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Protocol for a multicentre pre-hospital randomised controlled trial investigating tranexamic acid in severe trauma: The PATCH-Trauma trial

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Abstract

Introduction: Haemorrhage causes most preventable pre-hospital trauma deaths and about a third of in-hospital trauma deaths. Tranexamic acid (TXA), administered soon after hospital arrival in certain trauma systems, is an effective therapy in preventing or managing acute traumatic coagulopathy. However, delayed administration of TXA appears to be ineffective or harmful. The effectiveness of pre-hospital TXA, incidence of thrombotic complications, benefit versus risk in advanced trauma systems, and the mechanism of benefit remain uncertain.

Methods and analysis: The Pre-hospital Anti-fibrinolytics for Traumatic Coagulopathy and Haemorrhage (The PATCH-Trauma Study) is comparing TXA, initiated pre-hospital and continued in hospital over 8 hours, with placebo in patients with severe trauma at risk of acute traumatic coagulopathy. We present the trial protocol and an overview of the statistical analysis plan. There will be 1316 patients recruited by pre-hospital clinicians in Australia, New Zealand and Germany. The primary outcome will be the eight-level extended Glasgow outcome scale (GOSE) at 6 months after injury, dichotomised to favourable (GOSE 5-8) and unfavourable (GOSE 1-4) outcomes, analysed using an intention-to-treat (ITT) approach. Secondary outcomes will include mortality at hospital discharge and at 6 months, blood product usage, quality of life and the incidence of pre-defined adverse events.

Ethics and Dissemination: The study was approved by The Alfred Hospital Research and Ethics Committee in Victoria and also approved in New South Wales, Queensland, South Australia, Tasmania and the Northern Territory. In New Zealand, Northern A Health and Disability Ethics Committee provided approval. In Germany, Witten/Herdecke University has provided ethics approval. The PATCH-Trauma Study aims to provide definitive evidence of the effectiveness of prehospital TXA, when used in conjunction with current advanced trauma care, in improving outcomes after severe injury.

Trial registration: ClinicalTrials.gov Identifier NCT02187120

Keywords: Antifibrinolytic, Wounds and Injuries; Haemorrhage; Tranexamic acid; Coagulopathy; Trial; Protocol; Trauma; Bleeding; Resuscitation

Strengths and limitations of this study

- PATCH-Trauma is a randomised controlled trial of pre-hospital administration of tranexamic acid versus placebo in patients with major trauma.
- The trial aims to provide definitive guidance for clinicians on the utility of pre-hospital tranexamic acid during resuscitation after trauma.
- The primary outcome is patient-centric being favourable functional status at 6-months after injury
- The study is enrolling patients from Australia, New Zealand and Germany and results may not be generalisable to all trauma systems.

Introduction

Every year, over 5 million people die from injury worldwide.[1] In Australia injuries result in approximately 2,500 deaths per year, 5,000 survivors who are severely disabled, and 25,000 survivors who bear other long-term disabilities.[2] Acute haemorrhage is directly responsible for most preventable pre-hospital trauma deaths and about a third of in-hospital trauma deaths.[3] Haemorrhage and its management, often involving massive blood transfusion, also contribute to multi-organ failure leading to later mortality and morbidity.[4,5]

Normal circulatory homeostasis, ensuring both tissue perfusion and rapid plugging of damaged vessels to minimise bleeding, depends on a complex system of concurrent clot formation and clot breakdown (fibrinolysis). Following severe haemorrhage and tissue damage, many patients develop pathological hyper-fibrinolysis and a measurable acute traumatic coagulopathy (ATC). Patients with ATC are up to 8 times more likely to die within the first 24 hours than trauma patients without coagulopathy.[6,7] Acute traumatic coagulopathy on admission is also associated with a higher risk of development of acute renal injury, multiple organ failure, fewer ventilator-free days, and longer stay in the intensive care unit (ICU) and hospital.[8]

