (0.91 – 1.18), p=0.583. Table 16 describes the occurrence of missing pre-randomisation scans by baseline injury severity and split by treatment group.

Table 16. Baseline injury severity by treatment group in patients not scanned pre-randomisation.

	TXA group	Placebo group	RR (95% CI)	p value (two-tailed)
No pre-randomisation scan	313 / 881 (36%)	302 / 881 (34%)	1.04 (0.91 – 1.18)	0.583
<i>Glasgow Coma Score (GCS)</i>				
Mild (13-15)	0 / 47 (51%)	0 / 45 (49%)	-	-
Moderate (GCS 9-12)	93 / 261 (36%)	88 / 268 (33%)	1.09 (0.86 – 1.37)	0.499
Severe (GCS 3-8)	220 / 573 (38%)	214 / 568 (38%)	1.02 (0.88 – 1.18)	0.803
<i>Pupil reaction</i>				
Both react	209 / 635 (33%)	200 / 651 (31%)	1.07 (0.91 – 1.26)	0.399
One reacts	47 / 96 (49%)	58 / 104 (56%)	0.88 (0.67 – 1.15)	0.339
None react	50 / 124 (40%)	41 / 108 (38%)	1.06 (0.77 – 1.47)	0.715
Unable to assess	7 / 25 (28%)	3 / 18 (17%)	1.68 (0.49 – 5.71)	0.406

In those with severe GCS, 38% did not have a pre-randomisation scan in the TXA group and 38% in the placebo group. There is no evidence that TXA increases the risk of not having a pre-randomisation scan done in those with severe GCS: RR=1.02, 95% CI (0.88 – 1.18), p=0.803. In those with bilateral unreactive pupils, 40% did not have a pre-randomisation scan done in the TXA group and 38% in the placebo group. There is no evidence that TXA increases the risk of not having a pre-randomisation scan done in those with bilateral unreactive pupils: RR=1.06, 95% CI (0.77 – 1.47), p=0.715. The occurrence of missing pre-randomisation scans appears to be balanced between treatment groups.

4.2 Examination of post-randomisation scan missingness by injury severity

A total of 19% of patients were not scanned post-randomisation (n=335/1767). If patients who are lost from a study are a random sample of all patients in the study (i.e. missing completely at random), missing post-randomisation data from patients who are lost will reduce the precision of an analysis but not increase the risk of bias ¹⁸¹. In Table 17, I compared the baseline characteristics and outcomes of patients with post-randomisation scans against those without post-randomisation scans to help identify any patterns in the occurrence of missing post-randomisation scans.

Table 17. Baseline injury severity and head injury death in patients scanned post-randomisation compared with patients not scanned post-randomisation.

	Patients <u>with</u> post-randomisation scan (n=1431/1767)	Patients <u>without</u> post-randomisation scan (n=335/1767)
Glasgow Coma Score (GCS)		
Mild (GCS 13-15)	64 (4%)	28 (8%)
Moderate (GCS 9-12)	425 (30%)	106 (32%)
Severe (GCS 3-8)	942 (66%)	201 (60%)
GCS 3	459 (32%)	120 (36%)
Pupil reaction		
Both react	1,064 (74%)	224 (67%)
One reacts	174 (12%)	28 (8%)
None react	157 (11%)	75 (22%)
Unable to assess	35 (2%)	8 (2%)
Time from injury to randomisation		
<=3 hours	1,126 (79%)	223 (67%)
>3 hours	305 (21%)	112 (33%)
Head injury death	278 (19%)	128 (38%)

Compared to those with a post-randomisation scan, those without a post-randomisation scan appear less severely injured according to their GCS group (see Table 17). But the proportion of patients who had a GCS score of 3 was greater in those without a post-randomisation scan (32% vs 36%). The proportion of patients with bilateral unreactive pupils at baseline is greater in those without a post-randomisation scan (11% vs 22%). Furthermore, a larger proportion of patients without a post-randomisation scan subsequently died from their head injury compared to those who were scanned post-randomisation and then died from head injury (38% vs 19%). Compared to those without a post-randomisation scan, a larger proportion of patients with a post-randomisation scan were randomised within 3 hours of injury (67% vs 79%).

Injury severity may partly explain why some post-randomisation scans were not done, in that those not scanned post-randomisation seem to be more severely injured at baseline compared to those scanned post-randomisation. The CRASH-3 trial found that the effect of TXA on head injury death depended partly on baseline injury severity (as indicated by GCS score and pupil reaction). It is possible that the post-randomisation scan information, which was not available in more severely injured patients who often died, and not collected in mildly injured patients, may impact treatment effect estimates in the IBMS, and therefore affect the extent to which the IBMS can help explain the results of the CRASH-3 trial.

If TXA reduces intracranial haemorrhage expansion and the risk of death, patients who receive TXA may be more likely to be scanned post-randomisation compared to those who receive placebo. On the other hand, if TXA reduces or prevents intracranial haemorrhage expansion, post-

randomisation scanning may not be clinically indicated in these patients. A total of 19% of patients in the TXA group were not scanned post-randomisation (n=169/884) and 19% in the placebo group (n=166/882). There is no evidence that TXA increases the risk of having a missing post-randomisation scan: RR=1.02, 95% CI (0.84 – 1.23), p=0.874. Table 18 describes the occurrence of missing post-randomisation scans by baseline injury severity and split by treatment group.

Table 18. Baseline injury severity by treatment group in patients with missing post-randomisation scans.

	TXA group	Placebo group	RR (95% CI)	p value (two-tailed)
No post-randomisation scan	169 / 884 (19%)	166 / 882 (19%)	1.02 (0.84 – 1.23)	0.874
<i>Glasgow Coma Score (GCS)</i>				
Mild (GCS 13-15)	15 / 47 (32%)	13 / 45 (29%)	1.10 (0.59 – 2.06)	0.754
Moderate (GCS 9-12)	53 / 264 (20%)	53 / 267 (20%)	1.01 (0.72 – 1.42)	0.948
Severe (GCS 3-8)	101 / 573 (18%)	100 / 570 (18%)	1.00 (0.78 – 1.29)	0.971
<i>Pupil reaction</i>				
Both react	108 / 637 (17%)	116 / 651 (18%)	0.95 (0.75 – 1.21)	0.683
One reacts	14 / 97 (14%)	14 / 105 (13%)	1.08 (0.54 – 2.16)	0.822
None react	42 / 124 (34%)	33 / 108 (31%)	1.11 (0.76 – 1.62)	0.592
Unable to assess	5 / 25 (20%)	3 / 18 (17%)	1.20 (0.32 – 4.46)	0.785

There is no evidence that TXA increases the risk of having a missing post-randomisation scan in those with mild GCS (32% vs 29%), moderate GCS (20% vs 20%), severe GCS (18% vs 18%), bilateral reactive pupils (17% vs 18%), unilateral reactive pupils (14% vs 13%) or bilateral unreactive pupils (34% vs 31%) – see Table 18. There does not appear to be imbalance in the occurrence of missing post-randomisation scans between treatment groups.

4.3 Impact of missingness on treatment effect estimates

To explore the impact, if any, of missing outcomes on treatment effect estimates, best-worst and worst-best sensitivity analyses were done to further explore the effect of TXA on new haemorrhage, progressive haemorrhage, and cerebral infarction. For dichotomous outcomes, the best-worst scenario assumes that all patients who were not scanned post-randomisation in the TXA group did not have the bad outcome of interest and all patients not scanned post-randomisation in the placebo group had this outcome. The worst-best scenario assumes that all patients not scanned post-randomisation in the TXA group had the bad outcome and all patients not scanned post-randomisation in the placebo group had the good outcome.

Cerebral infarction

In the best-worst scenario, it was assumed that all patients without a post-randomisation scan in the TXA group *did not* have infarction, whereas all patients without a post-randomisation scan in the placebo group *did* have infarction. In this hypothetical scenario, 10% of patients in the TXA group (n=89/884) and 27% of patients in the placebo group (n=236/883) had infarction. If this scenario were true, there would be evidence that TXA reduces the risk of infarction: RR=0.38, 95% CI (0.30 – 0.47), p<0.0001.

In the worst-best scenario, it was assumed that all patients without a post-randomisation scan in the TXA group *did* have infarction, whereas all patients without a post-randomisation scan in the placebo group *did not* have infarction. In this hypothetical scenario, 29% of patients in the TXA group (n=258/884) and 8% in the placebo group (n=70/883) had infarction. If this scenario were true, there would be evidence that TXA increases the risk of infarction: RR=3.68, 95% CI (2.88 – 4.71), p<0.0001.

New bleeding

In the best-worst scenario, it is assumed that all patients without a post-randomisation scan in the TXA group *did not* have new bleeding, whereas all patients without a post-randomisation scan in the placebo group *did* have new bleeding. In this hypothetical scenario, 17% of patients in the TXA group (n=154/884) and 39% of patients in the placebo group (n=341/883) had new bleeding. If this scenario were true, there would be evidence that TXA reduces the risk of new bleeding: RR=0.45, 95% CI (0.38 – 0.53), p<0.0001.

In the worst-best scenario, it is assumed that all patients without a post-randomisation scan in the TXA group *did* have new bleeding, whereas all patients without a post-randomisation scan in the placebo group *did not* have new bleeding. In this hypothetical scenario, 37% of patients in the TXA group (n=323/884) and 20% in the placebo group (n=175/883) had new bleeding: RR=1.84, 95% CI (1.57 – 2.16), p<0.0001.

Progressive bleeding

In the best-worst scenario, it is assumed that all patients without a post-randomisation scan in the TXA group *did not* have progressive bleeding, whereas all patients without a post-randomisation scan in the placebo group *did* have progressive bleeding. In this hypothetical scenario, 20% of patients in the TXA group (n=115/568) and 51% of patients in the placebo group (n=296/579) had progressive bleeding. If this scenario were true, there would be evidence that TXA reduces the risk of progressive bleeding: RR=0.40, 95% CI (0.33 – 0.47), p<0.0001.

In the worst-best scenario, it is assumed that all patients without a post-randomisation scan in the TXA group *did* have progressive bleeding, whereas all patients without a post-randomisation scan in the placebo group *did not* have progressive bleeding. In this hypothetical scenario, 50% of patients in the TXA group (n=284/568) and 22% in the placebo group (n=130/579) had progressive bleeding. If this scenario were true, there would be evidence that TXA increases the risk of progressive bleeding: RR=2.22, 95% CI (1.87 – 2.65), p<0.0001.

If best-worst and worst-best scenarios did not give contradicting results for progressive bleeding, new bleeding, and cerebral infarction outcomes, the impact of missing scans on the effect of TXA on each of these outcomes may have been negligible¹⁸³. But because these scenarios give qualitatively different results in that the widest possible range of uncertainty spans benefit and harm, it is difficult to conclude what effect TXA has on any of these outcomes. This method may be useful in a study with a small amount of missing data where best-worst and worst-best scenarios would provide a narrower and more meaningful range of uncertainty. 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 scans¹⁸³.

5 CRITIQUE AND RECOMMENDATIONS

In this final chapter, I consider why the CRASH-3 IBMS was done and why the chosen methods may not provide valid and precise estimates of the effects of TXA. I reflect on the limits of this trial in the context of previous trials. I finish by considering the implications for research and practice.

5.1 Mechanism of action of TXA in traumatic brain injury

The CRASH-3 trial and IBMS were motivated by the premise that intracranial haemorrhage contributes to head injury death in patients with TBI. By inhibiting fibrinolysis, TXA may slow the rate of intracranial haemorrhage. The CRASH-3 trial hypothesised that TXA may prevent or reduce intracranial haemorrhage, which could in turn reduce the risk of death and disability^{109, 193}. The CRASH-3 trial was done in 12,737 TBI patients¹²¹. When patients with a GCS score of 3 or bilateral unreactive pupils at baseline are excluded, there is evidence that TXA reduces the risk of head injury death (RR 0.89 [95% CI 0.80–1.00]). TXA reduces the risk of head injury death by 22% in patients with mild to moderate GCS (RR=0.78, 95% CI 0.64-0.95). Early treatment is more effective than late treatment in this group ($p=0.005$). But there is no apparent reduction in head injury death in patients with severe GCS (RR=0.99, 95% CI 0.91-1.07), regardless of the time from injury to randomisation ($p=0.73$). Because the aim of the CRASH-3 trial was to assess the effect of TXA on head injury death, to simplify the trial procedures, the investigators did not collect CT scan data on the amount of intracranial haemorrhage in all patients. The occurrence of thromboembolic events, including stroke, were appropriately assessed using clinical outcomes. In the CRASH-3 IBMS, I examined routinely collected brain imaging (mainly CT scans) from 14% of CRASH-3 trial patients to see if TXA reduces intracranial bleeding and/or increases cerebral infarction¹²³.

5.2 Criteria for valid and precise treatment effect estimates

To provide valid and precise estimates of the effect of TXA on intracranial bleeding and infarction, the CRASH-3 IBMS must satisfy key criteria. We should randomly allocate a very large number of patients (with good allocation concealment) to receive TXA or placebo, and then obtain precise measures of the extent of intracranial bleeding and infarction in all randomised patients, with no loss to follow-up.

The treatment allocation sequence should be randomly generated and concealed to prevent bias¹⁹⁴. Random allocation should ensure that the two groups are similar at baseline¹¹⁵. This can be examined using a table of baseline characteristics of all randomised patients split by treatment group. This should provide an indication of whether randomisation produced two groups that are

similar apart from the treatment allocation. Problems in the randomisation process may be indicated by differences in the expected size of treatment groups, imbalance in key prognostic factors, or excessive similarity in baseline characteristics between treatment groups ¹⁹⁵. Adjusting for factors that are imbalanced between treatment groups does not mitigate failures of randomisation. However, if the randomisation process is not at risk of bias, and baseline differences between treatment groups arise by chance (e.g. if the sample is small), adjusting for baseline values of the relevant factors can improve the precision of the effect estimates. Furthermore, at baseline some patients may have very large bleeds whilst others have small bleeds in each treatment group. Adjusting for between patient variability in the analysis may lead to an increase in statistical power to detect a treatment effect if it exists ¹⁷⁵.

If there are missing outcomes, this must be minimal so that they could not make an important difference to the estimated effect of TXA ¹⁹⁵. A large proportion of missing outcomes would reduce power, and could bias the treatment effect estimates, especially if the trial treatment affected whether the outcomes were observed ¹⁸¹. Examples of large randomised trials at low risk of bias are CRASH, CRASH-2, CRASH-3 and WOMAN trials ^{35, 91, 121, 196}. These trials have minimal loss to follow-up and so provide valid estimates of the effect of TXA on outcomes like death that can be accurately measured.

5.3 Why might the CRASH-3 IBMS not provide valid and precise treatment effect estimates?

Small sample size

The sample size calculation is based on a specific difference in intracranial haemorrhage volume between treatment groups. If receiving TXA results in a smaller reduction in haemorrhage volume than assumed, this trial may be too small to detect it. Furthermore, the sample size calculation does not account for the impact of non-differential misclassification and baseline unsurvivability, which bias any treatment effect estimate towards the null. Therefore, even though this trial is larger than previous trials in this area, the sample size may still be too small to detect a clinically meaningful difference in haemorrhage volume between treatment groups.

It is logistically difficult to conduct a large randomised trial using imaging outcomes because CT scanning, neuro-radiological expertise and data collection are expensive. Estimates vary but the average cost of a non-contrast CT head scan is around £100 in the NHS ¹⁹⁷ and £550 privately in the UK ¹⁹⁸. Therefore, it would cost between £200,000 and £1.1 million to scan 1,000 patients before and after randomisation. It would take around 4-6 months of full-time work for an experienced neuro-radiologist to rate the scans and complete entry and outcome forms for 1,000 patients. Using

the average yearly salary of an experienced neuro-radiologist, this would cost around £50,000 in the NHS or £100,000 privately in the UK ¹⁹⁹. If estimated costs are based on each individual scan report, the cost is likely to be substantially higher. This is partly why routinely collected CT scans were used in the CRASH-3 IBMS. But the examination of routinely collected data is also time consuming and intensive. I examined routinely collected data from 1,767 trial patients over a period of 3 years. I visited 14 different hospitals using a research passport and rated scans on hospital software in various offices I did not have priority to be in. I spent extended and often isolating placements in different locations in the UK and Malaysia.

Null bias

One third of patients included in the IBMS had a GCS score of 3 at baseline. The median baseline GCS score of all patients is 7 (IQR 3 to 10). A total of 24% of patients had unilateral or bilateral unreactive pupils at baseline. Therefore, a large proportion of patients included in the IBMS had severe (and possibly unsurvivable) head injuries before they were randomised into the CRASH-3 trial. The baseline CT data suggest that patients with severe GCS and/or unreactive pupils have more extensive intracranial bleeding (and other intracranial pathologies) compared to those with moderate to mild GCS and/or reactive pupils. TXA may have had less potential to prevent intracranial haemorrhage progression in severely injured patients, and their inclusion may have diluted any treatment effect towards the null.

Because sites could randomise patients before a CT scan was done if the patient had a GCS score of 12 or less, many patients had their admission scan done very soon after randomisation. If patients had another scan done closer to 24 hours after randomisation, the later scan would be chosen as the post-randomisation scan. However, if the early scan was the only scan the patient had done after randomisation, it would be rated as the post-randomisation scan. A total of 17% of patients who had a post-randomisation scan had their scan done within 1 hour of randomisation (n=248). A total of 98% of these patients did not have a pre-randomisation scan. Figure 19 shows the distribution of the time from randomisation to the post-randomisation scan in patients who had their scan done within 48 hours of randomisation.

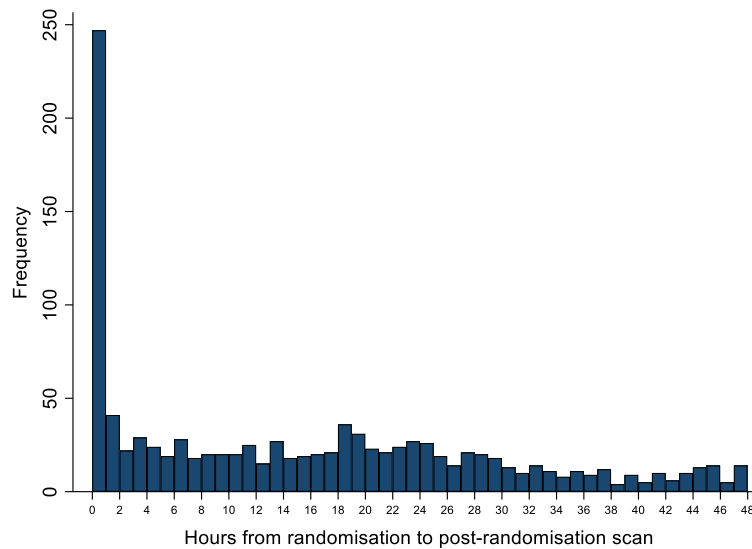


Figure 19. Time from randomisation to scan in patients scanned within 48 hours of randomisation.

Any effect of TXA may not have had sufficient opportunity to manifest on a CT scan done within minutes to a few hours after randomisation. Furthermore, patients who had their post-randomisation scan done this soon after randomisation were more severely injured than those who survived to the point of a later post-randomisation scan. A larger proportion of patients who had their post-randomisation scan done within an hour of randomisation (compared to >1h post-randomisation) had a GCS score of 3 (40% vs 30%), unilateral or bilateral unreactive pupils (33% vs 21%) and subsequently died from head injury (30% vs 17%). The inclusion of these patients may have diluted any treatment effect towards the null.

TXA might make bleeds more visible on CT

CT imaging may not be a valid method to examine whether TXA reduces intracranial haemorrhage. The appearance of intracranial haemorrhage on CT is determined by blood clot density changes over time ^{31, 200}. These physical density changes reflect clot formation, clot retraction, clot lysis and tissue loss ²⁰⁰. In the hyper-acute stage of injury, blood leaves the vascular system (extravastation). Post-traumatic hyper-acute intracranial bleeding has not yet clotted and so it has the same density as blood flowing through cerebral vessels on non-contrast enhanced CT ³¹. Therefore, hyper-acute bleeding does not have a distinct appearance on CT ³¹. Some hyper-acute bleeds have a mixed density appearance, as the complex mass of red blood cells, white blood cells and platelets is forming ²⁰⁰. Patients with mixed density bleeds may be actively bleeding whilst being scanned ^{201, 202}. In the first few hours of injury, when the hospital admission CT scan is often done, the fibrin and globin (protein) mesh has had opportunity to form. In this acute bleeding phase, the clotted

blood is more dense than brain tissue and so has a marked white appearance on CT (i.e. the bleed appears hyper-dense) ^{31, 200}. Intracranial blood clots can break down gradually over days to weeks, and in this sub-acute to chronic phase may appear as a similar density to the adjacent brain tissue (i.e. the bleed appears iso-dense) ³¹. Hyper-acute and sub-acute bleeding can therefore be difficult to identify and measure on CT. Figure 20 illustrates the density of intracranial bleeding according to the age of the bleed ³¹.

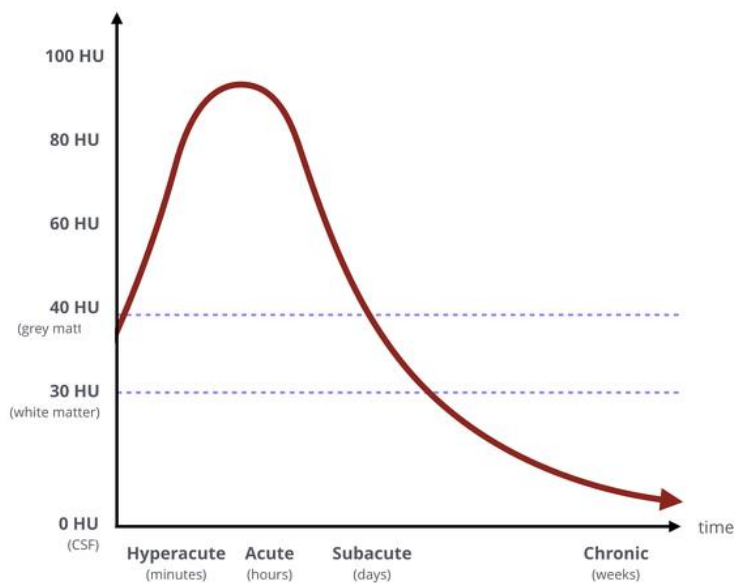


Figure 20. Density of intracranial bleeding (as indicated by Hounsfield Units, HU) by age of intracranial bleeding, on CT imaging. A higher HU value indicates more clotting. ^x

TXA inhibits the enzymatic breakdown of fibrin blood clots ⁷⁸. By inhibiting fibrinolysis and stabilizing the blood clot, TXA may make the appearance of intracranial haemorrhage on CT more apparent. If unclotted blood does not appear on CT in the hyper-acute phase of injury but bleeding clotted with TXA appears, the potential benefit of TXA in reducing early haemorrhage expansion may be indicated by the early *appearance* of intracranial haemorrhage on CT. But all studies in this area (including the CRASH-3 IBMS) hypothesised that a reduction in the appearance of intracranial haemorrhage with TXA would be considered evidence that TXA reduced intracranial haemorrhage ^{106, 107, 123, 203, 204}. In retrospect, imaging methods that use clot density to make bleeds visible may not be appropriate for the examination of the effects of TXA. This could help explain why no trial using CT data has clearly indicated that TXA reduces intracranial haemorrhage expansion.

^x Grey matter refers to neural cell bodies and unmyelinated axons, and white matter mainly refers to myelinated axons (that transmit signals to grey matter). Figure reproduced from Gaillard F et al. Intracranial haemorrhage. Radiopaedia; 2019. ³¹

If TXA reduces the need for neurosurgery, bleeding may appear to increase in TXA treated patients

A total of 21% of patients had neurosurgical haemorrhage evacuation before their post-randomisation scan. In these patients, it is not possible to separate the effect of TXA on intracranial haemorrhage from the effect of neurosurgery on intracranial haemorrhage. The haemorrhage seen on a post-randomisation and post-neurosurgery scan may reflect the combined effect of TXA and neurosurgical haemorrhage evacuation ²⁰⁵.

The decision for neurosurgery made after randomisation could be affected by the receipt of TXA. If TXA reduces intracranial haemorrhage, it may reduce the need for that haemorrhage to be surgically evacuated. Patients who receive placebo and go on to have their bleed evacuated may have less blood on their post-randomisation scan than those who receive TXA and then *do not* undergo neurosurgical haemorrhage evacuation. Therefore, TXA treated patients could present with more intracranial haemorrhage post-randomisation compared to placebo treated patients. But TXA is expected to reduce intracranial haemorrhage, and so such a finding would be difficult to interpret.

Outcomes were not accurately measured

The manual ABC/2 method of measuring haemorrhage volume was not validated in all types of intracranial haemorrhage that it was used for in the CRASH-3 IBMS (i.e. IVH) ^y. The accuracy of this method is reduced if bleeds are irregularly shaped or large ¹⁴⁶. The measurement of SDH was based on a novel approach developed by colleagues at the Queen Elizabeth Hospital in Birmingham. The rationale for this is that the ABC/2 method assumes bleeds are almost spherical but SDH is typically crescent shaped. Whilst this may be true, the reliability of their method for estimating SDH volume is to be confirmed. Finally, unclotted bleeding, micro-bleeding and infarction are not visible on CT done soon after injury ^{165, 200, 206-209}. Obviously, bleeds or infarcts that are not visible cannot be measured.

A progressive haemorrhage outcome may have limited clinical value

The clinical value of a progressive haemorrhage outcome is limited. This is often defined as any increase, or a 25% or 33% increase from pre- to post-randomisation. An apparent increase in haemorrhage between two scans may not be generalizable because this increase may have different clinical implications depending on the type of haemorrhage that expands. Even though SDH/EDH are typically larger than IPH/IVH, a 25% increase in SDH/EDH could be managed surgically in the

^y I believed that the ABC/2 method had been validated for the measurement of IVH, but I learnt whilst conducting the trial that I made an error when interpreting the results of one paper ¹⁴⁶. This paper reported the accuracy of ABC/2 compared to automated methods in IPH across several trials, one of which is called CLEAR-IVH. This trial included patients with both IPH and IVH, and ABC/2 was used for IPH but not IVH. Because I had already started using ABC/2 for the measurement of IVH when I learned this, I continued to use this method for all patients.

first few hours of injury with good prognostic outcome ^{61, 62}. In contrast, a 25% increase in IPH or IVH may have worse prognostic outcome ^{71, 72}.

Large proportion of missing outcomes

Outcome data could not be collected in all randomised patients, largely because not all patients required a post-randomisation scan or had the opportunity to have one because they had died. A total of 19% of randomised patients were not scanned post-randomisation. These missing outcomes could relate to whether a patient received TXA. We now know that TXA reduces the risk of head injury death, so TXA treated patients might not have needed a clinically indicated post-randomisation scan. Or they might have had one because they were alive and so available to be scanned. Absence of bias is not confirmed by the similar proportion of patients with missing post-randomisation scans in TXA and placebo groups ¹⁹⁵.

5.4 How have previous trials approached and reported these problems?

Please see Table 19 for the inclusion and exclusion criteria, and decisions to exclude patients after randomisation, in double-blind randomised trials in this area. Please see Table 20 for an assessment of their risk of bias across five domains: randomisation process, deviation from intended intervention, missing outcome data, outcome measurement, and selection of the reported results ¹⁹⁵.