Hyperfibrinolysis is the consequence of raised levels of tissue-type plasminogen activator (t-PA) causing excessive plasminogen activation of the fibrin surface and subsequent fibrin dissolution. Mechanistically, plasminogen binds to exposed lysine residues located on the fibrin surface. Once bound to fibrin, plasminogen partially unfolds becoming more accessible to tPA allowing plasmin to be generated. Tranexamic acid (TXA) is a lysine analogue that competitively inhibits the binding of plasminogen to fibrin thereby sparing fibrin from

plasmin-mediated fibrinolysis.[9] Many studies in elective surgery have demonstrated TXA reduces blood transfusion requirements.[10] The most significant study of TXA in trauma care was the Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage-2 (CRASH-2) trial, which measured the effects of TXA administered in hospital on death, vaso-occlusive events, and the receipt of blood transfusion in trauma patients at risk of significant haemorrhage.[11] The trial found that TXA was associated with significantly reduced deaths due to bleeding and all-cause mortality (RR 0.91; 95% CI: 0.85-0.97; p=0.0035), an effect that varied inversely with time to treatment. The researchers further found that the beneficial effects were seen when TXA was administered within 3 hours of injury, with potential for harm when administered after 3 hours.[12]

CRASH-2 was the largest randomised controlled trial enrolling patients in the early stages of trauma resuscitation, and its findings have influenced trauma care worldwide. It has also engendered considerable debate, however, and the following issues have prompted calls for further trials prior to indiscriminate application of this therapy in advanced trauma systems:[13-20]

1. Timing of intervention: The interpretation of the effects of tranexamic acid was complicated by an apparent increase in the risk of death due to bleeding if TXA was administered 3 hours or more following injury.[21] More detailed analysis of the timing of treatment suggested that while TXA was administered after hospital arrival, there appeared to be homogeneous improvement in outcomes with early administration of TXA.[22] This suggests that pre-hospital therapy may be of benefit, but this hypothesis has not yet been adequately explored.[23]

2. Generalisability: Almost all patients in CRASH-2 were in low-income and middle-income countries where pre-hospital care was limited, blood components were uncommonly used, and where injury mortality was high.[24] Seventy-four percent of the CRASH-2 patients were enrolled in Columbia, Ecuador, Georgia, Nigeria, Egypt and India; only 340 (1.7%) patients were from Australia, New Zealand, USA, Canada, Western Europe or the UK, where trauma system improvements have greatly reduced injury mortality and improved functional recovery. Subgroup analyses of CRASH-2 have not addressed this limitation.[21,22,25] In regions with advanced trauma care systems, where preventable trauma deaths have been reduced through other means, it is unclear whether the same risk-benefit ratio of TXA applies. If the number of trauma deaths that could be prevented by use of TXA is fewer, it is possible that the incidence of adverse effects (such as vascular occlusive events) will unfavourably shift

the balance of benefit and harm.[26] Furthermore, it is uncertain whether TXA administered in the pre-hospital setting alongside current advanced pre- and in-hospital trauma care including routine blood product use adds additional benefit.[27,28]

3. Effect size: CRASH-2 enrolled patients if they were 'at risk of significant haemorrhage', defined as a systolic blood pressure < 90mmHg or heart rate >110/min or both, or at clinician discretion. These measures are neither sensitive nor specific for haemorrhage or coagulopathy. It is possible these criteria decreased the proportion of patients who had hyperfibrinolysis and who could have benefitted from TXA, while exposing patients without ATC or significant bleeding to potential pro-coagulant harm.