Table 19. Inclusion/exclusion criteria & post-randomisation exclusions in randomised trials on effect of TXA on intracranial haemorrhage in TBI.

Perel et al, 2011	Effect of TXA in traumatic brain injury: a nested randomised, placebo controlled trial (CRASH-2 Intracranial Bleeding Study)
Inclusion criteria	Adult trauma patients with significant haemorrhage (systolic blood pressure <90 mm Hg or heart rate >110 beats per min, or both) or who were considered to be at risk of significant haemorrhage, and who were within 8 hours of injury - but they also had TBI (GCS ≤14 and a brain CT compatible with TBI)
Exclusion criteria	-
Post-randomisation exclusions	Pregnant women and patients for whom a second brain scan was not possible were excluded.
Yutthakasemsunt et al, 2013	TXA for patients with traumatic brain injury: a randomized, double-blinded, placebo-controlled trial
Inclusion criteria	All patients, older than 16 years, with moderate to severe TBI (post-resuscitation Glasgow Coma Scale (GCS) 4 to 12) who had a computerized tomography (CT) brain scan performed within eight hours of injury, and whom there was no immediate indication for surgery, were eligible for inclusion.
Exclusion criteria	Patients were excluded if they were pregnant, had evidences of coagulopathy, known to be receiving a medication which affects haemostasis, or had a serum creatinine over than 2 mg/decilitre. Coagulopathy was considered present if any of the following hematological parameters were observed: (1) platelet count less than 100,000 cells/mm ³ ; (2) Prothrombin time (PT) or international normalized ratio (INR) prolonged more than 1.5 times normal value; (3) activated partial thromboplastin time (aPTT) more than 10 seconds greater than normal value.
Post-randomisation exclusions	-
Fakharian et al, 2019	Effect of TXA on Prevention of Hemorrhagic Mass Growth in Patients with Traumatic Brain Injury
Inclusion criteria	Patients with isolated TBI or multiple trauma patients, with TBI as the main problem, who arrived at the hospital within 8 hours of trauma, aged 15 and older, with nonpenetrating injury and any kind of traumatic intracranial bleedings (subdural haemorrhage [SDH], subarachnoid hemorrhage, contusion, intraventricular hemorrhage, and epidural hematoma) in admission CT scans, no need for brain surgery during the first 8 hours, no coagulation disorder, serum creatinine <2 mg, and nonpregnancy were enrolled to the study.
Exclusion criteria	-
Post-randomisation exclusions	Major organ damage requiring surgical intervention within the first 8 hours, receiving any medication that disturbs homeostasis, those who do not have a secondary CT scan, and those who missed follow-up were excluded
May et al, 2019	Prehospital TXA Use for Traumatic Brain Injury
Inclusion criteria	Subjects for whom study drug administration was started and for whom two or more analyzable head CT scans were obtained prior to a hematoma evacuation.
Exclusion criteria	-
Post-randomisation exclusions	Excluded subjects primarily include those who died or withdrew before an initial or second CT scan was taken, who had a hematoma evacuation prior to a second scan, or who had only one negative CT.

Mahmood et al, 2019	A nested randomised trial of the effect of TXA on intracranial haemorrhage and infarction in TBI (CRASH-3 trial intracranial bleeding mechanistic study).
Inclusion criteria	Patients eligible for the CRASH-3 trial, with a GCS of 12 or less or intracranial bleeding on a pre-randomisation CT scan.
Exclusion criteria	-
Post-randomisation exclusions	New and progressive haemorrhage outcomes exclude patients without both pre-randomisation and post-randomisation scans.

Table 20. Epidemiological risk of bias assessment in randomised trials: effect of TXA on intracranial haemorrhage in TBI.

Risk of bias domain	Risk of bias assessment (low risk, some concerns, high risk) in each trial				
	Perel et al (2011) n=270: TXA 133, Placebo 137	Yuttha... et al (2013) n=240: TXA 120, Placebo 120	Fakha... et al (2019) n=156: TXA 78, Placebo 78	May et al (2019) n=1,063: TXA 718, Placebo 345	Mahm... et al (2019) n=1,767: TXA 884, Placebo 883
Randomisation process ^z	Low	Low	High	<i>No information</i>	Low
Deviation from intended intervention ^{aa}	Low	Low	Some	<i>No information</i>	Low
Missing outcome data ^{bb}	Some (8%)	Some (4%)	Low (1%)	High (55%)	High (19%)
Measurement of outcome ^{cc}	High	High	High	High	High
Selection of the reported result ^{dd}	Low	Some	Low	Low	Low
Overall judgement	High	High	High	High	High

^z Random sequence generation, adequate allocation concealment, treatment groups similar at baseline, exclusions reported

^{aa} Double-blind, deviations unlikely to affect outcome, appropriate analysis

^{bb} Outcome data for all (or nearly all) randomised patients, no evidence that the result could be biased by missing outcome data

^{cc} Method of measuring outcome sensitive to plausible intervention effects, measurement instrument has demonstrated validity, measurement of outcome does not differ between treatment groups

^{dd} There are not multiple outcome measurements and multiple analyses of the data, all reported results correspond to pre-specified plan

Although I previously judged the two trials done before the CRASH-3 IBMS started to be at low risk of bias ²¹⁰, I now judge all trials in this area to be at least some risk of bias. This is because the effect of TXA may not manifest on CT in the way people expect (discussed above), all trials excluded randomised patients who did not have a post-randomisation scan, and some trials excluded randomised patients who had neurosurgery post-randomisation. The potential implications of these issues are discussed below.

The CRASH-2 Intracranial Bleeding Study (IBS) reported that 8% of randomised patients had missing post-randomisation scans and these patients were excluded from the analysis ¹⁰⁶. The trial reports that 24% of the missing scans (n=5/21) were due to death. The trial done in Thailand reports that 4% of patients had missing scans, most of whom died (n=7/9). The smaller trial done in Iran also excluded patients with missing post-randomisation scans, but reports a small proportion of missing scans (1%) and does not confirm if these patients died ²⁰³. This trial appears to be at risk of bias across several domains. For example, there is insufficient information to assess how the allocation sequence was generated and concealed, and it is not clear whether the study contributor who was responsible for assigning codes for TXA and placebo syringes was a trial investigator or independent of the trial. Furthermore, the trial done in Washington reports that patients who died before the opportunity for scanning were not included in the outcome on progressive haemorrhage ²⁰⁴. In all these trials, the availability of post-randomisation scans could depend on whether a patient was treated with TXA. Because exclusions were made on the basis of information known post-randomisation, the treatment effect estimates in these studies are at risk of bias.

Some trials tried to deal with the occurrence of neurosurgical haemorrhage evacuation after randomisation by excluding these patients from the study ^{203, 204}. In the CRASH-3 IBMS, I learnt that some patients do not show evidence of neurosurgery until a second post-randomisation scan, or later. Therefore, the decision for neurosurgery can happen after randomisation and so could be affected by the receipt of TXA. If TXA reduces intracranial haemorrhage, it could reduce the need for neurosurgery. Or TXA treated patients might survive to the point of a post-neurosurgery scan because TXA reduced the risk of head injury death ¹²¹. In these trials, randomised patients were excluded on the basis of a post-randomisation event, and this could bias the treatment effect estimates.

The CRASH-2 IBS and trials from Thailand and Iran reported a small proportion of missing post-randomisation scans (8%, 4%, 1%) compared to the Washington trial and CRASH-3 IBMS (55%, 19%). The CRASH-2 IBS, Thai and Iranian trials mandated that scans should be done after randomisation. This is a limitation of the CRASH-3 IBMS and Washington trial. In the CRASH-3 IBMS, we did not have post-randomisation data from patients with milder injuries who the CRASH-3 trial results suggest probably benefited from TXA. It is expensive to mandate post-randomisation scans in a research protocol, which is why it is often only done in

very small trials. Ideally, we would have a very accurate outcome measure in all patients randomised into a large trial. But we must often decide between a small study with a very accurate method or a larger study with a less accurate method. In the CRASH-3 IBMS we chose the latter because we prioritized a reduction in random error over measurement error. But this came at the expense of the methodological problems associated with routine imaging. Mandating post-randomisation scans can avoid some of the bias that comes with using routine imaging. But it is almost impossible to avoid the substantial risk of bias that results from missing outcome scans as a result of death and neurosurgery.

5.5 How can we learn from the CRASH-3 IBMS?

Based on my experience of conducting the CRASH-3 IBMS, I would not recommend that trials in this area use radiological outcomes, especially not those measured on routine imaging. This is because the effect of TXA may not manifest on brain imaging in the way people expect, and the availability of post-randomisation imaging probably depends on the trial treatment. The National Institutes of Health recently proposed guidelines on how “the link between prevention of haemorrhage growth [with haemostatic therapy] and clinical outcome” can be studied using radiological outcomes ²¹¹. I am sceptical about the use of using such outcomes for this purpose. Efforts should be focused on large randomised trials that do not measure intracranial haemorrhage but a clinically relevant proxy that can be accurately measured in all randomised patients (e.g. TBI death within 24 hours of injury).

If despite these recommendations, such radiological outcomes are used, there should be marked effort to reduce bias and random error for valid inference. A large high-quality randomised trial must be done where all randomised patients are scanned after randomisation. Inclusion should not be based on information known post-randomisation or restricted in terms of injury severity. A trial in a smaller proportion of severely injured patients overall would reduce the need for neurosurgery before the post-randomisation scan is done. It would also reduce missing post-randomisation scans as a result of death, thereby reducing bias from unobserved outcomes. The problem of missing post-randomisation scans in patients who do not require a clinical scan should be addressed by mandating that a post-randomisation scan is done at a set time point post-randomisation. Patients who will not be scanned after randomisation because they die could be scanned soon after death. Imaging has historically been used as part of the post-mortem procedure to determine who needs an autopsy ²¹². The neuropathology of deceased patients could provide an insight into whether a reduction in death due to head injury with TXA is due to a reduction in intracranial haemorrhage. If patients have neurosurgery, the time this decision is made must be recorded so investigators can explore the extent to which this biases treatment effect estimates. MRI should be used because it is more sensitive than CT in detecting

micro-bleeding²⁰⁸ and infarction^{165, 209}. Investigators should clearly report the number of randomised patients, the proportion of randomised patients with post-randomisation scans, and the proportion of randomised patients who have missing post-randomisation scans by treatment group. There should be a clear effort to explore and report why there are missing scans. There should be a thorough consideration of the implications of missing outcomes on the validity of treatment effect estimates, before any conclusions are drawn and recommendations are made.

5.6 Additional contribution to knowledge

The baseline CT data improves understanding of the neuropathological presentation of TBI patients. The existing knowledge on intracranial haemorrhage, and other features of TBI, is based on smaller studies with different and restrictive inclusion criteria. The larger sample and less restrictive inclusion criteria of the CRASH-3 IBMS allowed this study to explore the natural occurrence of intracranial pathologies at baseline. These data suggest that compared to patients with mild to moderate GCS and/or reactive pupils, patients with severe GCS and/or unreactive pupils often present with extensive intracranial bleeding and a number of other intracranial pathologies. Patients with a mild to moderate GCS may be more likely to benefit from TXA because they have less intracranial bleeding at baseline. However, because intracranial bleeding occurs soon after injury, treatment delay reduces the benefit. On the other hand, patients with a severe GCS have less to gain from treatment because they already have extensive intracranial bleeding at baseline and/or other intracranial pathologies that TXA cannot plausibly affect. This supports the decision to exclude very severely injured patients from the CRASH-3 trial primary analysis, and exploration of the treatment effect by baseline injury severity. This could help explain why the CRASH-3 trial found that TXA appears to be more effective in patients who were less severely injured at baseline, and ineffective (or less effective) in patients with more severe injuries. In some patients, the immediate neurologic damage from the trauma may have been too severe to be alterable. TXA may have had little potential to reduce intracranial haemorrhage progression and the risk of head injury death in these patients.

This has implications for practice. The CRASH-3 trial treatment was given after arrival in hospital. Less than 20% of patients were treated within an hour of injury¹²¹. If severely injured patients had already bled extensively by the point of hospital admission, and this is why there is no apparent reduction in head injury death in patients with severe GCS, a proportion of severely injured patients might have benefited if treated pre-hospital. In many high-income countries, TXA is routinely administered by paramedics at the scene of the injury to treat acute severe bleeding²¹³. In low-income and middle-income settings, this is not always possible due to resource constraints and a lack of health workers who can administer intravenous drugs in the pre-hospital setting²¹⁴. Alternatives to intravenous administration of TXA such as intramuscular

injection would be easier, require less training, and may reduce time to treatment ²¹⁵. However, patients with severe injuries in settings with insufficient in-hospital resources may die despite an early reduction in intracranial bleeding. Evidence suggests that patients with severe TBI in low- and middle-income settings may be more likely to die compared to those in high-income settings ²¹⁶. More rapid administration of TXA in settings with adequate medical care for patients with major trauma could increase the proportion of TBI patients who have the potential to benefit.

APPENDICES

Appendix 1. Research paper 1: Retention of copyright / permission to publish.



Does tranexamic acid improve outcomes in traumatic brain injury?

Author: Abda Mahmood, Ian Roberts, Haleema Shakur, Tim Harris, Antonio Belli

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UNCERTAINTIES

Does tranexamic acid improve outcomes in traumatic brain injury?

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Intracranial bleeding is common after traumatic brain injury, and the larger the bleed the greater the risk of death and disability.^{4,5} Bleeding continues after hospital admission in 84% of patients with moderate or severe injuries,^{6,7} and can continue for up to 24 hours.⁸ About one third of patients have laboratory evidence of abnormal coagulation.⁹ High levels of fibrin degradation products are seen within the first three hours.¹⁰ Such patients have a higher risk of intracranial haemorrhage and mortality.

Worldwide at least 200 per 100 000 people are killed or admitted to hospital each year after traumatic brain injury.¹ This results in more than 10 million deaths or hospital admissions.² In the UK, around one million people attend emergency departments every year with a traumatic brain injury.³

Tranexamic acid reduces bleeding by inhibiting the enzymatic breakdown of fibrin blood clots (fig 1). Tranexamic acid is used routinely in some cases of trauma and in surgery. For example, it reduces the need for blood transfusion in surgical patients.^{11,12} In trauma patients with extracranial haemorrhage:¹³

- Tranexamic acid treatment within an hour of injury reduces the risk of death caused by bleeding by about one third
- Treatment between one and three hours reduces the risk by about one fifth
- There is no apparent benefit after three hours, and tranexamic acid might even be harmful
- If tranexamic acid is effective after traumatic brain injury, it should also be most effective when given soon after injury, when intracranial bleeding is ongoing⁸
- The potential for harm also exists however
- Tranexamic acid may increase the risk of ischaemia and cerebral thrombosis because it inhibits fibrinolysis.¹⁵ Cerebral ischaemia is already a known risk after traumatic brain injury, which worsens neurological outcome and increases mortality.^{16,17} For example, raised intracranial pressure can lead to

WHAT YOU NEED TO KNOW

- The effectiveness and safety of tranexamic acid in traumatic brain injury are uncertain, although randomised trials are under way to investigate the problem
- Tranexamic acid could reduce intracranial bleeding but might increase the risk of cerebral thrombosis and ischaemia
- We believe that tranexamic acid should not be used in routine clinical practice unless these trials show benefit

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

No patients were involved in the writing of this article.

Patients are involved in the design and conduct of CRASH-3 and these were reflected in the trial procedures. Organisations advised the investigators on outcome measures that matter most to patients, such as fatigue. Organisations also represent patients on the trial steering committee and are involved in the ongoing supervision of the trial.

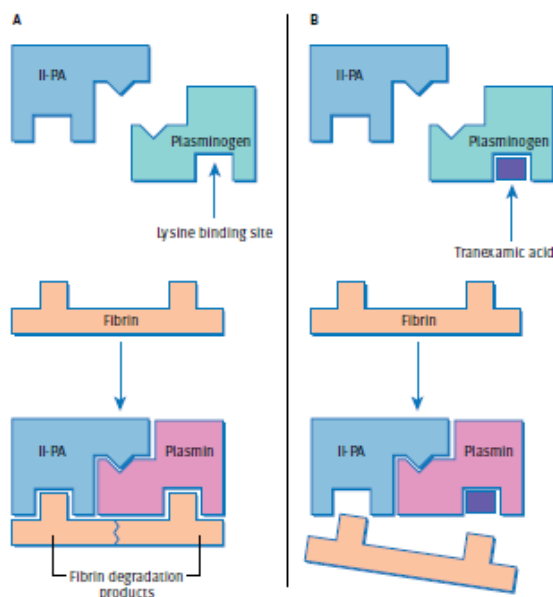


Fig 1 | A Normal fibrinolysis. B: Fibrinolysis inhibited by tranexamic acid. Plasmin binds to fibrin via lysine binding sites and then splits fibrin into fibrin degradation products. Tranexamic acid is a molecular analogue of lysine that inhibits fibrinolysis by reducing the binding of plasmin to fibrin

Table 1 | Patients with intracranial haemorrhage, cerebral ischaemia, and mortality outcomes in two randomised trials of tranexamic acid in patients with traumatic brain injury. Values are numbers (percentages) unless stated otherwise

Outcome	CRASH-2 intracranial bleeding substudy 2012 ²⁴			Yuthakasemsunt et al 2013 ²⁵		
	TXA	Placebo	Relative risk (95% CI)	TXA	Placebo	Relative risk (95% CI)
Intracranial haemorrhage	44 (36)	56 (44)	0.80 (0.59 to 1.09)	21 (18)	32 (27)	0.65 (0.40 to 1.05)
Focal ischaemic lesion/stroke	6 (5)	12 (9)	0.51 (0.20 to 1.32)	0	3 (3)	-
Deaths	14 (11)	24 (18)	0.60 (0.33 to 1.11)	12 (10)	17 (14)	0.69 (0.35 to 1.39)

Table 2 | Ongoing randomised trials of tranexamic acid use for traumatic brain injury

Trial	Trial type	Status	Proposed sample size	No of arms	Intervention	Comparison	Primary outcome	Secondary outcomes
Prehospital tranexamic acid use for moderate and severe traumatic brain injury (NCT02645552)	Double blind, randomised trial	Pending recruitment	400 patients with moderate to severe traumatic brain injury (Glasgow coma scale score < 12)	2	Arm 1: 1 g intravenous bolus of tranexamic acid over 10 minutes Arm 2: placebo intravenous bolus over 10 minutes	Placebo (sodium chloride, 0.9%)	Neurological outcome (based on extended Glasgow outcome scale score) at six months post-injury	Vascular occlusive events (myocardial infarction, stroke, pulmonary embolism, and deep vein thrombosis)
Prehospital tranexamic acid use for traumatic brain injury (NCT01990768)	Double blind, randomised trial	Currently recruiting	1002 patients with moderate to severe traumatic brain injury (Glasgow coma scale score < 12)	3	Arm 1: 1 g intravenous bolus of tranexamic acid followed by 1 g intravenous infusion of tranexamic acid over eight hours. Arm 2: 2 g intravenous bolus of tranexamic acid followed by placebo infused over eight hours. Arm 3: placebo intravenous bolus followed by placebo infused over eight hours*	Placebo (sodium chloride, 0.9%)	Neurological outcome (based on extended Glasgow outcome scale score) at six months after injury	Volume of intracranial haemorrhage, disability rating scale score, 28 day survival, neurosurgery, ventilator-free days, seizures, cerebral ischaemia, vascular occlusive events, alterations in fibrinolysis
Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage (CRASH-3) (NCT01402882)	Double blind, randomised trial	Currently recruiting	13 000 patients with major traumatic brain injury (Glasgow coma scale score < 12 or intracranial bleeding on computed tomography scan)	2	Arm 1: 1 g of intravenous bolus of tranexamic acid over 10 minutes followed by 1 g intravenous infusion of tranexamic acid over eight hours. Arm 2: placebo intravenous bolus followed by placebo infused over eight hours	Placebo (sodium chloride, 0.9%)	Death in hospital within 28 days of randomisation	Vascular occlusive events, disability (based on disability rating scale and patient oriented outcome measures), seizures, neurosurgery, days in intensive care, other adverse events

*Intravenous bolus administered in prehospital setting, and maintenance infusion initiated on arrival at hospital.

cerebral hypoperfusion.¹⁸⁻²⁰ Thrombotic disseminated intravascular coagulation might increase the risk of cerebral microthrombi, which are often seen in the brains of patients with traumatic brain injury who have died.²¹

- Seizures are also a risk because tranexamic acid is known to cross the blood-brain barrier.²² Although there was no evidence of any increase in seizures in the CRASH-2 trial of tranexamic acid in extracranial bleeding, seizure activity remains a concern because the blood-brain barrier is impaired after traumatic brain injury.²³

What is the evidence of uncertainty?

A 2015 systematic review identified two relevant completed randomised trials (table 1).^{24,25} We judged that both trials were at low risk of bias; however, neither was large enough to answer the question definitively—the confidence intervals were wide and the P values statistically insignificant. The first trial (n=249) examined the effect of tranexamic acid in patients with extracranial bleeding but who also had traumatic brain injury.²⁴ The second trial (n=229) examined the effect of tranexamic acid in patients with polytrauma and traumatic brain injury, or isolated traumatic brain injury.²⁵ Both trials recruited patients who were within eight hours of injury but the numbers were not large enough to determine the balance of risks and benefits from tranexamic acid and whether this varies by time to treatment. Furthermore, the patients

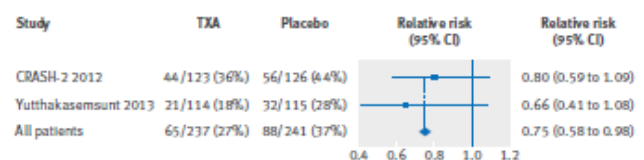


Fig 2 | Meta-analysis of effect of tranexamic acid versus placebo on intracranial bleeding in patients with traumatic brain injury

In one of the trials had extracranial bleeding in addition to intracranial bleeding.²⁴ Because tranexamic acid reduces mortality in extracranial bleeding (CRASH-2), the mortality reduction seen in this trial could be from the extracranial injury rather than any effect on the brain injury itself.

When the two randomised trials are combined in a meta-analysis (fig 2), there is a statistically significant reduction in intracranial haemorrhage, but because the confidence intervals are wide, the quality of this evidence is low.

- Intracranial haemorrhage—relative risk 0.75 (95% confidence interval 0.58 to 0.98); P=0.03;
- Mortality—relative risk 0.63 (95% confidence interval 0.40 to 0.99); P=0.05.

The effect of tranexamic acid on disability and thrombotic adverse effects including stroke remains uncertain.

Is ongoing research likely to provide relevant evidence?

We identified three ongoing randomised trials of tranexamic acid versus placebo in patients with isolated traumatic brain injury (table 2). These will evaluate the

Box 3 | Guidelines for general management of traumatic brain injury

The National Institute for Health and Care Excellence recommends to:²⁸

- First treat the greatest threat to life and avoid further harm by assessing Airway, Breathing, and Circulation
- Maintain cervical spine immobilisation until a full risk assessment indicates it is safe to remove the immobilisation device
- Ascribe depressed consciousness level to intoxication only after a major brain injury has been excluded
- Effectively manage pain, because it can lead to a rise in intracranial pressure
- Immediately manage patients who present to the emergency department with a Glasgow coma scale score of less than 15
- Immediately manage patients who return to the emergency department within 48 hours of transfer to the community with any persistent problem relating to the initial head injury; these patients should be seen by or discussed with a senior clinician experienced in head injuries, and considered for a computed tomography scan
- Immediately intubate and ventilate patients in a coma (Glasgow coma scale score ≤ 8), or patients who cannot protect their airway or have abnormal respirations
- Transfer patients with a Glasgow coma scale score of 8 or less to a neuroscience unit irrespective of the need for neurosurgery
- Perform a computed tomography scan within one hour of injury if patients present with certain risk factors—for example, Glasgow coma scale score of less than 13 on initial assessment; suspected skull fracture; post-traumatic seizure; focal neurological deficit; more than one episode of vomiting. Perform a computed tomography scan within eight hours of injury if patients have experienced loss of consciousness or amnesia since the injury and show certain risk factors (eg, age ≥ 65 , history of bleeding or clotting disorders, dangerous mechanism of injury). Perform a CT scan within eight hours of injury if patients are receiving warfarin treatment
- Monitor children closely and perform a computed tomography scan within an hour of injury if a relevant risk factor is identified—eg, suspicion of non-accidental injury, post-traumatic seizure without history of epilepsy
- Provide patients, family members, and carers with information about the nature and severity of the injury, risk factors that mean the patient should return to the emergency department—eg, loss of consciousness, amnesia for events before or after injury, headaches, vomiting episodes—details about what to expect during recovery, contact details of community and hospital services and support organisations, on discharge
- The Centers for Disease Control and Prevention and the American College of Emergency Physicians provide guidance on the management of adults with mild traumatic brain injury.²⁹ The guidelines focus on determining whether patients with known or suspected mild traumatic brain injury require a computed tomography scan of the brain or may be safely discharged.



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effect of tranexamic acid on death, disability, vascular occlusive events, and other adverse events in traumatic brain injury. The ongoing trials inform whether tranexamic acid can be given to those with traumatic brain injury.

In two of the ongoing trials (n=1402) patients are randomised within two hours of injury in the prehospital setting (NCT02645552, NCT01990768).

In the largest trial, the CRASH-3 trial (n=13 000), patients will be randomised in hospital and within eight hours of injury (NCT01402882).²⁶ The size of this trial should ensure that tranexamic acid and placebo groups are similar for known and unknown confounders, such as the concomitant degree of coagulopathy.²⁷ Therefore, it is unnecessary to standardise tranexamic acid and placebo groups for clinical management factors that may influence the extent of bleeding.

The results from the three ongoing trials should provide clinicians with information about whether the effect of tranexamic acid varies by time to treatment. Information on the effect of tranexamic acid administered within one hour, between one and three hours, and after three hours of injury may be more useful than the average effect of the treatment. Prespecified subgroup analyses in the CRASH-3 trial will provide information about the effect of tranexamic acid by time to treatment.

A substudy conducted within the CRASH-3 trial will use computed tomography scans to examine the effect of tranexamic acid on intracranial bleeding and thrombosis. These scans can detect traumatic haemorrhage (high attenuation) in the acute stage of traumatic brain injury. Ischaemic lesions (low attenuation) are visible on a computed tomography scan done several hours after injury. This substudy will provide information on the effect of tranexamic acid on intracranial haemorrhage and ischaemia and whether this varies by time to treatment.

Further research

Randomised trials looking at the effect of tranexamic acid in patients with isolated traumatic brain injury are currently ongoing. These trials will address the uncertainty of whether tranexamic acid improves outcomes in patients with traumatic brain injury. At this stage we do not make recommendations for further research in this area.

What should we do in light of the uncertainty?

The authors recommend that patients with isolated traumatic brain injury should not receive tranexamic acid outside the context of a randomised trial, and clinicians should consider enrolling their patients in one of the relevant trials wherever possible.

Box 3 signposts other aspects of management of traumatic brain injury.

Competing interests: We have read and understood BMJ policy on declaration of interests and declare the following: none.

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Appendix 4. Research paper 2: Published article.

Mahmood A, Roberts I, Shakur H: A nested mechanistic sub-study into the effect of TXA 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.