4. Assessment of potential adverse events: A potential concern relates to altering the delicate balance between thrombogenic and thrombolytic mechanisms in favour of systemic thrombosis, resulting in venous or arterial thromboembolism, ischaemic heart disease, or stroke. In CRASH-2, patients receiving TXA were not diagnosed with such vascular occlusive events more often than those who received placebo, and the overall incidence was lower than observed in other trauma cohorts.[29] This is at odds with a number of observational studies, in which TXA administration seemed to be an independent risk factor for venous thromboembolism, casting doubt on this finding.[20,30,31] Seizures, a known risk of high-dose TXA, did not seem to be a significant problem in the CRASH-2 study.[32]

5. Mechanism of benefit: An understanding of the mechanisms by which TXA may improve outcomes could assist in tailoring therapy to those who may benefit, while identifying sub-groups at risk of adverse events. Plasmin has roles unrelated to fibrinolysis (probably influencing inflammation, immunity, neurological function, and neuropathic pain) that may be blocked by TXA.[33] However, there was no detailed analysis of the immunomodulatory or haemostatic effects of TXA in CRASH-2. Indeed, the mechanism of mortality benefit observed in CRASH-2 was unclear, as there was no difference in transfusion requirements between TXA and placebo groups, and neither sepsis nor neurological outcomes were specifically reported.

Methods and Analysis

Design: PATCH-Trauma is an international, multi-centre, double-blind, randomised, placebo-controlled trial that aims to determine the benefits and harms of initiating TXA treatment in the pre-hospital setting for severely injured patients at high risk of developing

ATC.

Participants: Injured adult patients being transported by ambulance to major trauma services in three countries (Australia, New Zealand and Germany) are eligible for inclusion if assessed as being at high risk of ATC and if the first dose of study drug can be administered within 3 hours of injury. Details of eligibility are listed in Table 1.

COAST Assessment: The validated, five-item Coagulopathy of Severe Trauma (COAST) score is used to assess whether each patient is at high risk of acute traumatic coagulopathy (Table 2).[34-36] COAST is a score that can be easily and rapidly applied in the field by trained paramedics. Patients with COAST scores ≥ 3 are eligible for enrolment. Patients may be assessed for eligibility at any time in the pre-hospital setting.

Randomisation and Blinding: Trial packs are prepared by an independent pharmaceutical packaging company (PCI Pharma Services for Australia and New Zealand, Pharmacy University of Nuremberg Erlangen for Germany) with either TXA or placebo using a computer-generated sequence provided by a statistician at Monash University, Department of Epidemiology and Preventive Medicine. Packs are consecutively numbered, opaque, foil parcels with a tamper proof seal. Randomisation sequence is stratified for each state and country participating in the study. The pleiotropic activity of TXA, separate to its anti-fibrinolytic effect, may have disproportionate effects on patients with traumatic brain injury (TBI).[34] Therefore, patients are additionally being stratified by the presence of severe traumatic brain injury defined by a Glasgow Coma Scale (GCS) < 9 at the time of randomisation. All trial personnel, including the follow-up assessors and participants, are blinded to treatment allocation. Unblinding of the treatment assignment can only occur in the unlikely event of an emergency in which the appropriate treatment of the patient requires knowledge of the study drug.

Study interventions: Two 10 ml ampoules containing either 1000 mg TXA or 0.9% sodium chloride (NaCl) are in each trial pack, labelled with a unique study ID number. The attending clinicians deliver one dose of the trial drug intravenously to the patient as a bolus (over 10 minutes) as soon as practicable after initial assessment of the patient, and before the patient reaches hospital. Upon arrival to the Emergency Department of participating hospitals, the second 10 ml ampoule in the trial pack is added to one litre of 0.9% NaCl and infused over 8

hours (Figure 1). Study medications are ceased permanently for any serious adverse event such as seizure, cardiac arrest or anaphylaxis, and also in the setting of an exclusion criterion being discovered, e.g. positive urine or blood pregnancy test or when a 'Not for active treatment' directive becomes apparent or the participant declines further participation in the study. Ultimately the patient and treating clinician have the right to decide whether to discontinue treatment.