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Trials

STUDY PROTOCOL

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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])

Abda Mahmood^{*}, Ian Roberts and Haleema Shakur

Abstract

Background: Tranexamic acid prevents blood clots from breaking down and reduces bleeding. However, it is uncertain whether tranexamic acid is effective in traumatic brain injury. The CRASH-3 trial is a randomised controlled trial that will examine the effect of tranexamic acid (versus placebo) on death and disability in 13,000 patients with traumatic brain injury. The CRASH-3 trial hypothesizes that tranexamic acid will reduce intracranial haemorrhage, which will reduce the risk of death. Although it is possible that tranexamic acid will reduce intracranial bleeding, there is also a potential for harm. In particular, tranexamic acid may increase the risk of cerebral thrombosis and ischaemia. The protocol detailed here is for a mechanistic sub-study nested within the CRASH-3 trial. This mechanistic sub-study aims to examine the effect of tranexamic acid (versus placebo) on intracranial bleeding and cerebral ischaemia.

Methods: The CRASH-3 Intracranial Bleeding Mechanistic Sub-Study (CRASH-3 IBMS) is nested within a prospective, double-blind, multi-centre, parallel-arm randomised trial called the CRASH-3 trial. The CRASH-3 IBMS will be conducted in a cohort of approximately 1000 isolated traumatic brain injury patients enrolled in the CRASH-3 trial. In the CRASH-3 IBMS, brain scans acquired before and after randomisation are examined, using validated methods, for evidence of intracranial bleeding and cerebral ischaemia. The primary outcome is the total volume of intracranial bleeding measured on computed tomography after randomisation, adjusting for baseline bleeding volume. Secondary outcomes include progression of intracranial haemorrhage (from pre- to post-randomisation scans), new intracranial haemorrhage (seen on post- but not pre-randomisation scans), intracranial haemorrhage following neurosurgery, and new focal ischaemic lesions (seen on post- but not pre-randomisation scans). A linear regression model will examine whether receipt of the trial treatment can predict haemorrhage volume. Bleeding volumes and new ischaemic lesions will be compared across treatment groups using relative risks and 95% confidence intervals.

(Continued on next page)

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Discussion: The CRASH-3 IBMS will provide an insight into the mechanism of action of tranexamic acid in traumatic brain injury, as well as information about the risks and benefits. Evidence from this trial could inform the management of patients with traumatic brain injury.

Trial registration: The CRASH-3 trial was prospectively registered and the CRASH-3 IBMS is an addition to the original protocol registered at the International Standard Randomised Controlled Trials registry (ISRCTN15088122) 19 July 2011, and ClinicalTrials.gov on 25 July 2011 (NCT01402882).

Keywords: Tranexamic acid, Intracranial haemorrhage, Cerebral ischaemia, Traumatic brain injury

Background

Traumatic brain injury (TBI) occurrence

TBI is a leading cause of death and disability worldwide. According to the World Health Organization, TBI will continue to be a major cause of death and disability by 2020 [1]. At least 200 per 100,000 people are killed or hospitalised each year after TBI [2], resulting in over 10 million deaths or hospitalisations each year [3]. TBI is the leading cause of death and disability in people below the age of 45 [4].

TBI patients can experience a loss in physical, behavioural or emotional functioning after the injury [5]. Severe TBI often results in motor impairment that persists for at least 3 years after the injury [6] and cognitive impairments are present for at least 6 months after injury [7]. Problems with memory following TBI significantly affect an individual's quality of life [8]. Even with rehabilitation treatments, only 40–50% of TBI patients completely recover [9].

The increasing incidence of TBI can be explained by the rising frequency of traffic accidents in developing countries and rapidly motorising middle-income countries [10]. Projections of global mortality and burden of disease suggest that road traffic accidents will be the third major cause of death and disability by 2030, assuming a faster rate of socio-economic development [11]. Falls in older adults are the leading cause of TBI in high-income countries [12]. Given the global scope of this life threatening and potentially disabling condition, it is important to identify the most effective clinical care in this patient group.

Intracranial haemorrhage occurrence

Intracranial bleeding is common after TBI and the larger the bleed the greater the risk of death and disability [13, 14]. In patients with mild TBI (Glasgow Coma Scale score ≥ 13), although bleeding can continue for up to 24 hours after injury, most bleeds stop progressing within a few hours of hospital admission [15]. Intracranial haemorrhage progression has been observed in half of moderate to severe head injury patients who had a median Glasgow Coma Scale score of 8 on admission and repeat computed tomography (CT) scans performed within 24 hours of injury [16, 17]. Patients who were scanned earlier after injury (≤ 3.5 hours vs. > 3.5 hours) were more likely to have

expanding haematomas on CT performed 24 hours after injury (57% vs. 28%) [17]. If the initial CT scan was conducted more than 3.5 hours after injury, the percentage of patients with measurable changes in haematoma volume 24 hours after injury was reduced. In a subset of patients who had an intermediate scan (most of which were between 6 and 9 hours of injury), the mean volume change between the baseline and intermediate scan was 5.7 mL, whereas the difference in mean volume between the intermediate scan and the 24 hour scan was 0.03 mL [17]. Thus, the maximal change in intracranial haemorrhage volume occurs soon after injury.

A meta-analysis of 34 studies that reported the frequency of coagulopathy after TBI found that one third of patients with TBI have laboratory evidence of abnormal coagulation based on parameters such as fibrinogen, fibrin degradation products and antithrombin levels [18].

The risk of mortality in patients with coagulopathy after TBI is nine times higher than in TBI patients without coagulopathy (odds ratio (OR) 9.0, 95% confidence interval (CI) 7.3–11.6). The risk of unfavourable outcome as measured by the Glasgow Outcome Scale (score of 1–3) is more than 30 times higher in TBI patients with coagulopathy (OR 36.3, 95% CI 18.7–70.5) [18]. Decreased platelet counts, prolonged prothrombin time and partial thromboplastin time, and high levels of fibrinogen and D-dimer levels are observed in patients within the first 3 hours of TBI [19]. The highest D-dimer concentrations were found in the most severely injured patients [20], who have a higher risk of intracranial haemorrhage and mortality.

Effectiveness of tranexamic acid in reducing haemorrhage

Tranexamic acid reduces bleeding by inhibiting the enzymatic breakdown of fibrin blood clots. Plasmin binds to fibrin via lysine-binding sites and then splits fibrin into fibrin degradation products. Tranexamic acid is a molecular analogue of lysine that inhibits fibrinolysis by reducing the binding of plasmin to fibrin.

A systematic review of 104 randomised trials of tranexamic acid in surgical patients found that it reduced the number of patients receiving a blood transfusion by one-third and halved the need for further surgery to control bleeding [21].

A large randomised trial of tranexamic acid treatment within an hour of acute traumatic injury found that it reduced the risk of death due to bleeding by about one-third (relative risk (RR) 0.68, 95% CI 0.57–0.82; $P < 0.0001$) [22, 23]. Treatment between 1 and 3 hours reduced the risk by about one-fifth (RR 0.79, 0.64–0.97; $P = 0.03$). There was no apparent increase in the risk of vascular occlusive events with tranexamic acid following acute trauma (RR 0.69, 95% CI 0.44–1.07; $P = 0.096$).

Tranexamic acid as a potential treatment in TBI

Tranexamic acid is able to penetrate the blood–brain barrier and should be able to affect intracranial haemorrhage [24]. If tranexamic acid is effective following TBI, it should also be most effective when given soon after injury when intracranial bleeding is on-going [15]. Furthermore, if early increased fibrinolysis exacerbates bleeding and increases the risk of death [20], we would expect tranexamic acid to be most effective during this period.

However, there is also the potential for harm. In particular, tranexamic acid may increase the risk of cerebral thrombosis and ischaemia [25]. Cerebral ischaemia is an important secondary injury mechanism after TBI that worsens neurologic outcome and increases mortality [26, 27]. It can be precipitated by raised intracranial pressure, which can lead to cerebral hypo-perfusion [28–31]. In addition, thrombotic disseminated intravascular coagulation may increase the risk of cerebral micro-thrombi, which are often seen in the brains of TBI patients who die within 24 hours of injury [32]. By inhibiting fibrinolysis, tranexamic acid might increase the risk of cerebral ischaemia and thrombosis in TBI patients.

A systematic review identified two completed randomised trials of tranexamic acid in TBI patients [33]. The first randomised trial ($n = 249$) examined the effect of tranexamic acid in patients with extra-cranial bleeding but who also had TBI [34]. The second randomised trial ($n = 229$) examined the effect of tranexamic acid in patients with polytrauma and TBI or isolated TBI [35]. Both trials used information from pre- and post-randomisation CT scans to estimate the extent of bleeding and ischaemia. Both trials recruited patients who were within 8 hours of injury, yet they were not large enough to determine the balance of risks and benefits from tranexamic acid and whether this varies by time to treatment.

When the two randomised trials were combined in a meta-analysis, there was a statistically significant reduction in intracranial haemorrhage (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. In one trial, focal ischaemic lesions occurred in 5% of tranexamic acid-treated patients and 9% of placebo-treated patients (RR 0.51, 95% CI 0.20–1.32; $P = 1.17$) [34]. In the second trial, there were three strokes in the placebo group compared

with none in the tranexamic acid group [35]. However, because the CIs for intracranial haemorrhage, death and ischaemic lesion outcomes are so wide, the quality of this evidence is low. Furthermore, the patients in the trials had extra-cranial bleeding in addition to intra-cranial bleeding. Because tranexamic acid reduces mortality in extra-cranial bleeding (CRASH-2), the mortality reduction seen in this trial could be from the extra-cranial injury rather than any effect on the brain injury. The effect of tranexamic acid on intracranial haemorrhage and thrombotic adverse effects, including stroke, remains uncertain.

There are three ongoing randomised trials of tranexamic acid versus placebo in patients with isolated TBI (NCT02645552, NCT01990768, NCT01402882). These will evaluate the effect of tranexamic acid on death, disability, vascular occlusive events and other adverse events in TBI. The ongoing trials will inform whether tranexamic acid can be given to those with TBI. To date, 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 TBI [36]. The results from the three ongoing trials should provide clinicians with information about whether tranexamic acid is effective in reducing death and disability without increasing thrombotic events. The trials will also provide information about whether its effect varies by time to treatment.

However, these trials will not provide information about the mechanism by which tranexamic acid might exert its effects in TBI. If tranexamic acid reduces mortality by reducing intracranial haemorrhage, we would expect there to be less blood on head CT scans of tranexamic acid-treated patients, particularly those treated soon after injury [25]. If tranexamic acid increases the risk of cerebral ischaemia, we would expect to see more ischaemic lesions in tranexamic acid-treated patients, particularly in those treated after a more prolonged period following injury [37]. The CRASH-3 Intracranial Bleeding Mechanistic Sub-Study (CRASH-3 IBMS) will examine the effect of tranexamic acid on intracranial haemorrhage and cerebral ischaemia in a cohort of patients enrolled in the CRASH-3 trial. This paper outlines the protocol for the CRASH-3 IBMS and is in line with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines. The SPIRIT checklist and figure have been included as Additional file 1 and Fig. 1, respectively.

Aim

The CRASH-3 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 cerebral ischaemia.

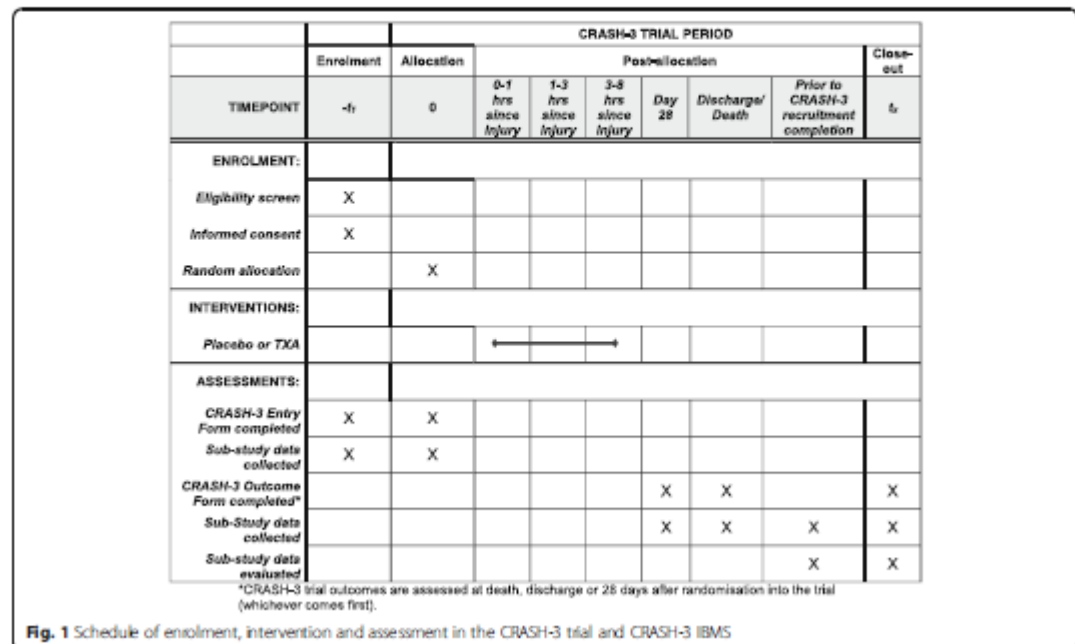


Fig. 1 Schedule of enrolment, intervention and assessment in the CRASH-3 trial and CRASH-3 IBMS

Trial design

The CRASH-3 IBMS is a mechanistic randomised controlled trial nested within a larger prospective, double-blind, multi-centre, parallel-arm, randomised, placebo controlled trial. The CRASH-3 IBMS is nested in a cohort of CRASH-3 trial participants (NCT01402882) (Fig. 2). The aims and methods of the CRASH-3 trial are presented in detail elsewhere [36].

Methods

Participating sub-study sites, eligibility and interventions

Participating hospitals

Hospitals participating in the CRASH-3 IBMS have been selected based on the number of patients enrolled into the CRASH-3 trial and the willingness of the Principal Investigator at site to take part. Four of the highest recruiting CRASH-3 trial hospital sites in the United Kingdom have been selected to take part (Royal London Hospital, London; Queen Elizabeth Hospital, Birmingham; University Hospital, Coventry; Salford Royal Hospital, Salford). Other hospitals participating in the CRASH-3 trial will be included to meet the planned sample size; these sites are to be confirmed. All regulatory and ethical approvals will be in place before the trial starts at each site.

Eligibility criteria

The CRASH-3 IBMS will be conducted in a cohort of approximately 1000 adult trauma patients enrolled in

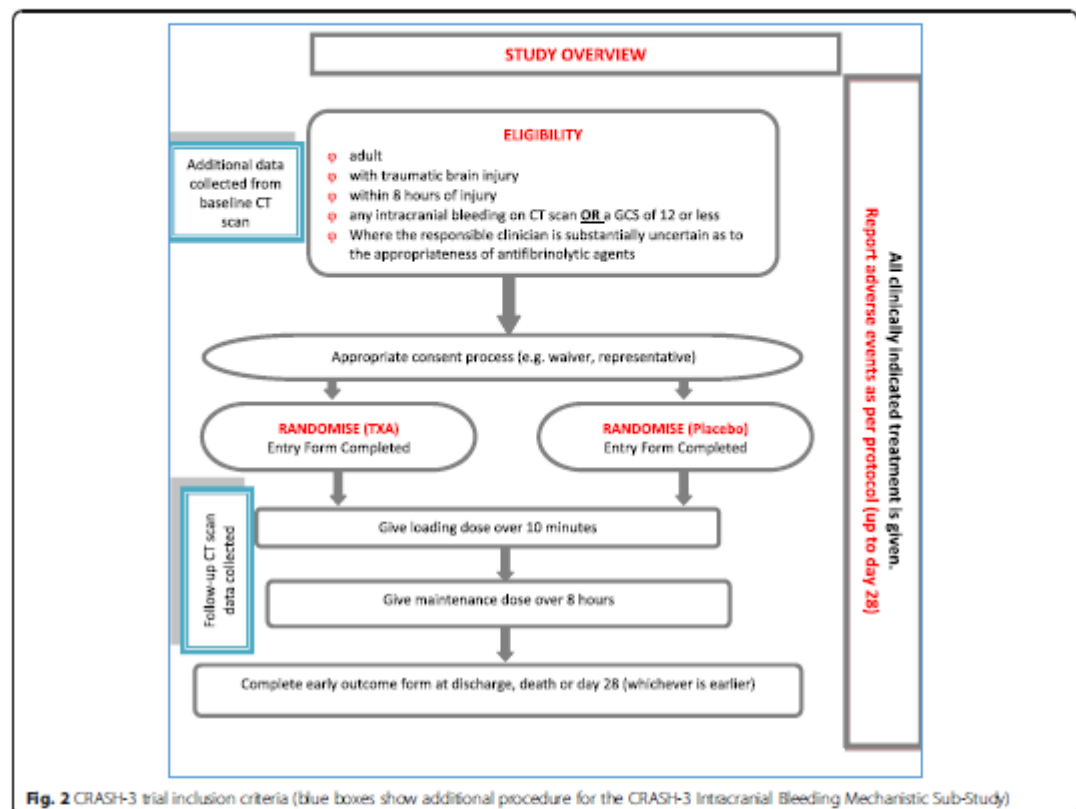
the CRASH-3 trial. Patients who have a Glasgow Coma Scale score of 12 or less or intracranial bleeding on a CT scan performed before randomisation into the CRASH-3 trial (i.e., a pre-randomisation CT scan), and fulfil the inclusion criteria for the CRASH-3 trial, are eligible for inclusion in the CRASH-3 IBMS [36].

Randomisation into the CRASH-3 trial

TBI patients eligible for inclusion into the CRASH-3 trial are randomly allocated to receive tranexamic acid or matching placebo (0.9% sodium chloride) and the trial treatment is started as soon as possible. Patients are randomised by selecting the lowest available numbered pack from a block of eight treatment packs. Randomisation codes are generated with a computer random number generator. There is no need to withhold any clinically indicated treatment in the CRASH-3 trial. Tranexamic acid or placebo is provided as an additional treatment to the usual management of TBI. The loading dose of the trial treatment is administered by intravenous injection immediately after randomisation (within minutes). The maintenance dose (by intravenous infusion) should start as soon as the loading dose is completed.

Adverse events in the CRASH-3 trial

Any untoward medical occurrence affecting a trial patient up to 28 days after randomisation will be reported in line with the CRASH-3 trial protocol. If the patient develops



an adverse event during the treatment phase, the trial drug should be stopped. In this situation, the patient should be treated in line with local procedures and then followed up. The independent Data Monitoring Committee may recommend for the early termination of the trial, and the final decision lies with the Trial Steering Committee.

Unblinding before the end of the CRASH-3 trial

If there are contraindications to tranexamic acid following randomisation, the trial treatment should be stopped and all standard clinical care provided. Unblinding is only necessary if the clinician believes that clinical management depends importantly upon knowledge of whether the patient received tranexamic acid or placebo. In this case, a 24 hour telephone service is available to confirm whether the patient received tranexamic acid or placebo.

Outcomes and outcome measurement

Primary outcome

The total volume of intracranial bleeding after randomisation, adjusting for total volume of intracranial bleeding at baseline if baseline volume is available.

Secondary outcomes

- (1) Frequency of progressive haemorrhage – number of patients with a post-randomisation CT scan with total haemorrhage volume of more than 25% of the volume on the pre-randomisation scan;
- (2) Frequency of new haemorrhage – number of patients with haemorrhage on the post-randomisation CT scan when there was not one on the pre-randomisation scan;
- (3) New focal ischaemic lesions – ischaemic lesions which appear on a post-randomisation scan but not on the pre-randomisation scan;
- (4) Total volume of intracranial bleeding after randomisation in patients who undergo surgical evacuation of haemorrhage, adjusting for volume of baseline bleeding.

All outcomes will be compared across treatment groups.

Outcome measurement: estimating haemorrhage volume

Patients often undergo one brain CT scan as part of routine medical care prior to randomisation into the CRASH-3

trial. The majority of patients are scanned again after randomisation into the CRASH-3 trial. In the CRASH-3 IBMS, we will measure the volume of intracranial haemorrhage on pre- and post-randomisation CT scans. A simple validated scale for measuring intracranial haemorrhage volume shows good agreement with the gold standard of computer-assisted volumetric analysis, which requires demarcation of the haemorrhage borders [38–49].

The ABC/2 method is a quick and easy technique used to estimate the volume of intracranial haemorrhage [50]. This method assumes haematoma volume is approximately equal to an ellipsoid shape (i.e., three dimensional oval shape). For ease of assessment, the formula for calculating the volume of an ellipsoid ($\frac{4}{3} \times \pi \times (A/2) \times (B/2) \times (C/2)$) can be simplified to ABC/2 if we assume π is equal to 3. This method selects a representative slice near the centre of the haematoma on which the bleed is most visible. On this slice, two measurements are taken: (A) the maximal diameter; (B) width perpendicular to A. For the measurement of depth, the maximal number of slices on which the haematoma is visible is multiplied by slice thickness (C). These three measurements are multiplied and the sum divided by two (ABC/2) to provide the volume measurement in cm^3 .

Whilst some researchers have found that the ABC/2 method overestimates lesion volume compared to computer-assisted methods [39, 44, 45, 47, 51–55], others claim the opposite [41, 56]. Haemorrhagic lesions that have a regular shape are more accurately estimated using the ABC/2 method compared to lesions with irregular or multi-lobular shapes [43, 45–56]. Furthermore, a number of variations of the ABC/2 method adjust for the depth of a lesion. Whilst some have found that adjusting for depth significantly underestimates volumes because smaller slice volumes are eliminated [57], others found that adjusting for depth is favourable [48].

Although the ABC/2 method is a less specific measure of haemorrhage volume and overestimation due to false positives would dilute the effect of the treatment towards the null, its low sensitivity and underestimation due to false negatives would not impact the effect of the treatment on haemorrhage. Furthermore, the more accurate method of estimating haemorrhage would have been more expensive and therefore administered in a smaller number of patients given the limited budget of a clinical trial. Although a more accurate method in a small trial would result in less measurement error, a less accurate method in a larger trial would result in less random error. We believe that the ABC/2 method is sufficiently accurate and therefore chose to use this method in a larger trial. Furthermore, the assessor rating the scans will be blind to treatment allocation and thus the

bias from measurement error should be balanced between treatment groups.

Total haemorrhage volume

The total haemorrhage volume on each scan will be calculated by totalling the volumes of intra-parenchymal, intra-ventricular, epidural and subdural haemorrhage.

Estimating intra-parenchymal, intra-ventricular and epidural haemorrhage volume using ABC/2

Volume estimation of intracranial haemorrhage is aided by the characterisation of haematomas. The final shape of a haematoma is influenced by its location. Intra-axial (or intra-cerebral) haematomas include intra-parenchymal haematomas, which occur in the brain tissue, and intra-ventricular haematomas, which occur in the ventricles of the brain. These haematomas tend to have regular shapes that are clearly definable in every dimension (i.e., their length, width and depth can be measured on a CT scan). Extra-axial haematomas occur between the three membranes that surround the brain (dura mater, arachnoid mater and pia mater). Epidural haematomas are a type of extra-axial haematoma and occur between the skull and outer membrane of the central nervous system (dura mater). They have a clear shape that can be measured in every dimension. The ABC/2 method assumes the haemorrhage has an ellipsoid shape and has been validated in intra-parenchymal [38], intra-ventricular [46] and epidural haematomas [47, 48]. We will estimate the volume of intra-parenchymal, intra-ventricular and epidural/extra-dural haemorrhage using the ABC/2 method.

Estimating subdural haemorrhage volume using maximum width

Subdural haematomas are another type of extra-axial haemorrhage and occur between the dura mater and the middle membrane of the central nervous system (arachnoid mater). Subdural haematomas are crescent shaped as they follow the pattern of the brain's convexity. The exact limits of a subdural haematoma are not clearly definable in any dimension. This type of haemorrhage can theoretically occupy the entire subdural space. Given that the ABC/2 method assumes the haemorrhage has an ellipsoid shape, it would not provide an accurate volume estimation of subdural haemorrhage. Indeed, there have been reports of underestimation in subdural haemorrhage volume when using an adapted version of the ABC/2 method compared with computer-assisted volumetric analysis [41, 56].

Some researchers and clinicians propose that it is more appropriate to estimate subdural haemorrhage volume using a formula which takes the difference between two spheres (representing the entire subdural space), divides by two (as subdural haemorrhage is usually

unilateral) and divide by two again (as subdural haemorrhage tends to be thicker at the centre and thinner at the sides). This method has been tested at the Neurosurgical Trauma Unit at the Queen Elizabeth Hospital in Birmingham (UK) and has been shown to provide more clinically relevant estimates of haemorrhage volume than the ABC/2 method [58]. Although this method overestimates subdural volume, it is less than the error provided by the ABC/2 method. The key measurement in determining the clinical significance of a subdural haemorrhage is its thickness (i.e., the B measurement when using the ABC/2 method) [59]. In the CRASH-3 IBMS, we will measure the maximum width of a subdural bleed, and compute its volume using the aforementioned formula.

Measurement of subarachnoid haemorrhage

Subarachnoid bleeds are another type of extra-axial haemorrhage and occur in the area between the arachnoid membrane and the innermost membrane surrounding the brain (pia mater). The shape of the subarachnoid space resembles a spider's web and therefore haemorrhage in the subarachnoid space cannot be clearly measured in any dimension. Although there are a number of CT grading scales that include the characterisation of subarachnoid haemorrhage [60, 61], they are criticised for being subjective and not comprehensive enough to serve as a primary grading scale for this type of haemorrhage [62]. For example, the Fisher scale and its modified version do not consider subarachnoid haemorrhage in isolation but in combination with intraventricular haemorrhage [63].

In the CRASH-3 IBMS, the size of a subarachnoid haemorrhage will be characterised as small, medium or large. Each bleed will then be described as focal (localised to a specific location), multiple (not localised but not widespread) or diffuse (widespread). This method is also subjective and may have low sensitivity and specificity, therefore misclassification would bias the effect of the treatment towards the null value. We hope that, by using this method in a large trial, the bias from measurement error would be offset by a reduction in random error.

Petechial haemorrhage

Petechial haemorrhage manifests as a very small dot on a CT scan. CT scans and accompanying radiology reports will be examined to indicate whether petechial haemorrhage is present.

Outcome measurement: focal ischaemic lesions

Ischaemic stroke is due to the compromise of blood and oxygen flow through either large or small arteries supplying the brain parenchyma. Thrombotic occlusion of intracranial vessels produce wedge-shaped cortical infarctions.

Cerebral ischaemia would reliably manifest on a CT scan performed at least 48 hours after randomisation [62]. However, given that clinical scans are performed for diagnostic purposes, it is not possible to carry out scans at set time points post-randomisation. Brain imaging techniques, including MRI diffusion weighted imaging, have higher sensitivity and specificity compared to CT in the early diagnosis of ischaemic infarction, and are often clinically warranted when there is a suspected stroke. Therefore, the assessor will examine all available brain scans performed within 28 days of randomisation and the accompanying radiology reports for evidence of focal ischaemic lesions and record the time from randomisation to detection.

Furthermore, given that CT imaging is the first and most common neuroimaging examination performed for emergency assessment of suspected acute haemorrhage and stroke around the world [64, 65], the majority of scans included in the CRASH-3 IBMS will be CT scans. Therefore, it is important to clarify how we will capture this endpoint when only CT scans are available. Cerebral infarction manifests as wedge-shaped low attenuation on a CT scan. Given that oedema also manifests as low attenuation on CT, the radiology reports that accompany CT scans should indicate whether the low attenuation is representative of oedema or infarction. Brain imaging reports often refer to cerebral infarction by the affected vascular territory (e.g., anterior cerebral artery, middle cerebral artery, posterior cerebral artery, lacunar, cerebellar, brainstem). The assessor will examine all available brain imaging to assess whether oedema or infarction can be excluded given the appearance of earlier scans. For example, some patients have oedematous haemorrhagic lesions, which on CT manifests as high density haemorrhage surrounded by low density oedema. In later scans the haemorrhage may resolve but the oedema may remain. If only considered alone, the later CT scan may have the appearance of infarction but could be representative of residual oedema. We will attempt to minimise such errors by comparing the appearance of cerebral infarction/oedema between consecutive scans, and consider the accompanying scan reports for radiological opinion. If the available scans and accompanying reports are unable to confirm the presence of an ischaemic lesion, we would seek further radiological and clinical opinion.

Outcome measurement: mass effect and other CT endpoints

Space-occupying intracranial lesions can displace brain tissue. The shift of midline structures past the centre line of the brain will be measured in millimetres. We will also record whether mass effect has caused ventricular and sulcal effacement.

All scans will be rated according to the Marshall classification – the most extensively used CT classification scale in TBI [66]. Three main characteristics define the Marshall classification, namely presence of mass lesion, degree of compression of perimesencephalic cisterns and degree of midline shift.

Sample size

Assuming the average baseline intracranial bleeding volume is 20 mL and assuming the same average increase (8 mL), standard deviation (28 mL) and correlation ($\rho = 0.6$) between baseline and follow-up bleeding volumes as in the control group of the CRASH-2 Intracranial Bleeding Sub-study [34], a study with at least 1000 participants 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). In the main CRASH-3 trial, we hypothesise that tranexamic acid will reduce intracranial bleeding by approximately 15%. The sample size estimates have been reviewed and approved by statisticians at the London School of Hygiene and Tropical Medicine.

Data collection, management and analysis

Procedures for data collection

The CRASH-3 trial database will be used to prepare a list of all patients with a Glasgow Coma Scale score of 12 or less or with a pre-randomisation CT scan at participating sub-study hospitals. The list will include unique randomisation (box and pack) numbers, date and time of randomisation, and time between injury and randomisation into the CRASH-3 trial. The randomisation numbers will be used at the participating site to identify the patient using their hospital number. The latter will be used at the participating hospital to identify the patient. The outcome assessor (research fellow with training in brain imaging assessment) will hold a letter of access at the participating hospital and use the patient hospital number to retrieve pre- and post-randomisation scans from the hospital imaging system. The outcome assessor will complete the outcome forms at each site using the relevant scans and accompanying radiology reports. All the data are collected by the same outcome assessor who is blind to treatment allocation.

If the patient does not have a pre-randomisation scan, only the post-randomisation scan form is completed. If the patient does not have a post-randomisation scan, only the pre-randomisation scan form is completed. We record whether pre- and/or post-randomisation scans are available such that we can examine missing data by trial arm.

In most cases, the post-randomisation scan is the first scan performed after randomisation, which is normally within 72 hours of randomisation. Furthermore, due to

ongoing clinical management, some patients are scanned within minutes of randomisation. Tranexamic acid would not have had sufficient opportunity to effect haemorrhage or infarction in such a way that would manifest on a scan this soon after randomisation. Therefore, for patients scanned within minutes of randomisation, we also measure all the outcomes of interest on the next available post-randomisation scan, which is normally closer to 72 hours of randomisation. All available brain imaging is examined for evidence of focal ischaemic lesions.

The time stamped on the scans will be used to calculate the following time intervals: (1) the time between injury and the pre-randomisation CT scan and (2) the time between randomisation into the trial and the post-randomisation scan. If a patient has undergone neurosurgery following their injury, information on the date and time of neurosurgery will be collected using prospective reports including patient anaesthetic charts. The outcome data is collected for all patients included in the CRASH-3 IBMS (unless consent was withdrawn) irrespective of whether the trial treatment was received (i.e., on an intention-to-treat basis). The outcome data is directly uploaded into an electronic database accessed at each sub-study site.

Data management plan

A data management plan will be prepared in advance of data collection (Additional file 2). This will detail all aspects of data collection and recording to ensure compliance with International Conference on Harmonisation Good Clinical Practice guidelines (ICH-GCP) [67], United Kingdom Clinical Trials Regulations and the Data Protection Act [68]. Data will be recorded in a database developed in line with relevant regulatory requirements, including ICH-GCP guidelines.

Statistical analysis

Primary outcome A linear regression model will examine the primary outcome; whether receipt of the trial treatment can predict total haemorrhage volume following randomisation. Mean haemorrhage volume will be compared between trial arms, adjusting for baseline haemorrhage volume. Adjusting for baseline haemorrhage volume is important as it is a strong predictor of haematoma increase [17, 69, 70], meaning that the baseline adjustment can increase the power of the comparison by reducing the impact of between-patient variability. We will conduct subgroup analysis to examine whether the effect of tranexamic acid on intracranial haemorrhage is modified by time to treatment. A subgroup analysis by time is important as previous evidence suggests that the effect of tranexamic acid is strongly dependent on how quickly after injury it is received (CRASH-2).

Secondary outcomes We will express the effect of tranexamic acid on the occurrence of dichotomous CT endpoints, including progressive haemorrhage or new haemorrhage, using relative risks and 95% CIs estimated using generalised linear models.

We will express the effect of tranexamic acid on new focal cerebral ischaemic lesions measured at several post-randomisation time-points using relative risks and 95% CIs estimated using generalised linear mixed models to account for the fact that this outcome could be measured at several time-points following randomisation.

Missing data In line with the Consolidated Standards of Reporting Trials [71], we will report the number of patients without pre- and post-randomisation scans by treatment arm. If the outcome of interest (haemorrhage expansion) is associated with the reason the data are missing (patients with haemorrhage expansion may be more likely to die before the second scan), imbalance in missing data by treatment group can cause bias. If we suspect that data are missing not at random [72], we will conduct sensitivity analysis to explore the implications.

Between-centre effects There is no evidence for the hypothesis that between-centre differences in unfavourable outcome affect the chance of demonstrating a treatment effect in randomised trials of TBI [73]. This study estimated the between-centre differences beyond the random variation that may result from some centres that only treat a small number of patients. Given this evidence and that we have no biological or mechanistic explanation to expect any variation in a treatment effect between centres, we do not anticipate to find centre effects in the CRASH-3 IBMS. Furthermore, the majority of hospitals included in the CRASH-3 IBMS are in western countries. The homogeneity in patient characteristics and care facilities is further reason not to expect a between-centre difference in treatment effect. However, for the purpose of transparency we will report the interaction between centre and treatment effect using a logistic regression model with interaction between centre and treatment.

Inter-rater reliability The inter-rater reliability of haemorrhage occurrence will be assessed using relevant Entry Form data from the CRASH-3 trial to examine consistency among ratings provided by the research fellow and clinical staff.

Interim and final analyses There are no interim analyses planned for the CRASH-3 IBMS. The final analysis for the CRASH-3 IBMS will be undertaken following completion of the main CRASH-3 trial. A complete statistical analysis plan will be published separately prior to completion of the CRASH-3 trial.

Monitoring

All data for the CRASH-3 trial will be subject to statistical monitoring and approximately 10% of data will be subject to on-site monitoring. Consent forms will be monitored centrally by the Trial Coordinating Centre (where permission is given to do so). Investigators/institutions are required to provide direct access to source data/documents for trial-related monitoring, audits, ethics committee review, and regulatory inspection. All trial-related and source documents must be kept for at least 5 years after the end of the trial. As all the CRASH-3 IBMS data will be collected directly from source data, additional monitoring will not be carried out for this data.

Potential risks

The effective radiation dose from a CT scan is about 2 mSv, which is approximately the amount received from background radiation in 8 months. Because CRASH-3 IBMS will mainly use data from CT scans undertaken as part of routine patient care, patients will not be exposed to extra radiation. There is no additional burden or risk to the patient as a result of CRASH-3 IBMS. It is standard care for all patients with TBI and associated clinical signs to have a CT scan. Follow-up CT scans are often conducted for diagnostic purposes around 24 to 72 hours after the initial scan. Steps taken to minimise the risks associated with handling personal data will be detailed in the Confidentiality section.

Confidentiality and dissemination

Confidentiality

Only staff with authorised access to the scans, either as clinicians or research contract holders, will be able to retrieve and review them. Completed scan data forms will be uploaded onto a secure database. The scan data forms will contain no patient identifiable data (Additional file 3). Scans include the date and time of the scan and this information could potentially be used by anyone with access to the hospital radiology system to identify the patient. For this reason, scan data forms will only include the randomisation number, the time interval between the injury and the scan (pre-randomisation scan form), and the time interval between randomisation and the scan (post-randomisation scan form). As no personal data will be collected, the anonymity of each patient will be protected.

Publication

The results from this trial will be published in peer-reviewed medical journals. Dissemination of results to patients will take place via the media, trial website (crash3.lshtm.ac.uk) and relevant patient organisations. All participating sites will be credited in key publications.

Discussion

Potential benefit of CRASH-3 IBMS: furthers knowledge about mechanism of action of tranexamic acid in TBI

The CRASH-3 IBMS is a nested randomised trial that will reliably examine the effect of tranexamic acid on intracranial haemorrhage and cerebral ischaemia. We hope that this trial will provide information about the mechanism of action of tranexamic acid in isolated TBI. An understanding of the mechanism of action of tranexamic acid and insight into factors that might affect this mechanism, is critical in the appropriate generalisation of trial results [74]. If patients who receive tranexamic acid have less intracranial bleeding on their CT scans compared to those who receive placebo, this information, along with the results of the main CRASH-3 trial, could inform the administration of tranexamic acid in TBI. If TBI patients who receive tranexamic acid soon after injury have less haemorrhage expansion compared to those who receive tranexamic later, then time between injury and treatment is a factor relevant to the mechanism of action which, with the results of the main CRASH-3 trial, should be considered when making treatment decisions. Furthermore, if we find evidence of cerebral ischaemia in patients who receive tranexamic acid and the effect varies by time to treatment, this information can be used to prevent adverse outcomes and ensure those receiving tranexamic acid are those most likely to benefit from it. Therefore, the knowledge gained from the nested CRASH-3 IBMS will add to the evidence base and could benefit the clinical management of patients with head injuries.

Furthermore, the patients included in the CRASH-3 IBMS are likely to have more severe head injuries compared to patients in the CRASH-3 trial but not included in the CRASH-3 IBMS. The patients in the sub-study are not a random sample of patients in the CRASH-3 trial, nor will they be comparable. It is not necessary for the sub-study population to be representative of the CRASH-3 trial population because knowledge about a causal mechanism facilitates generalisation and not representativeness of the trial patients [75]. If the sub-study used a random sample of patients from the CRASH-3 trial, the results would not necessarily apply to either more or less severe patients, but only to a hypothetical patient of average injury severity. Representativeness of trial patients does not help us to generalise our findings to other TBI patients. Knowledge about whether tranexamic acid reduces intracranial bleeding or increases cerebral ischaemia will inform the administration of tranexamic acid in TBI and allow us to appropriately generalise the trial results.

Potential dangers of CRASH-3 IBMS: power and alternative mechanisms leading to death in TBI

The CRASH-3 trial and CRASH-3 IBMS are based on the premise that intracranial haemorrhage is the mechanism

that leads to death in patients with TBI. We hypothesise that tranexamic acid will reduce intracranial haemorrhage, which will in turn reduce the risk of death and disability. We assume that, by inhibiting fibrinolysis, tranexamic acid increases blood viscosity, reduces blood flow and slows the rate of haemorrhage (Poiseuille's Law [76]). However, it is possible that tranexamic acid does reduce intracranial haemorrhage but the CRASH-3 IBMS might not have sufficient power to detect such an effect. Our sample size calculation is based on a specific difference in haemorrhage volume between treatment groups. If receiving tranexamic acid results in a smaller reduction in haemorrhage volume than we have assumed, the CRASH-3 IBMS might not detect it and we may falsely conclude that tranexamic acid does not reduce intracranial haemorrhage. This is a limitation of conducting this nested sub-study in a smaller population of the main trial population. There is a trade-off between a larger sample, which would allow us to detect a smaller treatment effect and time, and resources; therefore, we have estimated a realistic sample size based on the best available evidence in this area.

Furthermore, if tranexamic acid reduces intracranial haemorrhage in TBI patients and this is detected by the CRASH-3 IBMS, it is still possible that clinical outcomes may not improve. This could be because intracranial haemorrhage is not the mechanism that leads to death in TBI patients. It is also possible that the potential benefit of tranexamic acid in reducing intracranial haemorrhage may be offset by the increased risk of cerebral ischaemia [29, 30], particularly when administered several hours after injury when there is an increased risk of thrombotic disseminated intravascular coagulation [25]. The CRASH-3 IBMS will provide information on both endpoints and could aid the interpretation of results from the CRASH-3 trial.

Trial status

The first patient was enrolled in the CRASH-3 trial on 20 July 2012. Recruitment is currently ongoing. It is anticipated that recruitment for the CRASH-3 trial will be complete by 31 December 2017. Data collection for the CRASH-3 IBMS started in February 2016. All data for the CRASH-3 IBMS will be collected prior to completion of the CRASH-3 trial.

Additional files

Additional file 1: SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents. (DOC 122 kb)

Additional file 2: Data management plan. (DOCX 726 kb)

Additional file 3: CT scan outcome forms. (DOCX 52 kb)

Additional file 4: Confirmation of funding for the CRASH-3 trial from The Moulton Charitable Foundation. (PDF 527 kb)

Additional file 5: Confirmation of funding for the CRASH-3 trial from the Joint Global Health Trials Scheme. (PDF 137 kb)

Additional file 6: Confirmation of funding for the CRASH-3 trial from the National Institute for Health Research. (PDF 82 kb)

Additional file 7: Confirmation of funding for the CRASH-3 trial from the London School of Hygiene and Tropical Medicine. (PDF 264 kb)

Additional file 8: Letter of favourable ethical opinion from the Medical Research and Ethics Committee and Health Research Authority. (PDF 106 kb)

Additional file 9: Letter of favourable ethical opinion from the Observational/Interventions Research Ethics Committee at the London School of Hygiene and Tropical Medicine. (PDF 267 kb)

Abbreviations

CI: confidence interval; CRASH: Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage; CT: computed tomography; OR: odds ratio; RR: relative risk; SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials; TBI: traumatic brain injury

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Availability of data and materials

Not applicable.

Access to data

All authors will have access to the final trial dataset.

Indemnity

The London School of Hygiene and Tropical Medicine accepts responsibility attached to its sponsorship of the CRASH-3 trial and the CRASH-3 IBMS and, as such, would be responsible for claims for any non-negligent harm suffered by anyone as a result of participating in the CRASH-3 trial. The indemnity is renewed on an annual basis and the London School of Hygiene and Tropical Medicine assures that it will continue renewal of the indemnity for the duration of this trial.

Sponsorship and trial management

The CRASH-3 trial and the CRASH-3 IBMS are sponsored by the London School of Hygiene and Tropical Medicine and its responsibilities coordinated by the Clinical Trials Unit. The responsibilities of the Clinical Trials Unit are overseen by the Trial Management Group. The composition, roles and responsibilities of the Trial Management Group, Protocol Committee, Independent Data Monitoring Committee, Trial Steering Committee and other responsible committees are detailed elsewhere [36].

Authors' contributions

All authors are responsible for the conception and design of the study. AM drafted and revised this manuscript. IR and HS critically read and revised the manuscript. All authors have read and approved the final manuscript. IR and HS will provide scientific leadership for the CRASH-3 IBMS.

Authors' information

All authors are from the Clinical Trials Unit, Faculty of Epidemiology and Population Health at the London School of Hygiene and Tropical Medicine (University of London).

Ethics approval and consent to participate

The Medical Research and Ethics Committee and Health Research Authority reviewed the protocol and supporting documents for the CRASH-3 IBMS and provided a favourable ethical opinion on 8 June 2016 (Research Ethics Committee Reference 12/EE/0274; Additional file 8). These committees approved the CRASH-3 IBMS to be conducted at the Royal London Hospital (London), Queen Elizabeth Hospital (Birmingham), University Hospital (Coventry) and Salford Royal Hospital (Salford), and in additional sites yet to be confirmed. The Royal London Hospital (London), Queen Elizabeth Hospital (Birmingham), University Hospital (Coventry) and Salford Royal Hospital (Salford) have provided local approvals and letters of access for the CRASH-3 IBMS to be conducted at their respective sites. All relevant local ethical approvals will be gained from additional sites.

Favourable ethical opinion was received from the Observational/Interventions Research Ethics Committee at the London School of Hygiene and Tropical Medicine on 24 May 2016 (Reference 11535; Additional file 9). Important protocol modifications will be submitted to and reviewed by the Medical Research and Ethics Committee and Health Research Authority, and registries updated as appropriate.

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 [77]. 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. 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 CT scan data for the CRASH-3 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 access CT scans, particularly for patients who have deceased or are disabled as a result of their injuries where re-consent would be distressing and unwelcome. The London School of Hygiene and Tropical Medicine and national Ethics Committees extended their approvals to extract CT data from the CRASH-3 trial without further patient consent. Patients who withdrew from the main CRASH-3 trial would not be included in the CRASH-3 IBMS.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Appendix 5. Research paper 3: Retention of copyright / permission to publish.

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

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Appendix 6. Research paper 3: Published article.

Mahmood A, Roberts I, Shakur-Still H. A nested randomised trial of the effect of TXA on intracranial haemorrhage and infarction in traumatic brain injury (CRASH-3 trial intracranial bleeding mechanistic study): Statistical analysis plan. Wellcome Open Research 2019, 3:99.



METHOD ARTICLE

REVISOR 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 3; peer review: 3 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) versus placebo 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 versus placebo 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

	1	2	3	4
version 3 published 27 Nov 2019				report
version 2 published 08 Jan 2019			report	report
version 1 published 13 Aug 2018	report	report		

- 1 Surakrant Yuthakasemsunt , Khon Kaen Hospital, Khon Kaen, Thailand
- 2 John Hodson , King's College London, London, UK
- 3 Stephen Senn , Independent Consultant Statistician, Strassen, Luxembourg
- 4 Christian Gluud, Centre for Clinical Intervention Research, Copenhagen, Denmark

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](https://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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Author roles: Mahmood A: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; Roberts I: Conceptualization, Funding Acquisition, Methodology, Supervision, Writing – Review & Editing; Shakur-Still H: Conceptualization, Funding Acquisition, Methodology, Supervision, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

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.

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

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REVISED Amendments from Version 2

This third version of the SAP is in response to requests for clarification from peer reviewers 3 and 4. The main changes are detailed here. In response to peer reviewer 3 comments, the following sections were amended for clarification:

- Sample size (calculation)
 - Primary analysis (the main effect of site (which is treated as fixed) will be accounted for in the model, covariates will be included in the model).
- In response to peer reviewer 4 comments, the following sections were amended for clarification:
- In the Abstract, it has been clarified that this is a trial of tranexamic acid versus placebo.
 - In the Trial Status section, the dates the trial completed recruitment and unblinded have been clarified. It has been noted that the SAP was publicly available well before the trial unblinded.
 - In the primary analysis section, it has been clarified that the bleeding volumes are skewed and so will be log transformed before entered into the linear mixed model. The anti-log of the treatment effect estimate will be presented to aid interpretation.
 - Other small changes as requested (see peer reviewer report 4).

Any further responses from the reviewers can be found at the end of the article

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 appears to be 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 coagulation¹⁸.

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)¹⁹. The IBMS evaluates the effect of tranexamic acid on bleeding expansion using a validated method (ABC/2)²⁰ to measure the total bleeding volume on routinely collected CT scans done soon after randomisation. The blinded data from $\approx 1,000$ 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 elsewhere¹⁹.

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

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 ($1542 \times (1 - (0.6^2))$) (Borm, 2007).

Due to the large amount of missing data (only around half of patients are scanned both pre-randomisation and post-randomisation), we increased the sample size for the CRASH-3 IBMS to include around 1700 patients. This was the approximate maximum number of patients the scan assessor could feasibly collect data from before the CRASH-3 trial completed recruitment. Using the same expected treatment effect, standard deviation, correlation and baseline adjustment values as the original sample size calculation, this increased power to 95%. (at $\alpha=0.05$) 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.

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 IBMS 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

The first patient was enrolled in the CRASH-3 trial on 20 July 2012. Data collection for the CRASH-3 IBMS started in February 2016. The CRASH-3 trial completed recruitment on 31 January 2019. Routinely collected brain imaging data from patients included in the CRASH-3 IBMS were examined for the purpose of the IBMS and recorded in a web database before this date.

The first and second versions of this SAP were submitted for publication (and publicly available) well before the trials unblinded on 31 May 2019. The reviewer report from peer reviewer 4 was submitted on 6 June 2019. This third version of the SAP is in response to small requests for clarification from peer reviewer 4.

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 (hospital site)²⁷ will be included in the analysis to improve the precision of the effect estimate. The main effect of site (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 ($n = 1750$), we expect any loss in efficiency from this method (compared to the random centre effects method) to be minimal. The linear mixed model described above will include an interaction between each covariate and whether bleeding volume was measured before and/or after 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-randomisation and post-randomisation bleeding volumes are positively skewed. 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% 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.

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 with 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 a variable 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^{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 hours¹⁵, 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 arm²². 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 effect²³.

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)²³. 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 effect²⁴.

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)²³.

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 TBI²⁵. Nonetheless, the main effect of site will be included in the analyses.

Conclusion

This statistical analysis plan updates our previously published protocol¹⁶. 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.

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- Lingama HF, Roozenboek B, Paré 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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Version 3

Reviewer Report 04 December 2019

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Christian Gluud

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

I have read the responses to my comments and are satisfied with them. I have also read the article again and finds it improved and easier to understand. I therefore approve the article as it is.

During my read, I noticed the following minor things that you may decide on yourselves:

- LSHTM is not explained in the box under Grant information.
- In the box named revised, there ought to be a space between comments from reviewer 3 and from reviewer 4.
- Page 4, first column: LSHTM is not explained – but it is on p. 5.
- Page 4, second c: Full stop after 95% should come after the following parenthesis.
- Page 4, second c: double-blinded should become blinded.
- Page 5, second c: compared to placebo ought to become compared with placebo.
- Page 7, second c: 1-3 hours ought to become >1-3 hours.

Page 8, first c: compared to those who receive placebo ought to become compared with those who receive placebo.

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.

Version 2

Reviewer Report 06 June 2019

<https://doi.org/10.21956/wellcomeopenres.16363.r35534>

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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 mention 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 do 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 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?

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 do 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 ($1542 \times (1 - (0.6^2))$) (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

Biostatistics Department, National Institute for Health Research (NIHR) Biomedical Research Centre for Mental Health, Institute of Psychiatry, Psychology & Neuroscience (IoPPN), King's College London, London, UK

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).

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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

<https://doi.org/10.21956/wellcomeopenres.16049.r33681>

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Surakrant Yutthakasemsunt 

Department of Surgery, Khon Kaen Hospital, Khon Kaen, Thailand

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.

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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.

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

Appendix 7. Research paper 4. Retention of copyright / permission to publish.

From: Abda Mahmood [<mailto:Abda.Mahmood@lshtm.ac.uk>]

Sent: 22 November 2019 13:51

To: Journalpermissions

Subject: Submission id is: EJOT-D-19-00497

Dear colleagues

I am enquiring regarding permission to use the manuscript I submitted on 14 October 2019 to the European Journal of Trauma and Emergency Surgery. The title of the manuscript is **"Tranexamic acid in traumatic brain injury: an explanatory study nested within the CRASH-3 trial."** Submission id is: EJOT-D-19-00497

I am the lead author on this manuscript and would like to include it in my PhD thesis. But because it has only been submitted for publication consideration, I am not able to acquire the online license to re-use it. The thesis will be sent to two examiners in December 2019, and if the PhD is awarded, the earliest the thesis would be placed into a university repository is the end of March 2020. Should the article be accepted for publication, we will request for open access publication, which I believe includes permission to re-use the article as long as the authors are credited. If the article is accepted for publication and is published after March 2020, I can request for the thesis not to be made available until after publication, if preferred.

I would appreciate your advice on how to proceed.

Best wishes

Abda

Abda Mahmood

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Title: TXA in traumatic brain injury: an explanatory study nested within the CRASH-3 trial.

Authors: The CRASH-3 Intracranial Bleeding Mechanistic Study Collaborators

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Abstract

Purpose: The CRASH-3 trial is a randomised trial of TXA (TXA) on death and disability in patients with traumatic brain injury (TBI). It is based on the hypothesis that early TXA treatment can prevent deaths from post-traumatic intracranial bleeding. The results showed that timely TXA treatment reduces head injury deaths in patients with reactive pupils and those with a mild to moderate GCS at baseline. We examined routinely collected CT scans in a sample of 1767 CRASH-3 trial patients to explore if, why, and how patients are affected by TXA.

Methods: The CRASH-3 IBMS is an explanatory study nested within the CRASH-3 trial. We measured the volume of intracranial bleeding on CT scans using established methods (e.g. ABC/2).

Results: Patients with any un-reactive pupil had a median intracranial bleeding volume of 60ml (IQR 18ml to 101ml) and patients with reactive pupils had a median volume of 26ml (IQR 1ml to 55ml). Patients with severe GCS had median intracranial bleeding volume of 37ml (IQR 3ml to 75ml) and patients with moderate to mild GCS had a median volume of 26ml (IQR 0.4ml to 50ml). For every hour increase from injury to the baseline scan, the risk of new bleeding on a further scan decreased by 12% (adjusted RR=0.88 [95% CI 0.80–0.96], p=0.0047).

Conclusion: Patients with reactive pupils and/or mild to moderate GCS may have benefited from TXA in the CRASH-3 trial because they had less intracranial bleeding at baseline. However, because bleeding occurs soon after injury, treatment delay reduces the benefit of TXA.

Keywords

Traumatic brain injury, TXA

Introduction

The CRASH-3 trial is a multi-centre, randomised, placebo-controlled trial of the effects of TXA on death and disability in patients with traumatic brain injury (TBI) [1]. Adults with TBI who were within 3 hours of their injury and had a Glasgow coma scale score (GCS) ≤ 12 or any intracranial bleeding on CT scan were included in the primary analysis. We hypothesised that early administration of TXA might prevent deaths from post-traumatic intracranial bleeding. We found that rapid TXA treatment reduces head injury deaths in patients with mild to moderate head injury (RR=0.78 95% CI 0.64-0.95) but there was no apparent reduction in severe head injury (RR=0.99, 95% CI 0.91-1.07), regardless of time to treatment. Because our main aim was to assess the effect of TXA on head injury death, to simplify the trial procedures, we did not plan to collect data on the amount of intracranial bleeding in all patients. However, while the trial was underway, the data monitoring committee asked us to consider collecting these data on a sample of trial patients “to explore if, why, and how patients are affected by TXA.” In response, routinely collected brain imaging data (mainly CT scans) were assessed in 1,767 CRASH-3 trial patients. Because early TXA treatment is expected to be more effective than late treatment [2], to reduce time to randomisation, many patients were randomised into the CRASH-3 trial without a baseline CT scan. A total of 1,147 patients in the IBMS had a baseline (prior to randomisation) CT scan, of whom 812 patients had another clinically indicated brain scan. We measured the volume of intracranial bleeding on scans using established methods (e.g. ABC/2) [3] and collected data on other CT features of TBI. Here we consider the CRASH-3 trial results in light of the CT scan data.