<<Insert Figure 1 here>>

Concomitant care: Initial assessment and treatment of seriously injured patients follows usual practice. Pre-hospital clinicians attending the scene continue to resuscitate patients as per their usual ambulance service guidelines. Following arrival at hospital standard procedures for trauma reception and resuscitation are followed. Specifically, while the trial investigators, including those at each participating site, have confirmed equipoise about the benefit and harms of TXA in these patients and settings, open label administration of TXA is allowed at clinician discretion, and data on such administration is collected for analysis.

Outcomes: Details of all outcome measures are listed in Table 3. A purpose-built website with an electronic case report form is used for data collection at participating sites. All data are collected by trained research site staff directly from clinical source data. Trained assessors, blinded to the intervention, also collect data on the primary outcome measure at 6-months after injury. A study monitor from the Australian and New Zealand Research Centre, Monash University undertakes site visits and remote checks for study compliance, accuracy and completion of data collection.

Functional Recovery (the Primary outcome) is measured using the dichotomised Glasgow Outcome Scale Extended (GOSE) conducted by telephone interview 6-months after injury. GOSE is dichotomised into "unfavourable outcome" (GOSE 1-4), and "favourable outcome" (GOSE 5-8). A medium-term functional outcome measure incorporating death and disability, rather than a shorter-term measure such as hospital-based mortality, was chosen. The quality of recovery (rather than just survival) after trauma is increasingly understood to be an important research outcome, as many injured patients who survive have long-term disability and are dependent on high levels of care. In addition, plasmin is known to affect immune system and neurological function as well as coagulation, and recent trials in traumatic brain injury have found outcomes assessed at the time of hospital discharge correlated poorly with

long-term functional outcomes and, in at least one study, incorrectly predicted the direction of effect.[35]

Blood product usage (Secondary outcome 1), **ventilator-free days (Secondary outcome 5)** and **quality of life measures (Secondary outcome 9)** are recorded on case report forms using the appropriate tools.

Assessment for coagulopathy and acidemia (Secondary outcomes 2 and 3): Coagulation tests (INR, aPTT and fibrinogen levels) and full blood examinations including platelet counts are conducted for all patients as part of standard practice shortly after arrival to an Emergency Department. Laboratory analysis of venous blood lactate is also performed. Additional blood samples are collected at the end of the 8-hour infusion of the study drug, and 24 hours after the pre-hospital dose of study drug.

Assessment for venous thromboembolism (Secondary outcome 4): To minimise the potential for selective outcome bias, all participants in a subgroup of centres undergo bilateral compression Doppler ultrasound between 5 to 7 days post-injury to examine for proximal lower limb deep venous thromboses (DVTs). In all centres, where there is clinical suspicion of DVT or pulmonary embolism (PE), clinicians further investigate patients to confirm diagnosis. Results of any additional relevant diagnostic imaging are recorded. The incidence of DVT will be reported for the total study sample and in addition, among the sub-group of centres where routine Doppler ultrasound is protocolised.

Assessment for cause of death (Secondary outcome 7): In addition to all-cause death at 24-hours, 28-days and at 6-months (**Secondary outcome 6),** among patients that die within 6 months the primary cause of death is categorised as: death due to bleeding; death due to vascular occlusion (including pulmonary embolism, stroke or acute myocardial infarction); death due to multi-organ failure that is not a direct result of bleeding or vascular occlusion; death due to brain and/or neurological injury; or death due to another cause not classified. The principal investigator at each site is responsible for reporting the cause of death.

Assessment for sepsis (Secondary outcome 8): The cumulative incidence of sepsis will be collected up to 28 days or hospital discharge, whichever occurs first. Sepsis will be defined as: 1) Clinical suspicion or confirmed infection ≥48 hours after hospital admission; and 2) at least two criteria for systemic inflammatory response syndrome; and 3) commencement of antibiotics, or change to the current antibiotic regimen.