Methods

The protocols for the CRASH-3 trial and Intracranial Bleeding Mechanistic Study (IBMS) are published separately [4-5]. The CRASH-3 IBMS is an explanatory study nested within the CRASH-3 trial. Patients who fulfilled 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, were eligible for inclusion in the IBMS. Routinely collected CT scans were examined between February 2016 and January 2019 across 14 hospitals in the UK and Malaysia. Most patients in the IBMS were randomised into the CRASH-3 trial within 3 hours of injury (76%, n=1350); the rest were randomised between 3 and 8 hours of injury. Patients had a median age of 45 years, median systolic blood pressure of 136 mmHg, and median GCS of 7 (80% male, 20% female). In the CRASH-3 IBMS, a total of 65% of patients (n=1147) had a baseline CT scan done within a median of 2 hours after injury (IQR 1h to 2h), of whom 71% had another clinically indicated brain scan done within a median of 35 hours after injury (IQR 19h to 77h).

Simple validated scales were used to estimate intracranial haemorrhage volume on CT scans. The ABC/2 method is a quick and easy technique used to estimate intracranial haemorrhage volume. This method selects a representative slice near the centre of the haematoma on which the bleed is most visible. On this slice, two measurements are taken: (A) the maximal diameter; (B) width perpendicular to A. For the measurement of depth, the maximal number of slices on which the haematoma is visible is multiplied by slice thickness (C). These three measurements are multiplied and the sum divided by two (ABC/2) to provide the volume measurement in cm³ (ml). One cubic centimetre is equivalent to one millilitre. Clinical outcomes (e.g. GCS score, pupil reaction) were assessed as part of the CRASH-3 trial entry procedure [4].

Results

Intracranial bleeding on baseline CT scan

Figure 1 shows the type and frequency of intracranial bleeding on baseline CT scans according to baseline GCS. A total of 61% of patients with a baseline scan presented with more than one type of bleed. With the exception of epidural bleeding, which was more prevalent in patients with mild to moderate GCS, all other bleed types were more common in patients with a severe GCS. Subdural bleeds had a larger median volume of 46ml (IQR 27ml to 71ml) compared to epidural bleeds with 6ml (IQR 2ml to 20ml), intra-parenchymal bleeds with 1ml (IQR 0.2ml to 3ml), and intra-ventricular bleeds with a median volume of 0.4ml (IQR 0.1ml to 2ml).

Figure 2 shows the volume distribution of intracranial bleeding on baseline CT scans by pupil reactions and GCS. The median volumes of 64ml (IQR 26ml to 108ml) in patients with no reactive pupils and 48ml (IQR 3ml to 93ml) in patients with one reactive pupil were larger than 26ml (IQR 1ml to 55ml) in patients with two reactive pupils. The median volumes of 37ml (IQR 3ml to 75ml) in patients with a severe GCS were greater than 28ml (IQR 1ml to 53ml) for moderate GCS and 18ml (IQR 0.2ml to 41ml) in mild GCS. But there is substantial overlap in bleeding volumes between pupil reaction groups and GCS groups.

We used data on the time of injury and time of CT scan to estimate the time-adjusted volume of intracranial bleeding. Table 1 shows the time-adjusted volume of bleeding by pupil reaction, GCS score, and type of bleed. The time-adjusted volume of bleeding was largest in those with un-reactive pupils and in those with severe GCS. Subdural bleeding was more rapid than epidural, intra-parenchymal, and intra-ventricular bleeding.

Table 1 Baseline intracranial bleeding volume (adjusted for time from injury to baseline scan)

	Median (lower quartile, upper quartile) millilitres / hour
All patients (n=1,135)	16 (1, 36)
Pupil reaction	
None react (n=141)	32 (14, 55)
One react (n=94)	21 (2, 47)
Both react (n=867)	13 (0.5, 31)
Glasgow coma scale (GCS) score *	
Severe (n=388)	20 (2, 41)
Moderate (n=331)	13 (0.3, 29)
Mild (n=91)	8 (0.1, 20)
<i>Bilateral un-reactive pupils or GCS 3 * (n=131)</i>	28 (10, 54)
Type of intracranial bleeding	
Subdural (n=732)	25 (13, 42)
Epidural (n=215)	4 (1, 10)
Intra-parenchymal (n=709)	0.4 (0.1, 2)
Intra-ventricular (n=184)	0.3 (0.1, 1)

*Glasgow Coma Scale (GCS) score assessed before intubation / sedation (n=814 / 1,135) (72%)

But the bleeding rate may not be constant. We found a non-linear association between time and bleeding volume (see Figure 3). The majority of expansion occurred in the first 1 to 1.5 hours after injury. Patients with a severe GCS seemed to bleed more and faster than patients with moderate to mild GCS.

Other intracranial pathologies on baseline CT scans

TBI patients often present with intracranial pathologies in addition to intracranial bleeding. Compared to patients with mild to moderate GCS, the prevalence of sulcal effacement was greater in those with severe GCS (44% vs 59%; n=190/433 vs n=417/702), as was ventricular effacement (30% vs 47%; n=128/433 vs 328/702), and midline shift (39% vs 48%; n=169/433 vs. 337/702). Patients with a severe GCS and midline shift had a median shift of 7.4mm (IQR 4.1mm to 14.1mm) whilst those with moderate to mild GCS had a median shift of 4.3mm (IQR 2.8mm to 7.1mm).

Intracranial bleeding on follow-up CT scans

Seventy one percent (n=812) of patients with a baseline CT scan had a second or third clinically indicated CT scan. Over a third of these patients (n=318) had a bleed on a subsequent scan that was not seen on the first scan. Patients who had their first CT scan soon after injury were more likely to have a new bleed on a subsequent scan. The prevalence of new bleeds among those scanned ≤ 1.5 hours, >1.5 to 3 hours, >3 to 8 hours after injury was 46%, 38%, 31%, respectively. For every 1 hour increase from injury to the baseline scan, the risk of new bleeding on a further scan decreased by 12% (RR=0.88 [95% CI 0.80 – 0.96], p=0.0047) (adjusted for baseline GCS score, pupil reaction, and time from injury to follow-up scan). The sooner the first scan was done after injury, the greater the opportunity for a new bleed to manifest on a further scan.

Baseline intracranial bleeding, raised intracranial pressure, un-reactive pupils, and head injury death

An increase in the volume of intracranial bleeding (ml) was associated with an increase in the amount (mm) of midline shift (beta coefficient 0.10 [95% CI 0.09-0.10], $p < 0.0001$) (see Figure 4). An increase in midline shift (mm) was associated with an increase in the risk of having one or more un-reactive pupils (RR 1.08 [95% CI 1.07-1.10], $p < 0.0001$) (see Figure 5). Of those with baseline scans available for rating, 247 patients subsequently died from head injury. The median time-adjusted volume of intracranial bleeding among patients who died from head injury is 37ml/h (IQR 18ml/h to 58ml/h) and in those who survived head injury death is 11ml/h (IQR 0.3ml/h to 28ml/h). Patients who died of head injury within 24 hours of injury had a higher median time-adjusted bleeding volume of 51ml/h (IQR 28ml/h to 73ml/h), than those who died within 48-72 hours of injury with 39ml/h (IQR 19ml/h to 56ml/h), and beyond 72 hours of injury with 28ml/h (IQR 14ml/h to 52ml/h).

Discussion

The CRASH-3 trial results suggest that the effect of TXA on head injury death depends on the time interval between injury and the start of treatment and on the severity of TBI [1]. Early treatment of patients with a mild to moderate GCS reduces head injury death, but there is no evidence for benefit in patients with a severe GCS, regardless of time to treatment. The CT scan data are consistent with the hypothesis that TXA reduces head injury deaths by reducing intracranial bleeding. Patients with a mild to moderate GCS may be more likely to benefit from TXA because they have less intracranial bleeding at baseline. However, because bleeding occurs soon after injury, treatment delay reduces the benefit. On the other hand, patients with a severe GCS have less to gain from treatment because they already have extensive intracranial bleeding at baseline and/or other intracranial pathologies that are not affected by TXA. Our explanatory hypothesis is illustrated in Figure 6.

The CRASH-3 investigators anticipated in their statistical analysis plan [6] that TBI patients with GCS 3 or bilateral un-reactive pupils at baseline would have little potential to benefit from TXA and their inclusion in the analysis would dilute any treatment effect towards the null. They therefore pre-specified a sensitivity analysis that excluded these patients. Our CT data supports this decision, showing that these patients have extensive intracranial bleeding, and other intracranial pathologies, prior to treatment. However, whilst patients with bilateral un-reactive pupils were excluded, those with unilateral un-reactive pupils were not, despite having high volumes of intracranial bleeding at baseline. Patients with unilateral un-reactive pupils might also have brain herniation and their inclusion might have diluted the treatment effect. Indeed, when patients with GCS 3 and any un-reactive pupils at baseline are excluded, the effect of TXA on head injury death is noticeably larger [1].

Research in context.

Evidence before this study

Prior to this study, in 2015 we conducted a systematic search of all randomised trials of antifibrinolytic agents and identified two completed trials of TXA in TBI. These trials used CT scans to examine the extent of intracranial bleeding before and after randomisation. The following databases were searched: the Cochrane Injuries Group's Specialised Register, The Cochrane Library, Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid OLDMEDLINE(R), Embase Classic+Embase (OvidSP), PubMed and clinical trials registries. Both trials were judged to be at low risk of bias across several domains (sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting). When the two trials are combined in a meta-analysis, there is a statistically significant reduction in intracranial haemorrhage with TXA (RR 0.75; 95% CI 0.58 to 0.98, $p = 0.03$). However, the confidence intervals are wide and the trials are small ($n=249$, $n=229$). Furthermore, although both trials measured intracranial haemorrhage on baseline scans, they did not examine whether the effect of TXA in TBI varies by baseline severity.

Added value of this study

The findings from the current study may help explain the results of the largest randomised trial in TBI to date; the recently published CRASH-3 trial. If at baseline TBI patients present with intracranial bleeding and a number of other neuropathological changes that TXA cannot plausibly affect, their potential to benefit from TXA may reduce. Although clinical signs such as GCS score and pupil reaction were assessed at baseline, the CRASH-3 trial procedure did not involve examining the intracranial pathologies that may lead to these clinical signs. In severely injured patients, the immediate neurologic damage from the trauma may have been too severe to be alterable and TXA may have little potential to reduce intracranial bleeding progression and the risk of head injury death. In this study, we considered the occurrence of secondary neuropathological changes that occur after the primary TBI and before randomisation into the CRASH-3 trial. Knowledge of these changes can inform understanding of the potential for TXA to improve patient outcome, and may help explain any variations in treatment effect by baseline injury severity in the CRASH-3 trial.

Implications of all the available evidence

The CRASH-3 trial treatment was given after arrival at hospital. Less than 20% of patients were treated within an hour of injury. Although there was no apparent benefit in patients with a low GCS on hospital arrival, if our explanatory hypothesis is correct, some of these patients might have benefited had they been treated in the pre-hospital setting. In many high-income countries, TXA is routinely administered by paramedics at the scene of the injury to treat acute severe bleeding. In low- and middle-income settings, this is not always possible due to resource constraints and a lack of health workers who can administer intravenous drugs in the pre-hospital setting. Alternatives to intravenous administration of TXA such as intramuscular injection would be easier, require less training, and may reduce time to treatment. However, patients with more severe injuries in settings with insufficient in-hospital resources may die despite an early

reduction in intracranial bleeding. Evidence suggests that patients with severe TBI in low- and middle-income settings may be more likely to die compared to those in high-income settings. More rapid administration of TXA in settings with adequate medical care for patients with major trauma could increase the proportion of TBI patients who have the potential to benefit.

Abbreviations

CI: confidence interval; CRASH: Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage; CT: computed tomography; IQR: interquartile range; RR: relative risk; TBI: traumatic brain injury.

Author contributions

Abda Mahmood and Ian Roberts drafted and revised the manuscript. Kelly Needham provided expertise in data presentation, data integrity, and statistical analysis. Haleema Shakur-Still facilitated protocol development, study design, and conduct. David Davies provided expert guidance in rating CT scans and developing the method. Antonio Belli, Sabariah Faizah Jamaluddin, Tim Harris, Fatahul Laham Mohamed, Caroline Leech, Hamzah Lotfi, Phil Moss, Phil Hopkins, Darin Wong, Jason Kendall, Adrian Boyle, Mark Wilson, and Melanie Darwent facilitated data collection at their respective hospital sites. Ian Roberts provided epidemiological oversight. All authors critically read the manuscript and provided feedback for improvement.

Declaration of interests

Abda Mahmood, Adrian Boyle, Antonio Belli, Caroline Leech, Darin Wong, David Davies, Fatahul Laham Mohamed, Haleema Shakur-Still, Hamzah Lotfi, Ian Roberts, Jason Kendall, Kelly Needham, Mark Wilson, Melanie Darwent, Phillip Hopkins, Phil Moss, Sabariah Faizah Jamaluddin and Tim Harris have no conflicts of interest to declare. Antonio Belli was in receipt of a grant from the National Institute for Health Research during the conduct of the study.

Data sharing

Following publication of the analyses detailed in the CRASH-3 IBMS statistical analysis plan, individual de-identified patient data, including a data dictionary, will be made available via our data-sharing portal, The Free Bank of Injury and Emergency Research Data (freeBIRD) website (<http://freebird.Lshtm.ac.uk>) indefinitely. This will allow for maximum utilisation of the data to improve patient care and advance medical knowledge. The study protocol, statistical analysis plan and publications will be freely available at <http://www.txacentral.org/>. If additional analyses are proposed, we would request a protocol and expect that a data access agreement is in place.

Informed consent

In the CRASH-3 trial, patients were unable to provide consent and so consent was sought from the patient's relative, legal representative, or the responsible clinician. If and when the patient regained capacity to provide informed consent, they were informed about the trial and written consent sought to continue participation in the trial. If a patient or patient representative declined consent, they were withdrawn from the trial. For patients who were included in the trial but did not regain capacity, written informed consent was sought from a relative or legal representative. The requirements of relevant local and national ethics committees were adhered to at all times.

The CRASH-3 trial included consent to extract data from patient medical records. Collecting CT scan data for the explanatory study was consistent with the consent procedure used in the CRASH-3 trial. It would be impractical to re-consent patients or relatives/legal representatives to access CT scans, particularly for patients who had deceased or were disabled as a result of their injuries where re-consent would have been distressing and unwelcome. The London School of Hygiene and Tropical Medicine and national Ethics Committees extended their approvals to extract CT data from the CRASH-3 trial without further patient consent. Patients who withdrew from the main CRASH-3 trial were not included in the explanatory study.

Ethical approval

The Medical Research and Ethics Committee and Health Research Authority reviewed the protocol and supporting documents for the CRASH-3 explanatory study and provided a favourable ethical opinion on 8 June 2016 (Research Ethics Committee Reference 12/EE/0274). All participating hospitals provided local approvals and letters of access for the CRASH-3 explanatory study to be conducted at their respective sites. Favourable ethical opinion was received from the Observational/Interventions Research Ethics Committee at the London School of Hygiene and Tropical Medicine on 24 May 2016 (Reference 11535).

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Research Paper 3: Figures

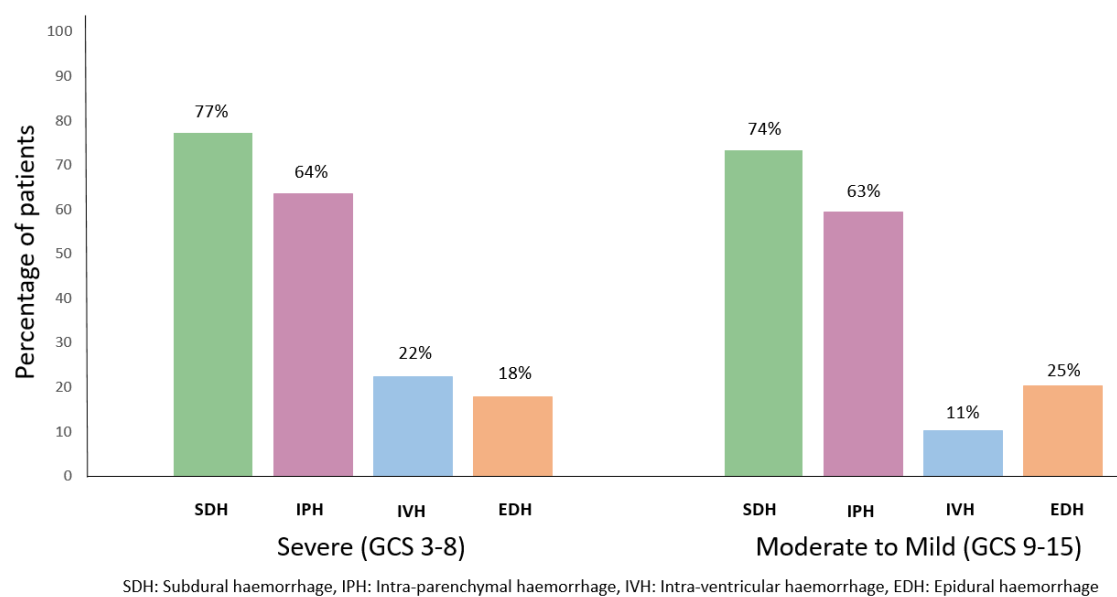


Fig. 1 Baseline prevalence and type of intracranial bleeding by Glasgow Coma Score (GCS)

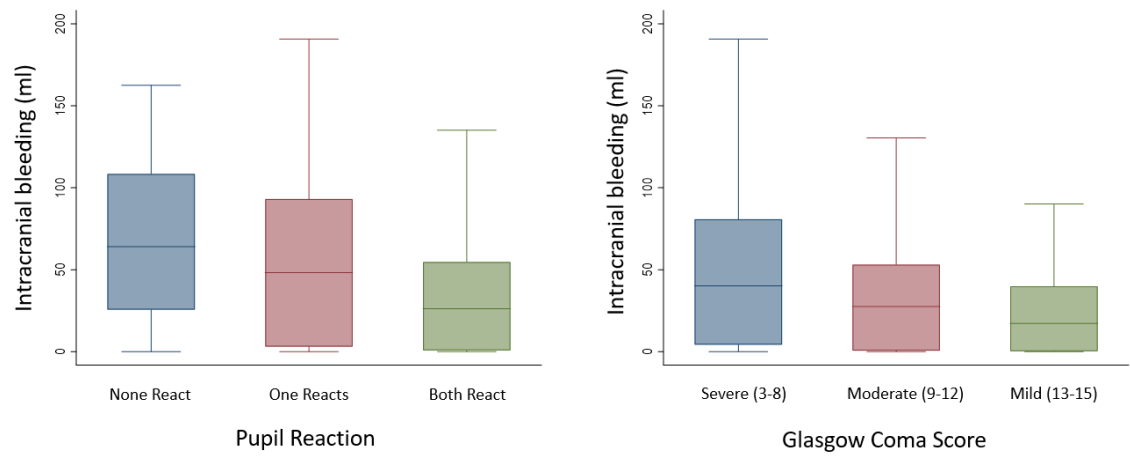


Fig. 2 Baseline intracranial bleeding volume distribution

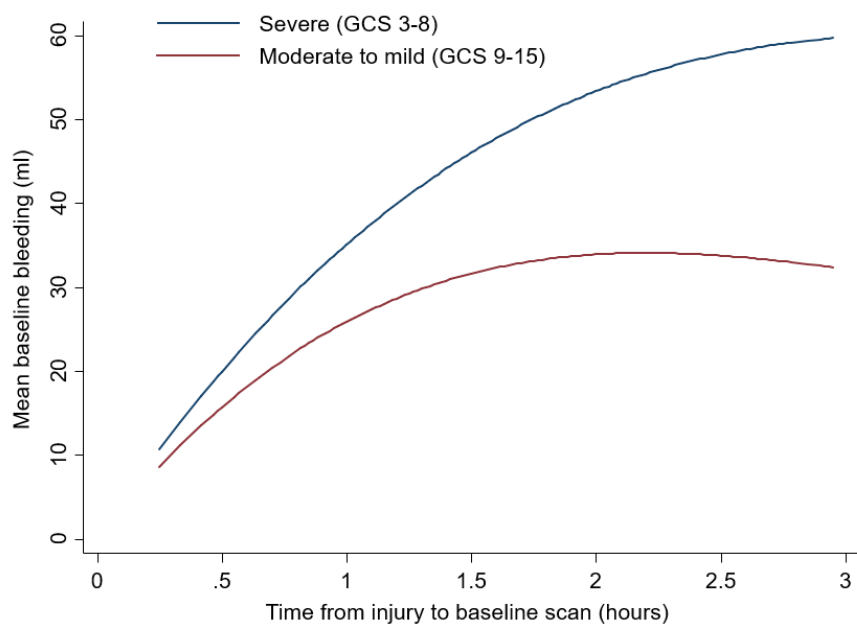


Fig. 3 Association between time from injury to baseline scan and intracranial bleeding on baseline scan

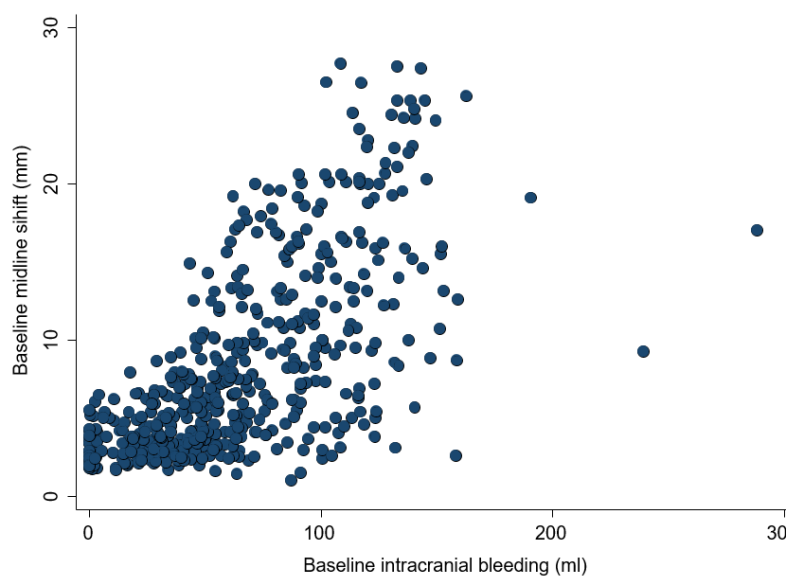


Fig. 4 Association between baseline intracranial bleeding (ml) and baseline midline shift (mm)

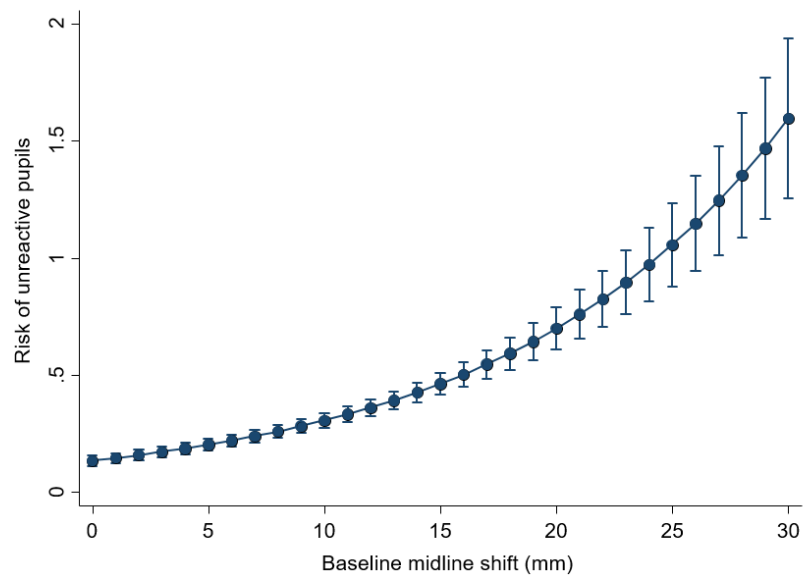


Fig. 5 Association between midline shift and risk of un-reactive (compared to reactive) pupils at baseline

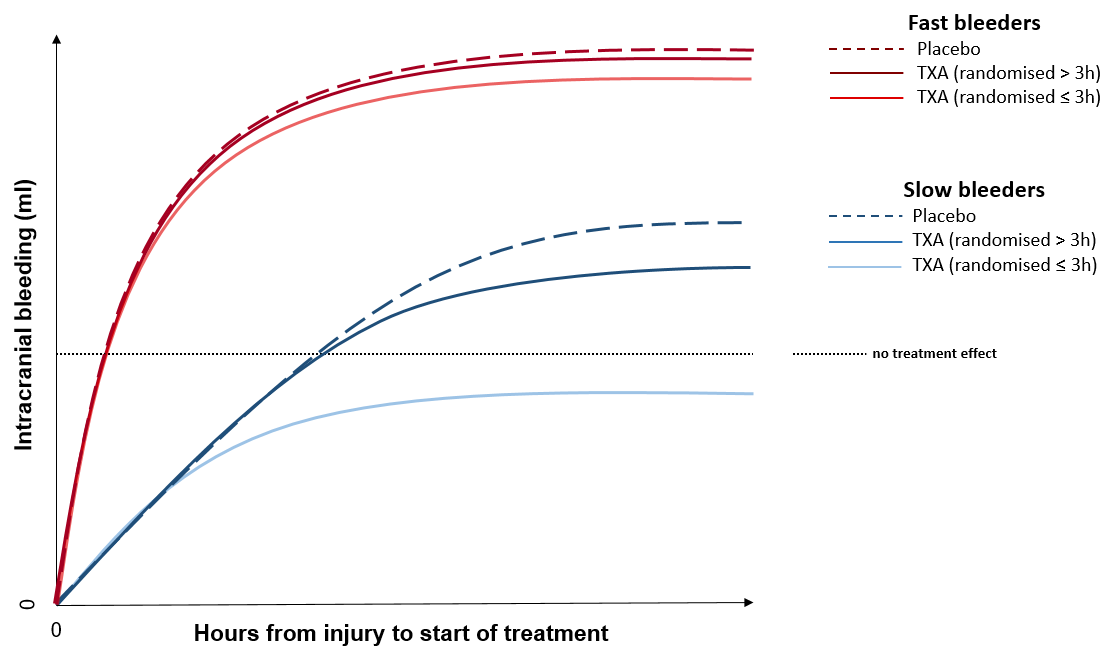


Fig. 6 Hypothesis: association between bleeding rate and treatment effect

Appendix 9. Working procedures: (01) data collection; (02) data management plan.

CRASH-3 Trial Intracranial Bleeding Mechanistic Sub-Study

Clinical Trials Unit (CTU)

London School of Hygiene & Tropical Medicine

Keppel St, London WC1E 7HT, UK



WORKING PRACTICE DOCUMENT 01: CRASH-3 INTRACRANIAL BLEEDING MECHANISTIC SUB-STUDY (CRASH-3 IBMS) DATA COLLECTION	
CURRENT VERSION WPD 1.2	
Trial title	The effect of TXA on intracranial bleeding and cerebral infarction in isolated traumatic brain injury: a randomised trial (CRASH-3 Trial Intracranial Bleeding Mechanistic Sub-Study [IBMS])
Current version date	25/04/2017
Review date	
Protocol code	ISRCTN15088122
Author:	CRASH-3 IBMS Lead: Abda Mahmood
Reviewed by:	Senior Trial Manager: Danielle Beaumont

Revision Chronology:		
Version Number	Effective Date	Reason for Change
1.0	15/08/2016	First effective version
1.1	20/01/2017	Second effective version. From site 2 onwards, all available post-randomisation imaging are examined for cerebral infarction as this outcome may not be detected on CT imaging done soon after injury.
1.2	25/04/2017	Third effective version. All available brain scans (e.g. CT, Angiogram, MRI) are examined for evidence of ischaemic infarcts as imaging methods other than CT are likely to be used to confirm the presence of ischaemic infarcts.