Sub-group analyses: The overall sample will be sub-grouped by the following variables and the effect of the intervention assessed: age dichotomised to ≥ 50 years; time from injury to first dose; first valid recorded systolic blood pressure categories (≤ 75, 76-89, ≥ 90 mmHg); mechanism of trauma (penetrating, blunt, burns) and baseline GCS < 9.

Statistical analysis: The analysis and reporting of the results will follow the CONSORT guidelines.[37] Baseline characteristics will be tabulated by using appropriate summary statistics. Principal analysis of the primary outcome will be by intention-to-treat (ITT), including all randomised patients.

A modified intention to treat supporting analysis will also be presented that excludes patients who did not receive the study intervention after being randomised, or who were not eligible for randomisation. In addition, a per-protocol analysis will be presented for patients who satisfied all inclusion / exclusion criteria, received both doses of the study drug and who did not receive any open-label TXA (Figure 2). All secondary endpoints will be analysed using the ITT population only. A nominal two-tailed 5% significance level will be employed.

<<Insert Figure 2 here>>

The primary outcome will be compared between treatment groups using a risk ratio (95% confidence interval), and p-value estimated by a log-binomial regression model. If model convergence is not achieved, then Poisson regression with robust standard errors will be applied. Supplementary analyses will adjust for the randomisation stratification variables. If the proportion of patients missing the primary outcome exceeds 5%, multiple imputation using chained equations will be employed using relevant baseline and post-baseline variables in the imputation models, constructed separately for each treatment arm. Post-hoc adjustment for any variables exhibiting substantial imbalance across treatment arms at baseline will be performed and regarded as sensitivity analyses. Assessment of heterogeneity of treatment effect across pre-specified subgroups will incorporate interaction term(s) in the regression models.

Binary secondary outcomes will also be analysed using log-binomial regression. Analysis of outcomes with approximately symmetric distributions will be analysed using linear

regression to estimate the difference in means between treatment arms together with 95% CIs and p-values. Analysis of skewed outcomes and ventilator-free-days will be analysed using quantile (median) regression, reporting the difference in medians between treatment arms together with 95% CIs and p-values. Additional analyses of binary outcomes at 28 days will be performed to take into account the competing risk of death using cumulative incidence functions, and similarly for analyses of causes of death at 6 months. For analysis of quality of life outcomes at 6 months, a value of 0 will be imputed for the EQ5D summary and VAS score for patients not alive at 6 months[38] and for WHODAS, in the absence of published guidelines for addressing mortality a score of 61 will be imputed, placing death as worse than the maximum scale score of 60. Supplementary analyses of these quality of life endpoints will use inverse probability of death weighting rather than imputation of values to accommodate truncation by death. A detailed statistical analysis plan will be finalised prior to locking of the trial database and unblinding of treatment codes, and will be posted on the PATCH-Trauma study web site.

Sample Size: Targeting 90% power to detect an increase in a favourable GOSE outcome (scored 5-8) from 60% to 69% with TXA this study would require 592 patients in each arm (1184 total) with a two-sided 5% significance level. In a protocol amendment (PATCH Protocol ANZIC-RC/Version 1.6 03 Feb 2020) accommodation for a 10% loss to follow-up, the required sample size was increased to 658 patients in each arm (1316 total).

This sample size is based on a conservative interpretation of results of the CRASH-2 study, in which the early mortality reduction was 13% and reduction of death due to bleeding was 32-39%. The PATCH study could be expected to observe a similar or greater effect of TXA because (1) it is enrolling only patients likely to be bleeding and coagulopathic, and (2) intervention to be within one hour, and often less than 30 minutes of injury. Because patients in PATCH are bleeding and coagulopathic (factors strongly associated with early haemorrhagic deaths and late deaths due to single- or multi-organ failure) and because patients with isolated head injury are excluded by COAST≥3, the relevant end point from CRASH-2 to guide the expected effect size is the effect on death due to bleeding rather than all-cause mortality.