ABBREVIATIONS

CRASH-3	Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage
CRASH3-3 IBMS	CRASH-3 Trial Intracranial Bleeding Mechanistic Sub-study
CT	Computed tomography
CTU	Clinical Trials Unit
EPIC	Epic systems corporation
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
ICH	International Conference on Harmonisation
LSHTM	London School of Hygiene & Tropical Medicine
PACS	Picture archiving and communication system
PI	Principal Investigator
R&D	Research and development
WPDs	Working Procedure Documents

PURPOSE

To define the CRASH-3 Trial Intracranial Bleeding Mechanistic Sub-Study (CRASH-3 IBMS) data collection process to ensure scan data and all other related data are collected and recorded across all relevant sites in a uniform way and according to the protocol, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) standards and applicable regulatory requirements.

INSTITUTIONAL SOP POLICY

All Working Practice Documents (WPDs) for the CRASH-3 IBMS are produced in conjunction with the London School of Hygiene & Tropical Medicine (LSHTM) policies and procedures and the WPDs of the Clinical Trials Unit (CTU) and the CRASH-3 trial.

OTHER POLICIES

The CRASH-3 IBMS will be carried out in accordance with the sub-study protocol, ICH GCP standards, national regulatory authorities' requirements, and the CRASH-3 IBMS WPDs.

RESPONSIBLE PERSONNEL

CRASH-3 IBMS lead (PhD Candidate)

LSHTM CTU | Email: crash@lshtm.ac.uk

Abda Mahmood (CRASH-3 IBMS Lead, PhD Candidate) is responsible for ensuring that all data for the CRASH-3 IBMS is collected and recorded completely and accurately. Abda Mahmood holds letters of access (and Research and Development (R&D) approvals where relevant) for data collection at all participating hospitals. Where additional participating hospitals join the

CRASH-3 IBMS, letters of access and R&D approvals, where relevant, will be obtained prior to data collection at each site.

BACKGROUND

Before data collection can take place at a site, the CTU Co-Directors will work with the CRASH-3 IBMS lead to make contact with the Principal Investigators (PIs) at each selected site to facilitate the data collection process. If the relevant PI approves for the CRASH-3 IBMS to be conducted at their site, the CRASH-3 IBMS lead will send all relevant documents to apply for a Letter of Access and any relevant R&D approvals. Relevant documents include the CRASH-3 IBMS protocol, ethics and regulatory submissions and approvals, a recent Good Clinical Practice training certificate and an updated CV for the CRASH-3 IBMS lead, and other requested documents. The CRASH-3 Trial Manager, and Senior Trial Manager, will support the CRASH-3 IBMS lead to ensure that all relevant regulatory and site-specific approvals are in place for the CRASH-3 IBMS prior to beginning data collection at each site. The CRASH-3 Trial Manager will work with the CRASH-3 IBMS lead to ensure that any substantial amendments to the protocol are documented in accord with regulatory guidelines. The CRASH-3 Trial Manager and Senior Trial Manager will support the CRASH-3 IBMS lead to ensure that the Trial Master File for the CRASH-3 IBMS meets all relevant regulatory requirements.

PROCEDURE

- The CRASH-3 trial Entry Form data (see CRASH-3 trial protocol) in the CRASH-3 trial database will be used to prepare a list of all trial patients at the sub-study site with a Glasgow Coma Scale score of 12 or less. The list will include randomisation (box and pack) numbers, date and time of randomisation, number of hours and minutes between injury and randomisation (i.e. time since injury) and whether or not a CT scan was done before randomisation. The CRASH-3 trial Entry Data for patients who have withdrawn from the CRASH-3 trial will not be included in the above list.
- Once at the participating CRASH-3 IBMS site, the CRASH-3 IBMS lead will provide the hospital research staff with a list of randomisation numbers for patients included in the sub-study. The hospital research staff will access their clinical and research records (including the Randomisation Log) to identify the patients and provide the CRASH-3 IBMS lead with a list of corresponding hospital numbers. Although the CRASH-3 Entry Form records the patient hospital numbers so patients can be identified on site, patients sometimes have

several hospital numbers (e.g. older patients, patients transferred from other hospitals, patients enrolled using trauma numbers). The on-site Randomisation Log will have a log of each patient's hospital numbers and other information including the patient name and date of birth; which can all be used to identify patients on site.

- Case report form (CRF) data will be directly recorded in a web based sub-study database designed, developed and validated in consultation with appropriate regulatory authorities, including ICH GCP guidelines (see WPD 02 Data & Database Management Plan). The web database will be accessed at each participating site to enter the CRF data directly into the database.
- In rare cases when the data cannot be recorded directly into the database, for example, if the database cannot be accessed at the site because of a poor internet connection or inadequate facilities, data will be recorded using paper CRFs (see Appendix 1 of CRASH-3 IBMS Protocol). These paper CRFs will be transcribed into the database as soon as possible, within 1 week of data collection completion at each site and quality controlled at the end of the trial (see WPD 02 Data & Database Management Plan).
- Two online data forms will be completed for each patient (pre-randomisation scan form and post-randomisation scan form – see Appendix 1 of CRASH-3 IBMS Protocol). A second post-randomisation scan form may be completed if the patient has had neurosurgery after the first post-randomisation scan and re-scanned following neurosurgery.
- If there are multiple post-randomisation scans, the post-randomisation scan CRF will be completed using the first post-randomisation scan. The first scan is sometimes done very soon after randomisation (from a few minutes to a few hours) because sites are encouraged to randomise patients into the CRASH-3 trial on the basis of total GCS score rather than bleeding on CT. If this is the only post-randomisation scan available, it will be rated as the post-randomisation scan. If there is a later scan done closer to 24 hours post-randomisation (and without evidence of neurosurgical haemorrhage evacuation), this scan will be rated as the post-randomisation scan. All scans done within 28 days after randomisation will be examined for evidence of cerebral infarcts.
- If the patient does not have a post-randomisation scan, only the pre-randomisation scan form will be completed. If a post-randomisation scan has not been done, the pre-

randomisation scan form will still be completed and it will be recorded on the database that there is no post-randomisation scan for this patient.

- If the patient does not have a pre-randomisation scan, only the post-randomisation scan form will be completed. It will be recorded on the database that there is no pre-randomisation scan for this patient.
- All data will be collected as per the data collection CRFs (Appendix 1 of CRASH-3 IBMS Protocol). Using methods detailed in the protocol (Section 3.8 Outcome Measurement, Page 7), scans will be evaluated alongside the accompanying radiology report for evidence of intracranial haemorrhage, ischaemic infarcts, haemorrhagic oedema, mass effect (ventricular effacement, sulcal effacement and midline shift), neurosurgery and other endpoints defined on the CRFs.
- Additional data, including the date and time of each patient's pre-randomisation scan and post-randomisation scans, and the date and time of neurosurgery (if relevant), will be recorded in an excel spreadsheet held on a protected network drive with restricted access (see WPD 02 Data & Database Management Plan). The excel spreadsheet will be used to calculate: (1) time of injury (*time of randomisation* minus *hours since injury*); (2) number of hours and minutes between randomisation and post-randomisation scan; (3) number of hours between randomisation and neurosurgery. These time intervals will be calculated and recorded in the CRFs so the CRFs do not contain patient identifiable data (such as the dates and times of scans).
- If the sub-study data suggests that patients have been scanned very soon after injury (i.e. from a few minutes to an hour), the Emergency Sheets on the relevant hospital clinical portal system and/or medical records will be checked where possible to confirm that the recorded Time Since Injury on the CRASH-3 Trial database is plausible given the mechanism of injury and patient/relative correspondence with the emergency services. If this check reveals that the data recorded on the CRASH-3 Trial Entry Form is inaccurate, the discrepancy is logged on a CRASH-3 Source Data Verification form, signed by the relevant Principal Investigator/Research Nurse, and amended on the CRASH-3 trial database by the Data Manager/Delegate.
- All CRASH-3 IBMS data will be reviewed on an ongoing basis (see WPD 02 Data & Database Management Plan). The CRASH-3 IBMS Lead will work with the trial management staff at

the Trial Co-ordinating Centre, clinical trial staff at relevant hospitals, Project Directors and the Chief Investigator of the CRASH-3 trial, and statistical advisors for the CRASH-3 IBMS, to ensure that all data is collected, reviewed and published completely and accurately.

ASSOCIATED DOCUMENTS

- CRASH-3 Trial Protocol
- CRASH-3 Trial IBMS Protocol
- WPD 02: CRASH-3 IBMS Data & Database Management Plan

WORKING PROCEDURE 02: CRASH-3 INTRACRANIAL BLEEDING MECHANISTIC SUB-STUDY DATA AND DATABASE MANAGEMENT PLAN	
CURRENT VERSION SOP 1.0	
Trial title	The effect of TXA versus placebo on intracranial haemorrhage and cerebral ischaemia in isolated traumatic brain injury: a randomised trial (CRASH-3 Intracranial Bleeding Mechanistic Sub-Study [IBMS])
Current version date	Feb-2016
Review date	Feb-2016 (Danielle Beaumont) Feb-2016 (Danielle Prowse)
Protocol code	ISRCTN15088122
Author (role: name)	CRASH-3 IBMS Lead: Abda Mahmood
Reviewed by (role: name)	Assistant Data Manager: Danielle Prowse Senior Trial Manager: Danielle Beaumont

Revision Chronology:		
Version Number	Effective Date	Reason for Change
1.0	Feb-2016	First effective version

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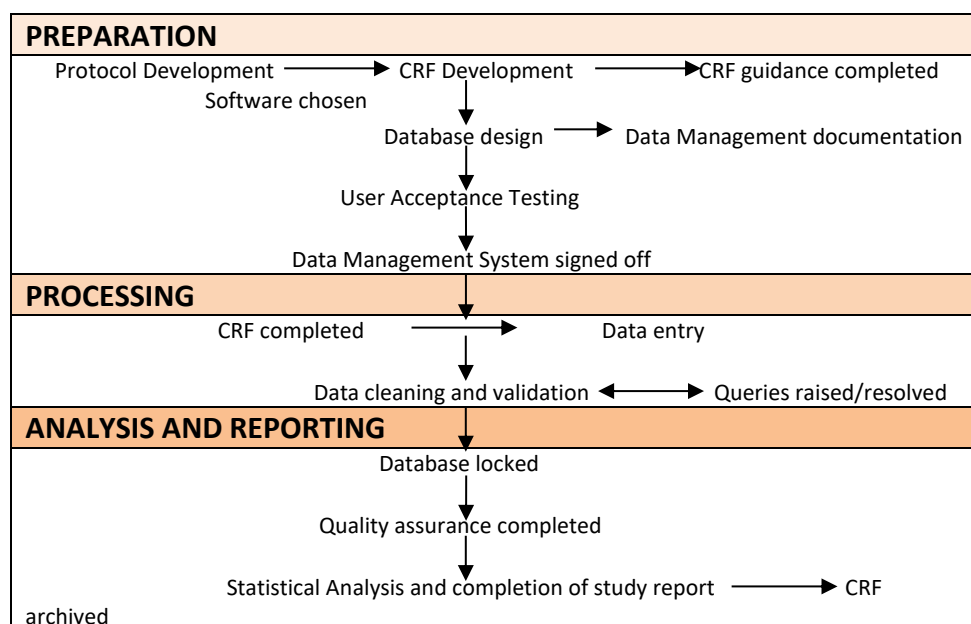
DATA & DATABASE MANAGEMENT PLAN

Abbreviations

CRASH-3	Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage
CRASH-3 IBMS	CRASH-3 Trial Intracranial Bleeding Mechanistic Sub-study
CRF	Case report form
CT	Computed tomography
CTU	Clinical Trials Unit
DMP	Data Management Plan
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
LSHTM	London School of Hygiene & Tropical Medicine
SDV	Source Data Verification
SOP	Standard Operating Procedure
TMF	Trial Master File
UAT	User Acceptance Testing
WP	Working Procedures

Purpose

The Data Management Plan (DMP) documents procedures that should be followed for the processing of data for the CRASH-3 Trial Intracranial Bleeding Mechanistic Sub-Study (CRASH-3 IBMS). The DMP ensures that the integrity of the data is maintained in accord with the CRASH-3 IBMS protocol, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP)¹ standards, and applicable regulatory requirements.



Institutional Working Procedure Policy

All Working Procedures (WPs) for the CRASH-3 IBMS are produced in conjunction with the London School of Hygiene & Tropical Medicine (LSHTM) policies and procedures and the WPs of the Clinical Trials Unit (CTU).

Other Policies

The CRASH-3 IBMS will be carried out in accordance with the ICH GCP¹ standards, national regulatory authorities' requirements, and the CRASH-3 Trial IBMS WPs.

Background

The CRASH-3 IBMS is nested within the CRASH-3 trial and examines the effect of TXA on intracranial bleeding and infarction in patients with isolated traumatic brain injury. A potential benefit of TXA is that it will reduce intracranial bleeding. The CRASH-3 IBMS aims to quantify any difference in bleeding volume between TXA and placebo groups. A potential harm of TXA is that it will increase the risk of cerebral thrombosis and infarction. The CRASH-3 IBMS aims to examine whether patients treated with TXA are more likely to experience these endpoints compared with patients treated with placebo. The CRASH-3 IBMS will be conducted in a selection of approximately 1,000 patients enrolled in the CRASH-3 trial.

Many traumatic brain injury patients undergo a brain scan (e.g. computed tomography (CT) as soon as possible after arriving in the emergency department, as part of routine medical care (i.e. before they are randomised into the CRASH-3 trial). Many patients will be scanned again for clinical diagnostic purposes (i.e. after they are randomised into the CRASH-3 trial). This sub-study will examine pre-randomisation and post-randomisation brain scans as per the data collection forms (see Appendix 1 of the CRASH-3 IBMS Protocol) and methods detailed in the protocol (see CRASH-3 IBMS Protocol). The Data & Database Management Plan for the CRASH-3 IBMS should be read in conjunction with the CRASH-3 trial Data Management Plan (CRASH-3 02 Data Management Plan).

Anonymized data will be recorded in a web database, exported in a csv format, and summarised and analysed using Stata IC 15 software. In order to ensure the integrity of the data:

- (1) the sub-study protocol details the aims, methods and plans for statistical analyses;
- (2) the protocol and statistical analysis plan will be published in peer reviewed medical journals;
- (3) the Working Procedure 01 document details the procedure of data collection;
- (4) all data points in entry and outcome forms are labelled with identifiable headings and descriptions;
- (5) all columns in exported reports will have unique and identifiable headings.

Responsible Personnel

CRASH-3 IBMS lead (PhD Candidate) roles

LSHTM CTU

Email: crash@lshtm.ac.uk

The CRASH-3 IBMS lead (Abda Mahmood) is responsible for:

- the overall conduct and management of the CRASH-3 IBMS;
- working with the CRASH-3 trial staff at the trial coordinating centre and research staff at the relevant hospitals to gain the LSHTM, regulatory and site-specific ethical approvals for the sub-study;
- working with the CRASH-3 trial manager, the senior trial manager, the project director, and the CRASH-3 chief investigator to ensure compliance with ICH GCP¹ standards, national regulatory authorities' requirements, and the CRASH-3 Trial IBMS WPs;
- working with the IT manager to develop the web database;
- collecting, managing, cleaning and analysing data for the CRASH-3 IBMS;
- working with the hospital research staff to extract the patient data using anonymised trial information;
- working with hospital clinical staff (including the site Principal Investigator) to resolve queries regarding scan assessment and data monitoring;
- working with a delegate from the data team to validate any electronic CRFs that are transcribed from paper CRFs;
- working with the project director, chief investigator of the CRASH-3 trial, and statistical advisors for the CRASH-3 IBMS to discuss methodological issues that may arise during data collection;
- working with other investigators following data collection and analysis, to write up and submit the results for publication in peer reviewed medical journals as per the protocol and statistical analysis plan, and disseminate the sub-study findings using patient organisations and relevant online platforms.

CTU IT Manager and Database Developer roles

LSHTM CTU

Email: crash@lshtm.ac.uk

The IT Manager (Hakim Miah) is responsible for developing the web database for the purpose of the CRASH-3 IBMS in consultation with the sub-study lead and in accord with the data collection forms, Specification document and Form Specification Matrix (see Appendix 1 of the CRASH-3 IBMS Protocol, the Specification Document and Form Specification Matrix) and ICH GCP standards. The IT manager is responsible for responding to release requests and development testing. The IT manager and sub-study lead are responsible for ensuring that all changes made to the database are documented using release request forms and user acceptance testing forms.

CTU Data Assistant/Data Manager/Delegate roles

LSHTM CTU

Email: crash.data@lshtm.ac.uk

A delegate from the Data Team is responsible for working with the sub-study lead to ensure that any changes in the CRASH-3 trial entry and outcome data (i.e. following CRASH-3 IBMS data collection) are recorded appropriately with the relevant Source Data Verification forms and the CRASH-3 trial database is updated accordingly.

CTU CRASH-3 Trial Manager and Senior Trial Manager

LSHTM CTU

Email: crash@lshtm.ac.uk

The CRASH-3 trial manager (Lauren Frimley), and senior trial manager (Danielle Beaumont), are responsible for working with the sub-study lead to ensure all relevant regulatory and local ethical approvals are in place for the CRASH-3 IBMS, and all amendments are documented in accord with regulatory guidelines. The trial managers are responsible for working with the sub-study lead to ensure that the trial master file for the CRASH-3 IBMS meets all relevant regulatory requirements.

CTU Project Director and CRASH-3 Chief Investigator (i.e. CTU Co-Directors) roles

LSHTM CTU

Email: crash@lshtm.ac.uk

The CTU Co-Directors are responsible for working with the CRASH-3 IBMS lead to oversee the scientific progress and development of the CRASH-3 IBMS.

Time plan of Trial Activities

Data collection starts	Feb 2016
Data collection ends	~ January 2019
Database hardlock	~ Feb 2019
Start of Result Analysis	~ Feb 2019
Completion of Close out and Publication	~ September 2019
Study Archive	~ December 2019

Case Report Form (CRF) Development and Piloting

The Case Report Forms (baseline and follow-up outcome forms) will be designed according to the *LSHTM SOP 025 CRF Design and Approval* and will be part of the protocol development. The Protocol Committee is responsible for final approval of the CRFs as part of the protocol. The CRFs (see Appendix 1 of the CRASH-3 IBMS Protocol) will be piloted at the Neurosurgical Trauma Unit at the Queen Elizabeth Hospital in Birmingham (Site 1) as per the methods detailed in the protocol (see Protocol for CRASH-3 IBMS). The on-site piloting process will take place under the supervision of Clinical Research Fellow and Neurosurgical Registrar at the Queen Elizabeth Hospital in Birmingham, Mr Dave Davies.

Data Flow***Blinding of the trial drug/placebo***

The CRASH-3 IBMS is nested in a cohort of CRASH-3 trial patients. As such, the blinding of the trial drug and placebo is the same as that detailed in the CRASH-3 trial Data Management Plan (DMP) v.1.1.

Randomisation

The randomisation process is the same as that detailed in the CRASH-3 trial DMP v.1.1.

Inclusion criteria

Patients who have a Glasgow Coma Scale score of 12 or less or intracranial bleeding on a CT scan performed before randomisation into the CRASH-3 trial, and fulfil the inclusion criteria for the CRASH-3 trial, are eligible for inclusion in the CRASH-3 IBMS.

Consent to participate

The CRASH-3 trial includes consent to extract data from patient medical records. Collecting CT scan data for the CRASH-3 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 access CT scans, particularly for patients who have deceased or are disabled as a result of their injuries where re-consent would be distressing and unwelcome. The London School of Hygiene and

Tropical Medicine and national Ethics Committees extended their approvals to extract CT data from the CRASH-3 trial without further patient consent. Patients who withdrew from the main CRASH-3 trial would not be included in the CRASH-3 IBMS.

Protocol deviations and violations

Any unintentional (protocol deviation) or intentional (protocol violation) failures to adhere to the CRASH-3 trial protocol will be dealt with as per the procedure detailed in the CRASH-3 trial Data Management Plan v.1.1. The sub-study lead will create a list of all patients eligible for the CRASH-3 IBMS and will collect the CRASH-3 IBMS data directly from the source data at each relevant site. There are no expected protocol deviations or violations for the CRASH-3 IBMS.

Unblinding during the trial

The unblinding process for the CRASH-3 trial is detailed in the CRASH-3 trial DMP v.1.1 (see Work Procedure: Unblinding). The sub-study involves retrospective analysis of CT scans that were done for clinical reasons, therefore, it will not be necessary to unblind a patient after their CT scans have been assessed for the CRASH-3 IBMS.

Adverse Event Reporting

Any adverse events will be reported in accordance with the procedures followed in the CRASH-3 trial.

Pre-randomisation CT data and post-randomisation CT data transmission

The data will be collected by the sub-study lead in accord with the CRASH-3 IBMS Working Procedure 01: Data Collection. The sub-study lead will manually enter the CRASH-3 IBMS pre-randomisation scan data and post-randomisation scan data into the web database from the source data at each participating site. In rare cases where it is not possible to enter the data directly into the web database, the paper CRFs will be completed on site and these uploaded to the web database as soon as possible, ideally within 1 week of data collection completion at the relevant site. Paper CRFs that are transcribed to the web database will be quality controlled as detailed in the QA/QC section.

Queries

Following data collection at each site, where possible, queries will be resolved on site by accessing the site clinical systems and in consultation with the site staff. If it is not possible to resolve queries when on site, queries will be collated and emailed to the trial staff on site as soon as possible, within 1 month following data collection completion at the relevant site. These may include the trial entry form stating that a patient was scanned before randomisation but the time of the first CT on the hospital imaging system is recorded as being done a substantial

period after randomisation. All queries will be followed up before the end of the trial. Once any queries have been confirmed, the database will be updated as soon as possible, within 1 week of the query being resolved. Any query resolution correspondence will be documented in the Trial Master File.

A query may concern the CRASH-3 trial data in addition to the CRASH-3 IBMS data, for example, querying a short duration between injury and first CT scan may highlight an error in the time between injury and randomisation. If there is an error in the CRASH-3 trial entry or outcome data, the sub-study lead will complete the relevant Source Data Verification (SDV) form and any relevant additional documents, including emails, will be attached to the SDV. If an error is found between trial and source data at the participating site and the SDV form is completed at site, the site staff will be asked to sign the SDV to confirm the discrepancy. Paper SDVs will be passed on to the CRASH-3 trial Data Team who will update the CRASH-3 trial database accordingly. The sub-study lead may also send corrections of the CRASH-3 trial entry or outcome data to the CRASH-3 Data Team via email. If relevant, the Data Team will advise the relevant on site team to amend their on-site records.

All queries will be resolved or reconciled prior to hardlock. If a query cannot be resolved, the sub-study lead will discuss the query with the Project Director and CRASH-3 Chief Investigator to decide how to proceed.

Self-evident corrections

Following data collection at each site, the data will be exported as reports using a download report facility in the web database. If the error is self-evident, the relevant CRF will be corrected by the sub-study lead without prior permission from the site. Any self-evident corrections immediately following detection. For example:

- If the post-randomisation scan forms indicate that the patient has had neurosurgical haemorrhage evacuation (Neurosurgery fields) but the Marshall Classification (which also records whether a patient has had a haemorrhage evacuation) does not record neurosurgical haemorrhage evacuation, the outcome form will be re-checked and the Marshall Classification or Neurosurgery fields amended, as appropriate.
- If the patient has been recorded as having a very large and improbable haemorrhage volume (i.e. several thousand milliliters), the volume will be re-estimated using the recorded A (maximum length of haemorrhage), B (maximum width perpendicular to A) and C (depth of haemorrhage), to ensure that the total volume recorded is correct. If there has been a simple error in multiplication ($A \times B \times C$), the total volume will be corrected using a self-evident correction. If there has been an error in the A, B or C fields

and this is self-evident, this will be corrected (e.g. all fields are recorded to 1 decimal place and one value does not contain a decimal place, resulting in a very large number). If the error is not self-evident and requires further investigation, this will be confirmed using the source data as detailed in the Query section above.

Database Development, Testing and Validation

- The web database for the CRASH-3 IBMS will be developed in consultation with the following:
 - *CRASH-3 SOP: Database Development and Validation Plan,*
 - *CTU SOP: Data Management Systems Development and Validation,*
 - *CTU IT SOPs: 001 IT Systems; 002 Server Setup & Conventions; 003 Backup, Logical & Physical Security of Data; and 004 Software Development,*
 - appropriate regulatory authorities, including ICH GCP guidelines (1).
- A *Risk Analysis* will be performed to identify and minimize risks and hazards of using a custom developed web database. The *Risk Analysis* will be saved here: J:\TCC\CRASH3\CT scan substudy\6. Data management\Database\Risk Analysis.
- The database will be developed in accord with the approved CRFs, the *Specification Document* and the *Form Specification Matrix*. The database will include required fields; certain questions must be answered otherwise a form cannot be submitted and saved. More details about these rules is provided in the Computerized Validation Checks section below. The *Specification Document* and *Form Specification Matrix* will be saved here: J:\TCC\CRASH3\CT scan substudy\6. Data management\Database\Specification.
- Prior to release, the electronic CRFs will be tested in a test database against the *Form Specification Matrix*. The sub-study lead will check that data can be entered in the correct format in all fields. The pre-submission data will be compared to the submitted data, and the data in the csv reports, to ensure that it has not been transformed. Once all UAT has passed, a live version of the database will then be released. All relevant database testing documents will be saved here: J:\TCC\CRASH3\CT scan substudy\6. Data management\Database\Testing.
- Any change made to the live version of the database will be requested by the sub-study lead in the form of a Release Request form and approved by the IT Manager. All testing forms and release requests will be saved here: J:\TCC\CRASH3\CT scan substudy\8. Web Database\4_Release Requests and User Acceptance Testing.
- Once all UAT has passed, the latest version of the database will be signed for release.

- Anonymised data (identifiable using box-pack numbers only) will be directly entered into the web database from the source data at each participating site. The data will be automatically uploaded into a central server on form submission.
- All submitted forms will be editable and any revisions to a form following submission will be 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 will be highlighted in each amended version of a form.
- The sub-study lead will enter all data into the database and will not be able to delete a form following submission and upload. If it is later found that the form was entered in error, the sub-study lead must formally request for the relevant form to be deleted, by the IT manager, with an explanation for why the form must be deleted. Then, the IT Manager must access the relevant form from the back end of the server and delete the erroneous data.
- After data collection is complete at each site, using a download report facility, the data will be exported in a csv format and checked in STATA IC 15 for any missing or irregular data. If necessary and appropriate, the data will be amended (i.e. if the error is self-evident, the error will be corrected using a self-evident correction as detailed in the self-evident corrections section above). If the sub-study data is not consistent with the CRASH-3 trial entry or outcome data, the sub-study lead will query with the research/clinical staff on site and assess whether the queries can be confirmed when on site or if required will re-attend the relevant site to examine queries. For example, if the trial entry data says that a patient was scanned before randomisation but the time of the first CT scan is a substantial period after randomisation, this will be investigated further using the paper case report forms, ambulance sheets and the relevant onsite clinical portal. More details of how Queries will be dealt with is provided in the Queries section below.
- As the CRASH-3 trial and CRASH-3 IBMS are ongoing, the CRASH-3 IBMS lead will analyse the blinded data to explore the frequency and distribution of the outcomes.
- When the CRASH-3 trial has completed recruitment, the CRASH-3 IBMS lead will analyse the unblinded data as per the protocol and statistical analysis plan, and in consultation with the CTU Project Director, CRASH-3 Chief Investigator, and statistical advisors for the CRASH-3 IBMS.

Data Validation

The data collection will be done in line with the CRASH-3 IBMS Working Procedure 01: Data Collection. Data review will be done on an ongoing basis by the sub-study lead to ensure the integrity and accuracy of the data. Both manual and electronic validation checks will be carried out on the data from the CRASH-3 IBMS.

Manual checks

The web CRFs will be manually checked once submitted onto the database to ensure that the data has not been changed from entry to submission. This manual check should also identify any outliers and irregularities. The following checks will be performed for the following questions.

Has this patient been scanned before randomisation?

This question is in the pre-randomisation scan form only.

- The sub-study lead will check that this box has been selected if the patient has been scanned before randomisation. She will also check that if this box is selected, the pre-randomisation form must be complete, or an explanation given in the Notes section at the end of the form for why the form has not been completed (e.g. the scan was done but not available to review because the patient was scanned at another site before being randomised into the trial).

Box-pack

- The sub-study lead will check that the box and pack fields are the correct length (i.e. four numbers for Box, two numbers for Pack).

Is there any intracranial bleeding on the scan?

- The sub-study lead will check that if the answer to this question is Yes, that the type and, if relevant, volume of haemorrhage has been recorded. If the answer to this question is No, then there shouldn't be any information in the following haemorrhage fields. If this has been selected No, but there is information regarding type and/or volume of haemorrhage in the proceeding fields, it is likely that this question should have been answered Yes. The sub-study lead will review the relevant scan on site and amend the answer accordingly.

*Is this a new bleed? * This question is on the post-randomisation scan forms only*.*

- This should be answered Yes if there is a new bleed seen after randomisation that was not seen before randomisation. If there is a new bleed, the sub-study lead will highlight which of the recorded bleeds are new in the Note section associated with this question (e.g. parenchymal haemorrhage in left frontal lobe is new).

Marshall classification

- If there is no bleeding on the scan, the 'is there any intracranial bleeding on the scan' question should be answered as No, and the Marshall Classification should be '*Diffuse injury I – no visible pathology*'. The sub-study lead will check for consistency across these fields.
- If *Diffuse Injury II or III* is selected and there is evidence of midline shift, the *midline shift degree* field should be less than 5mm, and the volume of intracranial bleeding should also be less than 25ml. These fields will be checked for consistency.
- If *Diffuse Injury IV* is selected, the degree of *midline shift degree* field should be more than 5mm, and the volume of intracranial bleeding less than 25ml. These fields will be checked for consistency.
- If *Evacuated Mass Lesion* is selected, the Neurosurgery fields should be complete.
- If *Non-evacuated Mass Lesion* is selected, the volume of intracranial bleeding should be more than 25ml.

Is there any evidence of acute focal ischaemic lesion?

- The sub-study lead will check that this field has been answered (Yes/No).

Is there any evidence of an oedematous lesion?

- The sub-study lead will check that this field has been answered (Yes/No).

Is there any sign of ventricular effacement?

- The sub-study lead will check that this field has been answered (Yes/No).

Is there any sign of sulcal effacement?

- The sub-study lead will check that this field has been answered (Yes/No).

Is there any sign of midline shift?

- The sub-study lead will check that this field has been answered (Yes/No). If there is evidence of midline shift, the sub-study lead will check that the degree of mass effect has been entered. The sub-study lead will check that the number is plausible (usually between 3mm and 30mm), and that it is consistent with the rating of the Marshall Classification (see above).

Has the patient had neurosurgery (Yes/No)?

- The sub-study lead will check that if the answer is Yes, that the type of neurosurgery has been specified. If the type of neurosurgery has been entered but whether the patient has had surgery is selected as No, the sub-study lead will re-assess the scan and amend the answers accordingly.
- If the patient has had a neurosurgical haemorrhage evacuation, the Marshall Classification should be answered '*Evacuated Mass Lesion*'. The sub-study lead will check for synchrony between these two fields.

Date of scan reading

- The sub-study lead will check that the correct date has been entered.

Was the patient scanned after randomisation? * This question is in the pre-randomisation scan form only. *

- The sub-study lead will check that if this has been entered as Yes, the post-randomisation scan form is complete, and if the scan was done and not available to rate, there should be a comment in the notes section to this effect.

Computerised validation checks (CVCs)

Computerised validation checks (CVCs) will be built into the CRASH-3 IBMS web database according to the *Database Development, Testing and Validation* section above. Rules will be built into the form builder so that certain entries will be flagged upon submission, and to ensure that certain fields are complete before the form is submitted.

- For example, if the same randomisation number is entered for more than one patient, an error box will appear when submission is attempted. The person entering the data will be able to edit the form with the correct randomisation number and save the amended version of the form with the correct randomisation number.
- If in a time field (i.e., HH:MM), a semi-colon (;) is used rather than a comma (:), an error will appear when submission is attempted and the form will not save until the data is in the HH:MM format.
- All details regarding the CVCs will be detailed in the CRASH-3 IBMS Form Specification Matrix.
- On each CRF there will be an option to 'ignore validation rules' in order to allow the user to switch off the CVCs, if necessary. The 'ignore validation rules' field at the end of the pre-randomisation scan form will be selected in case the patient has not been scanned before randomisation. Selection of this field will mean that all rules built into the form builder will be ignored for that particular form. Selection of this field will allow submission of an empty pre-randomisation scan form so that the post-randomisation scan form data can be entered if the patient was scanned after randomisation and not before.

Data review

The sub-study lead will extract all data using a download report facility within the database and review the data for logical inconsistencies. If possible, this review will be done on site when data collection is complete at each site so that any necessary amendments can be made in consultation with the site source data. If it is not possible to do this review on site, it will be done after leaving the site, and any necessary amendments made by revisiting the site, or by

consulting the site staff via email. This review will include checks to ensure that the data can be exported into the relevant reports, that any outliers (e.g. very large haemorrhage volume) are flagged, and any queries are raised as per the process detailed in the *Queries* and *Self-Evident Corrections* sections. The review will also include checks to confirm that the data is able to capture expected relationships and is not completely random. For example, statistical software Stata IC 15 will be used to check whether patients with larger bleeds on the pre-randomisation scan are more likely to undergo neurosurgery before the post-randomisation scan. The data review for all CRASH-3 IBMS data should be done within 1 month of data collection completion at each site. Any data that the sub-study lead first enters manually on paper CRFs on site and then transcribes into the web database at the CTU will be cross-checked by a delegate as detailed in the *Quality Control and Quality Assurance* section.

Inter-rater reliability

The CRASH-3 trial Entry Form collects data on the location of intracranial haemorrhage on a CT scan done before randomisation (see CRASH-3 Trial Protocol: Entry Form Questions 13 and 14). This information is often from a CT radiology report written by a trainee radiologist and confirmed by a consultant radiologist. The relevant CRASH-3 trial Entry Form data will be cross-checked against the pre-randomisation scan data collected as part of CRASH-3 IBMS to check for inter-rater reliability.

Quality Control and Quality Assurance

Quality control procedures will be built into each of the data management activities:

- CRF Design
- Clinical trial database user acceptance testing

Quality control of CRF Design

Case report forms will be designed according to CTU SOP 003 Case Report Form Design and Approval.

Clinical trial database design and development

The sub-study database will be designed and developed by the sub-study lead and IT Managers at the CTU.

- The sub-study lead will create the database specification as per the approved protocol CRFs.
- The IT Manager will review the database specification and make necessary suggestions.
- The sub-study lead and IT Managers will build the web CRFs as per the final specification and perform development testing on a test version of the database.

- The sub-study lead will conduct UAT on the test version of the database. This test will include entering data into all the fields to check that: 1) data can be entered in all fields and in the required format; 2) data does not change from entry to submission; 3) the required rules have been built into the form; 4) data can be exported into the report using the download report facility.
- Once the database has been tested by the sub-study lead in the test version of the database, any feedback will be relayed to the IT Manager who will make any relevant amendments.
- Once all UAT has been passed, and the sign-off document has been approved, the current database version will go live.
- Any amendments made to the live version of the database will be requested by the sub-study lead using a Release Request form. For example, if a new site has agreed to participate in the sub-study as the sub-study is ongoing, the sub-study lead will ask the IT Manager to add this site to the list of site names in the sub-study database, using a release request form. The IT manager will advise whether the requested change is feasible and update the test database with the proposed revision. The sub-study lead will conduct UAT on all revisions in the test database and communicate any feedback to the IT manager. The IT Manager is responsible for development testing. The live version of the database will be updated with approval from the sub-study lead, IT Manager and Project Director.

Source Data Monitoring

The CRASH-3 IBMS data will be collected directly from the imaging system and other clinical portals at each relevant site (i.e. the source data) and manually entered into the web database. Therefore, source data monitoring is not relevant for the CRASH-3 IBMS.

Data Monitoring Committee

The rules and responsibilities of the Data Monitoring Committee are laid down in the DMC Charter and CRASH-3 trial Protocol. The CRASH-3 IBMS is nested within the CRASH-3 trial and does not have its own Data Monitoring Committee.

Quality Assurance (QA)/Quality Control (QC) of CRF data

- CRASH-3 IBMS data that is manually entered from the source data into the web database will have less transcription error than data entered manually onto paper CRFs from the source data and then transcribed to the web database. Therefore, direct database entry will be prioritised at all participating sites to minimize transcription error. CVCs have been built into the web database in order to minimize transcription error.

- In cases where the web database is temporarily inaccessible at a site (in cases of poor internet connection or inadequate facilities) and the data is first recorded using paper CRFs and then transcribed into the web database, the data in the paper forms will be cross-checked against the corresponding data in the web database at a later date. A delegate will check all the paper CRFs for inconsistencies in data between paper and web versions. The sub-study database will be updated accordingly if there are any errors in transcription.
- The delegate may be an independent person (not related to the trial) and will be used for CRF quality control / assurance activities (e.g. before any medical review meeting or database locks).
- After database lock, QA will be carried out (see below Database Lock and Unlock).

QC/QA of Data Queries

All open data queries will be checked by the sub-study lead on an on-going basis. The sub-study lead will correct any inconsistencies found and will update the trial database as necessary as per query responses.

QA of the IMP blinding procedure

The quality assurance of the blinding procedure is detailed in the CRASH-3 trial DMP.

Database Lock and Unlock

Soft Lock

The CRASH-3 trial will conduct regular interim analyses of the data and soft lock will take place three months prior to a scheduled Data Monitoring Committee Meeting (see CRASH-3 DMP). There are no interim analyses planned for the CRASH-3 IBMS, therefore soft lock is not relevant for the CRASH-3 IBMS.

Hard Lock and Read Only Access

Hard lock of the CRASH-3 trial database will take place at the end of the trial; within 3 months of the end of CRF data collection and once data has been cleaned. Hard lock will adhere to the principles in CTU SOP Database Lock, Release and Unlock (see Work Procedure: Database lock and unlock and Work Procedure: Extracting data).

The CRASH-3 IBMS database will be locked by restricting access to Read Only; within 3 months of the end of CRF data collection and once data has been cleaned. The IT Manager is responsible for restricting access. Prior to data extraction, the sub-study lead will ensure that the database hard lock checklist has been completed (see Appendix 1). All unresolved queries

will be resolved or reconciled prior to data extraction. The sub-study lead, in discussion with the Project Director and CRASH-3 Trial Chief Investigator, will prepare guidance on the database handling of unresolved queries and will produce a report on database status at time of lock (see Appendix 2). When lock has taken place, the sub-study lead will sign the Certification of Lock (see Appendix 3). The treatment allocation code file will be sent to the sub-study lead after database hard lock (CRASH-3 trial) and access has been changed to Read Only (CRASH-3 IBMS database). The unblinded codes will be stored in a secure folder.

Data Extraction

All data stored on the database will be extracted using the download report facility within the database. The csv output will be stored in the CRASH-3 IBMS folder (J:\TCC\CRASH3\CT scan substudy) and automatically password protected and zipped. Prior to beginning the analysis, a check will be done to see if the csv file is accurate and the data has not been transformed from the individual CRF data.

Final Analysis

As soon as possible following database hard lock, the CRASH-3 IBMS lead will unblind the data and run the analysis as per the protocol and statistical analysis plan, using Stata IC 15. The statistical analysis will also be done by the statistical advisors for the CRASH-3 IBMS to check for consistency in results.

Unlock

In the event that the database has to be unlocked, permission to unlock must be given by the Project Director. Access must be restricted to a member of the team who has remained blinded to the results (treatment allocation). The data will be extracted prior to re-lock as detailed under hard lock. The database should then be relocked and certified as such. The CRASH-3 IBMS lead will check the system log to confirm that the actions detailed were carried out and no other changes were made, and sign off the report (see Appendix 3).

Security

- All CRASH-3 IBMS data will be held on a web database and in a protected network drive.
- LSHTM IT Support will be responsible for all security, backups and recovery issues.
- The CTU Database Developer will be responsible for all CTU systems security, backup and recovery.

Access

The data will be held securely with restricted access that is logged.

- a) Data will be stored on a dedicated server by Rackspace who are ISO27001 accredited. Copies of the data forms (image files) sent as email attachments or uploaded onto the CTU secure server will also be held on a protected network drive.
- b) Access to the server is only possible for authorised individuals, who have login accounts and passwords. Only individuals employed by the CTU will have access and the network folders are visible only to them. External access to the LSHTM network from the internet is protected by a firewall which operates a deny-all policy so that only identified traffic to certain allowed hosts is permitted.
- c) All staff have confidentiality clauses in their contracts.

Environment

All data will be held in a secure environment (electronic).

- a) The LSHTM buildings are protected by an electronic entry system and by a security guard on-site to ensure 24-hour protection.
- b) Servers are held in secure data centres within the LSHTM buildings.
- c) Servers are also held by Rackspace in their secure London data centre. Rackspace manage the servers patching and updating the software.

Backup

To prevent accidental loss of data there is a network-wide backup system.

- a) The LSHTM backup system involves nightly, weekly and monthly backups of the network to tape and disk. Backups are kept in a secure area with access via electronic keypad. Tapes are stored in secure fireproof safes.
- b) Backup of the entire network is made on two sites separated geographically, and in the event of a major systems failure the mirror site will retain a full backup.
- c) Rackspace have daily back ups going back the last two weeks. There is an encrypted daily back up of the databases sent to the LSHTM secure network drive.

Archive and destruction

Any paper data will be kept in a secure archive for a period of five years as per the CRASH-3 protocol section 2.14 monitoring. The data shall then be shredded and all storage media shall be destroyed. A Certificate of Destruction will be issued by the company who carries out the destruction under contract to the LSHTM. The CTU and the archivist will retain copies of the Certificate of Destruction. Some data held in the database will be made freely available at

FreeBIRD (freebird.lshtm.ac.uk). Any information which might lead to identification as to where the data originated from will not be made publicly available.

Confidentiality

The CRASH-3 IBMS will only collect data relevant to the trial. No patient names or patient identifiable information will be collected. Only unique randomisation numbers will be recorded on data forms. The randomisation number and hospital ID number will only be used to establish the identity and existence of patients at the participating sites and to cross check the CRFs and CT scans associated with a patient.

Two methods of data collection will be designed/managed to ensure confidentiality:

- 1) The CRASH-3 IBMS lead will directly enter data into the online CRFs (identifiable using box-pack numbers only) held on the web database and accessed at the participating site. The CRASH-3 IBMS lead will be issued with a unique username, password and PIN to access the database. The CRASH-3 IBMS web database is accessible to a restricted number of users (CRASH-3 IBMS lead, IT Manager, CTU Co-Directors) who have a unique username, pin and password to access the database. Only designated CTU staff (IT managers, data assistants and managers) have access to the server. Uploads are automatically logged with the source IP address, date and time.
- 2) This method should only be used if it is not possible to use the web database when on site. Paper CRF entry at site and web entry at the CTU. Paper CRFs will be stored in the sub-study Trial Master File (TMF) (more details in Data Storage below).

Database Authorisation

Only authorised personnel will have access to the CRASH-3 IBMS database. Access to the trial database will be gained through a password system which includes a username, password and pin.

- The IT Manager will grant/remove access as well as managing granularity of access to the database.
- A log file of login successes/failures/attempts will be available.

File Transfer security

All file transfers will be done through secure protocols and files held on secure servers.

Data Storage

- A hard copy of the TMF is held in a locked filing cabinet at the CTU – keys are held securely and restricted to trial staff only. An electronic copy of the TMF is saved on the

LSHTM Shared Network (*J:\TCC\CRASH3\CT scan substudy*). All relevant folders are saved in the order they are referred to in the TMF Index.

- The database is stored on secure servers (ISO27001 accredited data centre in London, by Rackspace) and protected by privileged password protected access. Supplementary data is stored on the LSHTM Secure Network Drive (J Drive).
- Each patient's anonymised CT scan data is saved in the secure online database under the unique patient randomisation number. When the data is exported, it will be organized by pre-defined variable names as per the Database Specification.
- An excel datasheet with pre-loaded anonymised data (from the CRASH-3 Trial Entry Form) and the time of scans has been labelled with column headings and structured so data is entered chronologically (i.e. date and time of injury, date and time of pre-randomisation scan, date and time of post-randomisation scan, data and time of neurosurgery). This datasheet is used to collate the randomisation numbers, date and time of randomisation, and time since injury, for patients eligible for the sub-study. It is also used to record the dates and times of scans, and calculate the intervals between injury and scan (pre-randomisation scan form), scan and randomisation (post-randomisation scan form), and randomisation and neurosurgery (post-randomisation scan form). This spreadsheet does not contain any outcome data and is only used to supplement the CRFs. This spreadsheet is held on a LSHTM Secure Network Drive (J Drive).

Downloadable Reports

Data from each form will be collated in reports, which are available for download from the CRASH-3 IBMS web database. There will be one report with the pre-randomisation data from all patients (pre-randomisation data form). There will be three forms for the post-randomisation scan data (first post-randomisation scan form, second post-randomisation scan form, third post-randomisation scan form). The second and third forms tend to be relevant if the patient has had neurosurgery following randomisation and therefore has been scanned several times. All reports will have unique and identifiable column headings.

Archiving of Data Collection Documents

'Data collection documents' are, for example, image files or paper data forms.

Paper archive

Paper archiving will follow the paper archiving format as the CRASH-3 trial DMP (see WPD 007 Managing Paper Data and Self Evident Corrections).

Electronic archive

Electronic archiving of files will follow the same electronic file structure as the CRASH-3 trial DMP (see CRASH-3 Trial DMP Appendix 9).

Dissemination

- In order to fulfil ethical obligations to participants and the research community and reduce publication bias, the sub-study is registered on www.clinicaltrials.gov and ISRCTN. The protocol and statistical analysis plan will be published in a peer reviewed medical journals prior to unblinding the trial results.
- The results will be reported to trial collaborators and published in peer reviewed medical journals. Dissemination of results to patients will take place via the media, trial website (www.crash3@lshtm.ac.uk) and relevant patient organisations. Credit in key publications will be assigned to collaborators at participating hospitals.

DATA MANAGEMENT PLAN: REFERENCES

ICH-GCP Guidelines

Located at:

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2_Step_4_2016_1109.pdf

- ICH Harmonised Tripartite Guideline for Good Clinical Practice (2016)

Protocols

Located at J:\TCC\CRASH3\Protocol (generic)\Generic

- CRASH-3 Trial Protocol

Located at J:\TCC\CRASH3\CT scan substudy\1. Protocol and outcome forms\Protocol

- CRASH-3 Trial IBMS Protocol

SOPs/WPs

Located at J:\TCC\CRASH3\Standard Operating Procedures

- CRASH-3 Trial Database Development and Validation Plan
- CRASH-3 Trial Data Management Plan v1.1
- CRASH-3 WP: Unblinding
- CRASH-3 WP: Database lock and unlock
- CRASH-3 WP: Extracting data
- CRASH-3 WPD 007 Managing Paper Data and Self Evident Corrections

Located at J:\TCC\CRASH3\CT scan substudy\6. Working Procedures

- CRASH-3 IBMS WP 01 Data Collection

Located at J:\TCC\GENERAL_TCC\01 SOPs, Policies and GUIDANCE DOCS\03CTU SOPs

- CTU SOP: Database Lock, Release & Unlock

Associated Documents

Located at J:\TCC\GENERAL_TCC\01 SOPs, Policies and GUIDANCE DOCS\03CTU SOPs

- CTU SOP: 031-02 Data Management Systems Development and Validation
- CTU IT SOP: 001 IT Systems
- CTU IT SOP: 002 Server Setup & Conventions
- CTU IT SOP: 003 Backup, Logical & Physical Security of Data
- CTU IT SOP: 004 Software Development

Located at J:\TCC\CRASH3\CT scan substudy\8. Web Database

- CRASH-3 CT Sub-study Risk Analysis
- CRASH-3 CT Sub-study Specification
- CRASH-3 CT Sub-study Testing
- CRASH-3 CT Sub-study post-release changes

Located at J:\TCC\GENERAL_TCC\01. SOPs, Policies and GUIDANCE DOCS\02LSHTM SOPs

- LSHTM SOP 025 Case Report Form Design and Approval

DATA MANAGEMENT PLAN APPENDICES

Data Management Plan Appendix 1

Trial Name: CRASH-3 Intracranial Bleeding Mechanistic Study (CRASH-3 IBMS)

HARD LOCK CHECKLIST	
DETAILS	STATUS
Investigators informed about forthcoming hard lock	DONE
Sealed Envelope Ltd informed of date treatment allocation code file should be sent to CTU Co-Director.	DONE – AS PER CRASH-3 TRIAL
All paper CRFs entered on the database	DONE
All outcomes complete	DONE
All queries resolved or reconciled	DONE

COMMENTS:


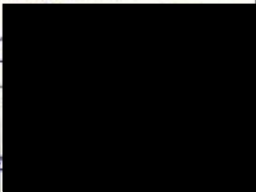
Date: 30 May 2019

Name of CRASH-3 IBMS lead: Abda Mahmood



Signature CRASH-3 IBMS lead:



Data Management Plan Appendix 2

		DATABASE LOCK STATUS REPORT		DATE: 30 May 2019
TRIAL NAME		CRASH-3 Intracranial Bleeding Mechanistic Sub-Study (CRASH-3 IBMS)		
DATABASE/VERSION		1.15		
TOTAL RANDOMISATIONS		1766 1767 <i>ASell</i> 30/5/19		
TOTAL PRE-RANDOMISATION SCAN FORMS		1148		
TOTAL POST-RANDOMISATION SCAN FORMS		1443		
DETAILS		RANDOMISATION NUMBER	ACTION NECESSARY/TAKEN	
Neurosurgery date-time could not be confirmed for 64 patients. In these cases, there will be a missing response for question 8c (post-randomisation scan form).		List attached.	None.	
Pre-randomisation CT Head Scan done but not available for reading due to technical reasons.		7142-76 3097-32 3157-34 5130-58 3158-33	None	
Post-randomisation scan done but not read due to technical reasons / scan quality / error in recorded time of randomisation.		3325-35 5067-57 7052-73 5208-54	None.	
Trial protocol deviations		N=79		
Trial protocol violations		N=4		
CONFIRMATION OF STATUS AT LOCK				
NAME: <i>ABDA</i> <i>MAHMOOD</i>		SIGNATURE: 	DATE: <i>30/5/19</i>	
NAME: <i>J.P. Shahan Stiel</i>			DATE: <i>30/5/19.</i>	


Data Management Plan Appendix 3

 <p>CRASH-3 Critical Randomisation of an Anti-Seizure in Epilepsy Trial</p>	CERTIFICATION OF DATABASE LOCK		DATE: 30 May 2019
TRIAL NAME	CRASH-3 Trial Intracranial Bleeding Mechanistic Sub-Study (CRASH-3 IBMS)		
DATABASE/VERSION	1.15		
In accordance with CRASH-3 trial Working Practice Document: Database Lock and Unlock the database was locked:			
DATE: 30 May 2019			
LOCKED BY: MBWANA MOHAMMED			
TOTAL PRE-RANDOMISATION SCAN FORMS: 1148 TOTAL POST-RANDOMISATION SCAN FORMS: 1443 TOTAL UNRESOLVED QUERIES: N/A			
Certification of Database Lock			
Name: ABDA MAHMOOD		Date: 30/5/19	
Name: + SHAKIL - SILE		Date: 30/5/19.	
MBWANA MOHAMMED		30/5/19	

CRASH-3 INTRACRANIAL BLEEDING MECHANISTIC STUDY | DATABASE LOCK DOCUMENTS
 Date: 30 May 2019

Page 3 of 3

Data Management Plan Appendix 4

	DATABASE UNLOCK REPORT		DATE:
TRIAL NAME	CRASH-3 Intracranial Bleeding Mechanistic Sub-Study (CRASH-3 IBMS)		
DATABASE/VERSION			
AUTHORISATION			
In accordance with Working Practice Document: Database Lock and Unlock authorisation to unlock was given by:			
Name:	Signature:	Date:	
DATA CORRECTIONS/AMENDMENTS			
Changes were made to the data as detailed in the attached document.			
Name:	Signature:	Date:	
LOG CHECK			
Name:	Signature:	Date:	

Appendix 10. Formula to estimate subdural haemorrhage volume.

$$\frac{[4/3 \pi (6.85)^3 - 4/3 \pi (6.85-r)^3]}{8}$$

8

We used the longitudinal diameter (temporal-temporal): 137mm or 13.7cm (6.85cm radius) ¹⁷².

r is the maximum diameter of the subdural haemorrhage.

For example, for a subdural haemorrhage with a diameter of **7.7mm** (i.e. 0.77cm):

$$4/3\pi(6.85)^3 = 1346.35728$$

$$4/3\pi(6.85 - \mathbf{0.77})^3 = 4/3\pi(6.08)^3 = 941.45452$$

$$1346.35728 - 941.45452 = 404.90276$$

$$404.90276 / 8 = 51\text{cm}^3 \text{ (i.e. 51ml)}$$

For example, for a subdural haemorrhage with a diameter of **3.5mm** (i.e. 0.35cm):

$$4/3\pi(6.85 - \mathbf{0.35})^3 = 4/3\pi(6.5)^3 = 1150$$

$$1346 - 1150 = 196$$

$$196 / 8 = \mathbf{25ml}$$

For example, for a subdural haemorrhage with a diameter of **6mm** (i.e. 0.6cm):

$$4/3\pi(6.85 - \mathbf{0.6})^3 = 4/3\pi(6.25)^3 = 1023$$

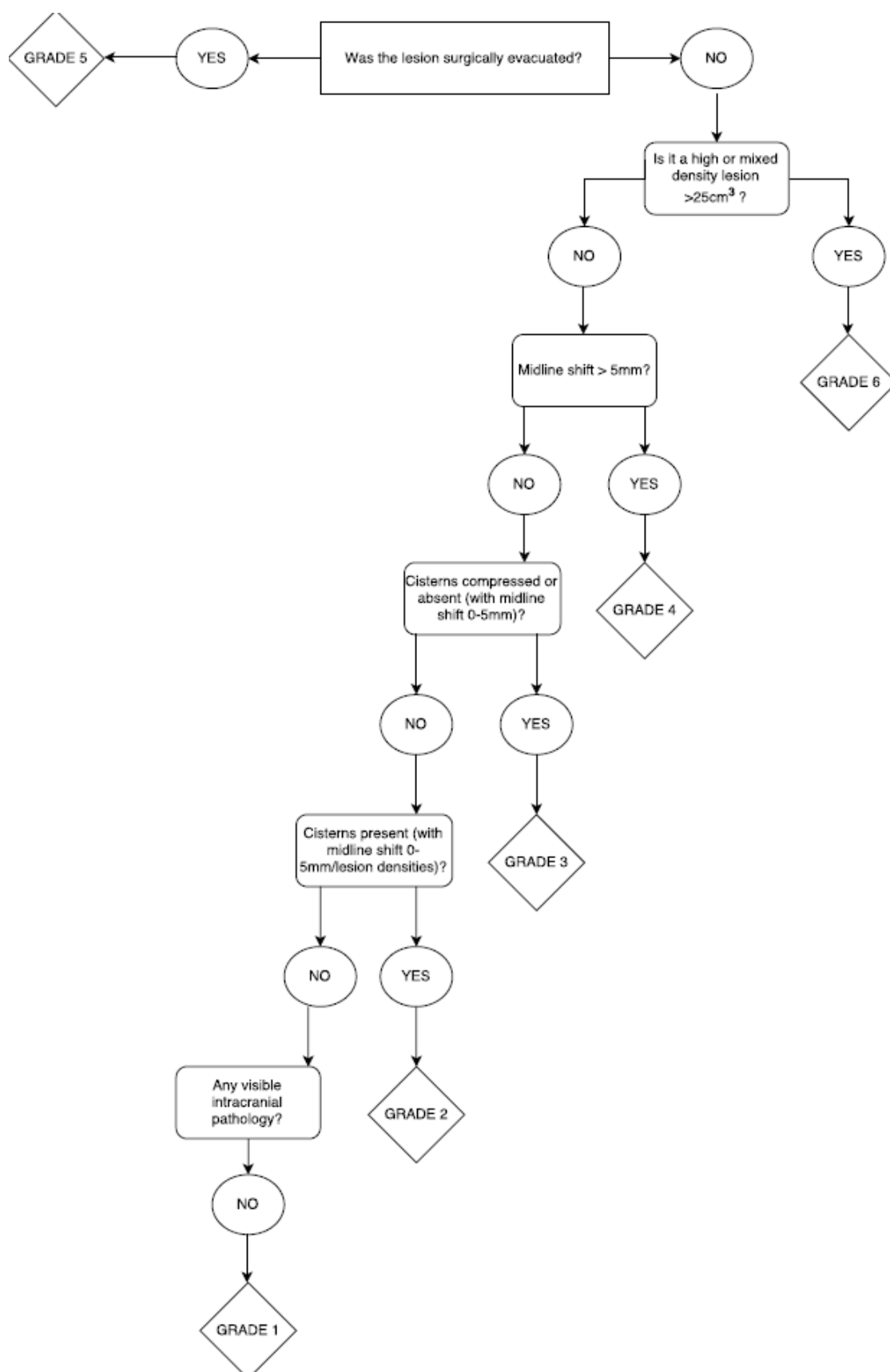
$$1346 - 1023 = 323$$

$$323 / 8 = \mathbf{40 \text{ ml}}$$

Reference #172

J. Talairach and P. Tournoux, "Co-planar Stereotaxic Atlas of the Human Brain: 3-Dimensional Proportional System - an Approach to Cerebral Imaging", Thieme Medical Publishers, New York, NY, 1988

Appendix 11. Marshall Classification flowchart.



Appendix 12. Pre-randomisation and post-randomisation CT scan forms (paper version adapted into web version for data collection).

CRASH-3: CT Scan Sub-Study – ISRCTN 15088122

PRE-RANDOMISATION CT SCAN FORM

CRASH-3 SUB-STUDY: PRE-RANDOMISATION CT SCAN FORM <i>Complete as requested and circle where appropriate, please do not leave blanks.</i>				1. a. <input type="checkbox"/> first reader b. <input type="checkbox"/> second reader
2.	a.Box b.Pack	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	3. Has this patient been scanned before randomisation? YES / NO Time between injury and scan (hrs): _____	

4. Haemorrhagic findings

a. Is there any intracranial bleeding on CT scan? (circle one option on each line)				YES	NO	If NO, go to Question 5 If YES, continue				
Please specify type and volume of haemorrhage:										
b. Parenchymal	YES	NO								
bii. Code	A	B	C	(ABC/2)/1000	HU*	Note	Codes L: Left R: Right T: Temporal F: Frontal P: Parietal O: Occipital BG: Basal Ganglia B: Brainstem Abbreviations A: maximal diameter (mm); B: maximal diameter perpendicular to A (mm); C: number of slices on which haemorrhage is visible multiplied by slice thickness (mm); HU: Hounsfield Unit F: Focal M: Multiple D: Diffuse			
c. Subdural	YES	NO	(measure width only*)							
cii. Code		B			HU	Note				
d. Epidural	YES	NO								
dii. code	A	B	C	(ABC/2)/1000	HU	Note				
e. Intraventricular	YES	NO								
eii. code	A	B	C	(ABC/2)/1000	HU	Note				
f. Petechial	YES	NO	Note:							
g. Subarachnoid	YES	NO	(tick one option per line for each haemorrhage)							
gii. code	Small			Medium			Large			HU
	F	M	D	F	M	D	F	M	D	

5. CT characteristics

Marshall Classification (circle YES to the most severe option only)		
a. Diffuse injury I (no visible pathology)	YES	NO
b. Diffuse injury II (cisterns present with midline shift 0-5mm; no lesion >25cm ³)	YES	NO
c. Diffuse injury III (cisterns compressed/absent with midline shift 0-5mm; no lesion > 25cm ³)	YES	NO
d. Diffuse injury IV (midline shift > 5mm; no lesion > 25cm ³)	YES	NO
e. Evacuated mass lesion (any lesion surgically evacuated)	YES	NO
f. Non-evacuated mass lesion (lesion >25cm ³ ; not surgically evacuated)	YES	NO

6. Non-haemorrhagic findings (circle one option on each line)

a. Is there any sign of acute focal ischaemic lesion?	YES	NO	Volume:	A: ____ mm	B: ____ mm	C: ____ mm	ABC/2: ____ cm ³
b. Are there any oedematous lesions?	YES	NO	bi. total volume in ml				

7. Mass effect findings (circle one option on each line)

Please specify if any of the following <i>mass effect</i> signs are present:			
a. Sulcal effacement	YES	NO	
b. Ventricular effacement	YES	NO	
c. Midline shift	YES	NO	ci. approximate shift (mm)
If yes to any of the above, is the mass effect caused by:			
d. Haemorrhage	YES	NO	
e. Oedema	YES	NO	
f. Both	YES	NO	

8. Neurosurgery

a. Did the patient undergo neurosurgery?	YES	NO	b. Type of surgery:	c. Date of surgery	____/____/____ (dd/mm/yyyy)
--	-----	----	---------------------	--------------------	--------------------------------

9. Details of reading

a. Name of the person completing the form	_____	b. Date of reading	____/____/____ (dd/mm/yyyy)
---	-------	--------------------	--------------------------------

Has this patient been scanned after randomisation into the trial?	YES / NO
Any relevant patient notes	_____

* Place cursor on most visually dense portion of lesion

** If the width of a subdural bleed is greater than 6mm, we can assume the volume is 27cm³ (i.e. to aid rating the Marshall Classification)

5. CT characteristics

Marshall Classification (circle YES to the most severe option only)		
a. Diffuse injury I (no visible pathology)	YES	NO
b. Diffuse injury II (cisterns present with midline shift 0-5mm; no lesion >25cm ³)	YES	NO
c. Diffuse injury III (cisterns compressed/absent with midline shift 0-5mm; no lesion > 25cm ³)	YES	NO
d. Diffuse injury IV (midline shift > 5mm; no lesion > 25cm ³)	YES	NO
e. Evacuated mass lesion (any lesion surgically evacuated)	YES	NO
f. Non-evacuated mass lesion (lesion >25cm ³ ; not surgically evacuated)	YES	NO

6. Non-haemorrhagic findings (circle one option on each line)

a. Is there any sign of acute focal ischaemic lesion?	YES	NO	Volume:	A: ____ mm	B: ____ mm	C: ____ mm	ABC/2: ____ cm ³
ai. Is this a new acute focal ischaemic lesion (not seen on the pre-randomisation scan)?	YES	NO					
b. Are there any oedematous lesions?	YES	NO	bi. total volume in ml				

7. Mass effect findings (circle one option on each line)

Please specify if any of the following mass effect signs are present:				
a. Sulcal effacement	YES	NO		
b. Ventricular effacement	YES	NO		
c. Midline shift	YES	NO	ci. <i>approximate shift in mm</i>	
If yes to any of the above, is the mass effect caused by:				
d. Haemorrhage	YES	NO		
e. Oedema	YES	NO		
f. Both	YES	NO		

8. Neurosurgery

a. Did the patient undergo neurosurgery?	YES	NO	b. Type of surgery:	c. Hours between surgery and CT scan: _____

9. Details of reading

a. Name of the person completing the form	_____	c. Date of reading	____/____/____ (dd/mm/yyyy)
---	-------	--------------------	--------------------------------

10. Ischaemic lesions on further post-randomisation scans

ai. Is there a second post-randomisation scan?	YES	NO
aii. If there is a second post-randomisation scan, is there a new focal ischaemic lesion?	YES	NO
bi. Is there a third post-randomisation scan?	YES	NO
bii. If there is a third post-randomisation scan, is there a new focal ischaemic lesion?	YES	NO

Any relevant patient notes (including info on further scans)	_____
--	-------

Appendix 13. Analysis of covariance (ANCOVA) compared to Linear Mixed Models.

```
. * Data generation
. clear

. set seed 131063

. set obs 1000
number of observations (_N) was 0, now 1,000

. gen id=_n

. gen x1=rnormal()

. gen covar=x1+rnormal()

. gen group = (_n>500)

. gen x2=group+0.5*x1+0.3*covar+rnormal()

.
. * Model 1 - ANCOVA no additional covariate
. regress x2 i.group x1
```

Source	SS	df	MS	Number of obs	=	1,000
Model	813.073565	2	406.536782	F(2, 997)	=	379.20
Residual	1068.88095	997	1.07209724	Prob > F	=	0.0000
				R-squared	=	0.4320
				Adj R-squared	=	0.4309
Total	1881.95451	999	1.88383835	Root MSE	=	1.0354

x2	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]	
1.group	.8809155	.0655542	13.44	0.000	.7522755	1.009556
x1	.7732421	.0330459	23.40	0.000	.7083946	.8380896
_cons	.035865	.0463205	0.77	0.439	-.0550319	.1267619

```
. * Model 2 - ANCOVA with additional covariate
. regress x2 i.group x1 covar
```

Source	SS	df	MS	Number of obs	=	1,000
				F(3, 996)	=	301.00
Model	894.890242	3	298.296747	Prob > F	=	0.0000
Residual	987.06427	996	.991028383	R-squared	=	0.4755
				Adj R-squared	=	0.4739
Total	1881.95451	999	1.88383835	Root MSE	=	.9955

x2	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]	
1.group	.8752111	.0630301	13.89	0.000	.7515241	.9988981
x1	.4849312	.0449033	10.80	0.000	.3968153	.5730472
covar	.2984211	.0328437	9.09	0.000	.2339704	.3628719
_cons	.0391011	.0445362	0.88	0.380	-.0482945	.1264967

```
. * Linear mixed model requires a reshape
. reshape long x, i(id group covar) j(visit)
(note: j = 1 2)
```

Data	wide	->	long
Number of obs.	1000	->	2000
Number of variables	5	->	5
j variable (2 values)		->	visit
xij variables:	x1 x2	->	x

```
. replace visit=visit-1
(2,000 real changes made)
```

```
.
. * Note that it is best not to use the # shortcut to
. * incorporate an interaction term in the linear mixed model
. * because we need to constrain the treatment effect at baseline
. * to be zero and it is slightly fiddly to persuade Stata to do this
. gen inter=group*visit
```

```
. * Model 1 analog, "inter" is the treatment effect
. * Estimate of treatment effect is identical, SE nearly so
. mixed x i.visit inter || id: , reml res(ind, by(visit))
```

Obtaining starting values by EM:

Performing gradient-based optimization:

```
Iteration 0: log restricted-likelihood = -2921.0446
Iteration 1: log restricted-likelihood = -2916.1878
Iteration 2: log restricted-likelihood = -2870.0988
Iteration 3: log restricted-likelihood = -2869.868
Iteration 4: log restricted-likelihood = -2869.8678
```

Computing standard errors:

```
Mixed-effects REML regression          Number of obs    =      2,000
Group variable: id                     Number of groups  =      1,000

Obs per group:
      min =          2
      avg =         2.0
      max =          2

Wald chi2(2)      =      381.58
Prob > chi2       =      0.0000

Log restricted-likelihood = -2869.8678
```

x	Coef.	Std. Err.	z	P> z	[95% Conf. Interval]	
1.visit	.0337063	.0468261	0.72	0.472	-.0580711	.1254838
inter	.8809155	.065453	13.46	0.000	.75263	1.009201
_cons	.0095198	.0313812	0.30	0.762	-.0519864	.0710259

Random-effects Parameters		Estimate	Std. Err.	[95% Conf. Interval]	
id: Identity					
	var(_cons)	.7614755	.0471046	.6745295	.8596287
Residual: Independent, by visit					
	0: var(e)	.223307	.0340269	.1656528	.3010273
	1: var(e)	.8983529	.051715	.8025024	1.005652

```
LR test vs. linear model: chi2(2) = 504.02      Prob > chi2 = 0.0000
```

Note: LR test is conservative and provided only for reference.

```
. * Model 2 analog, note the need for the interaction between
. * visit and the covariate
. mixed x i.visit#c.covar inter || id: , reml res(ind, by(visit))
```

Obtaining starting values by EM:

Performing gradient-based optimization:

```
Iteration 0: log restricted-likelihood = -2577.8477
Iteration 1: log restricted-likelihood = -2500.4798
Iteration 2: log restricted-likelihood = -2490.2573
Iteration 3: log restricted-likelihood = -2489.8617
Iteration 4: log restricted-likelihood = -2489.8616
```

Computing standard errors:

```
Mixed-effects REML regression      Number of obs      =      2,000
Group variable: id                 Number of groups   =      1,000
```

```
Obs per group:
      min =      2
      avg =      2.0
      max =      2
```

```
Wald chi2(4)      =    1571.74
Prob > chi2       =      0.0000
Log restricted-likelihood = -2489.8616
```

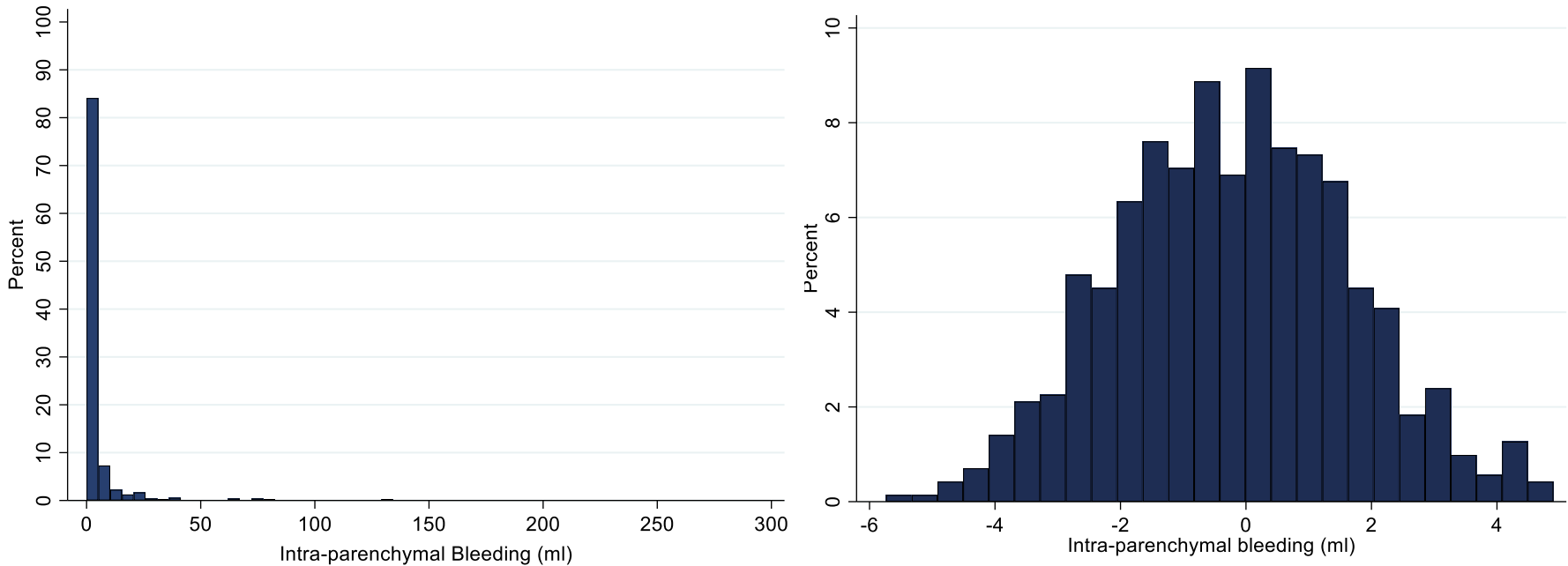
x	Coef.	Std. Err.	z	P> z	[95% Conf. Interval]	
1.visit	.0363059	.0459557	0.79	0.430	-.0537656	.1263774
covar	.5173805	.0163748	31.60	0.000	.4852865	.5494745
visit#						
c.covar						
1	.0319346	.0247112	1.29	0.196	-.0164984	.0803676
inter	.8752111	.0629784	13.90	0.000	.7517758	.9986464
_cons	.0054268	.0221996	0.24	0.807	-.0380836	.0489373

Random-effects Parameters		Estimate	Std. Err.	[95% Conf. Interval]	
id: Identity					
	var(_cons)	.2389771	.024569	.1953642	.292326
Residual: Independent, by visit					
	0: var(e)	.253829	.0248657	.2094862	.307558
	1: var(e)	.8669448	.0446883	.7836366	.9591096

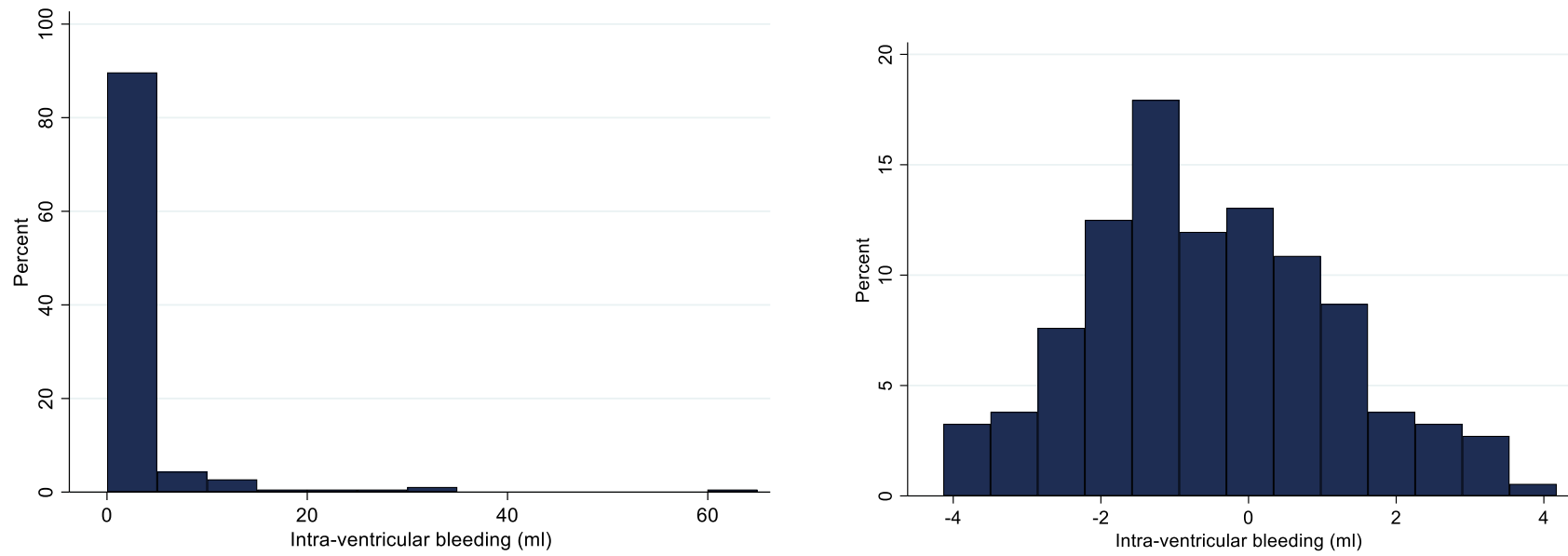
```
LR test vs. linear model: chi2(2) = 269.12      Prob > chi2 = 0.0000
```

Note: LR test is conservative and provided only for reference.

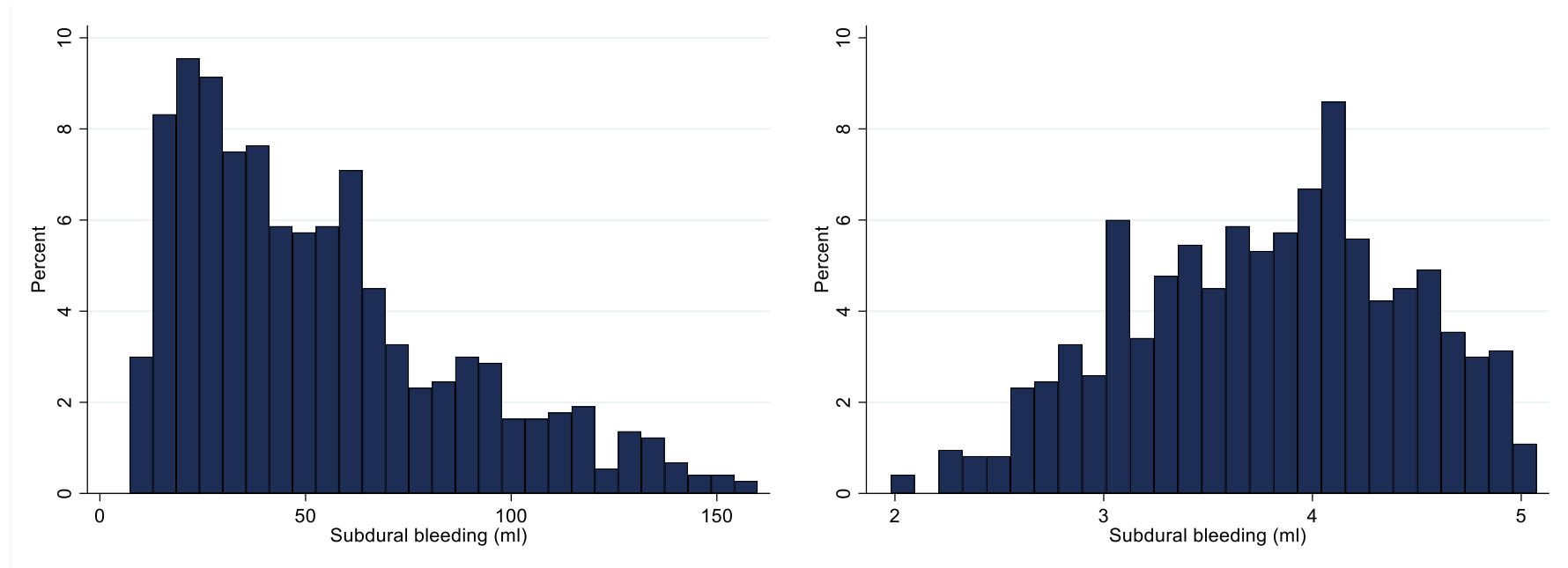
Appendix 14. Histograms of original baseline intracranial haemorrhage volume and log-transformed intracranial haemorrhage volume.



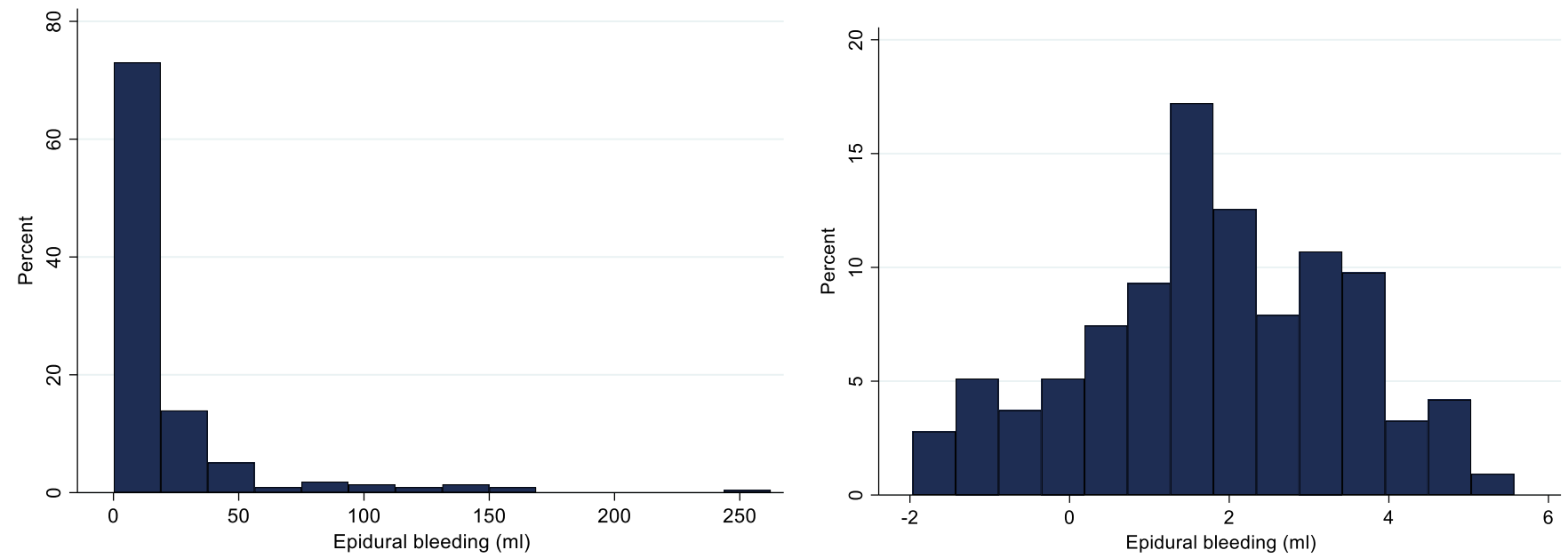
Original intra-parenchymal haemorrhage distribution (left plot) and its log transformation (right plot). *Note the y-axis scales are different.*



Original intra-ventricular haemorrhage distribution (left plot) and its log transformation (right plot). *Note the y-axis scales are different.*



Original subdural haemorrhage distribution (left plot) and its log transformation (right plot).



Original epidural haemorrhage distribution (left plot) and its log transformation (right plot). *Note the y-axis scales are different.*

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