On the other hand, the observed effect of TXA in the PATCH study might be reduced because (1) given that high velocity blunt injury mechanism is responsible for most major trauma in Australia and New Zealand, some included multiply-injured patients will have

unsurvivable brain injury; and (2) hospital-based clinicians will be aware that patients were enrolled in the study, and may know that a high proportion of enrolled patients will have ATC. With that knowledge, hospital clinicians may adjust their management to improve the underlying coagulopathy, hence the death/disability rate in the control group may be less than currently estimated (54%).

Data and safety monitoring, and interim analyses: Two planned interim safety analyses for potential harm have been performed by the independent data and safety monitoring committee (DSMC) at 25% and 50% patient enrolment. Both analyses examined in-hospital and 28-day mortality using the Haybittle-Peto conventional 3-standard deviation threshold of a standardised statistic (i.e. $|Z_k|>3$) calculated from a normal approximation to the difference in mortality proportions. Based on the observed effects of the study drug and adherence to the study protocol in these analyses, the members of the DSMC were unanimous in recommending to the management committee continuation of the study to full enrolment.

Patient and public involvement: A patient representative (AB) is part of the investigator group and provided input into the study design from prior to first enrolment.

Endorsement, ethics and dissemination

This study is endorsed by the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS-CTG). The study is performed in accordance with the ethical principles of the Declaration of Helsinki (June 1964 and amended 1975, 1983, 1989, 1996, 2000, 2008 and Note of Clarification 2002 and 2004), ICH GCP Notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with Therapeutic Goods Administration comments, the NHMRC National Statement on Ethical Conduct in Research Involving Humans (March 2007); the New Zealand Interim Good Clinical Research Practice Guidelines (Volume 2 1998 and Volume 3 2000) and ICH GCP Notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95).

The study was approved by The Alfred Hospital Research and Ethics Committee project ID HREC/13/Alfred/9 (Local Reference: Project 214/13). The study is also approved in other Australian states and their respective ethics committee. Specifically, New South Wales (2019/ETH00262), Queensland (HREC/14/QRBW/501), South Australia (490.14 - HREC/15/SAC/14), Tasmania (Project ID 14471), Northern Territory, (Reference ID 2016–1683). In New Zealand, Northern A Health and Disability Ethics Committee provided

approval with project reference 14/NTA/123/AM11. In Germany, Witten/Herdecke University has provided ethics approval, project reference F-48/2020.

This study constitutes emergency research. Consistent with Principle 29 of the Declaration of Helsinki, patients who have suffered major trauma and are unable to provide informed consent are nonetheless entitled to participate in clinical research. In Australia, the NHMRC Statement makes provision for delayed and/or waiver of consent in time-critical interventions within the emergency or critical care setting. The study is performed in each centre where there is also a legal framework allowing for delayed and/or waiver of consent for research in emergency situations. Justifications for deferred/waived consent in this trial include the requirement for treatment to be administered as quickly as possible for maximum efficacy, and the perceived low risk of TXA.

Serious adverse events and suspected unexpected serious adverse reaction are reported within 24 hours of identification by telephone or email to the local principal investigator and the coordinating centre. However, consistent with the advice of Cook et al., adverse events already defined and reported as study outcomes (mortality, vascular occlusive events) will not be labelled and reported a second time as serious adverse events.[39]

Conclusions

Death from major trauma is common and disproportionately affects young adults. Early management with TXA has the potential to reduce haemorrhage and improve outcomes. The benefit of pre-hospital TXA in advanced trauma systems, when administered in conjunction with pre- and in-hospital care that includes blood products, rapid angio-embolisation and/or surgery, and early access to specialised critical care and rehabilitation, is currently uncertain. The PATCH-Trauma RCT aims to provide definitive guidance for clinicians on the utility of TXA during resuscitation after trauma.

Authors' contributions

RG, BM and SB initiated the research and with AF and MR, obtained initial funding. CM is the project lead for New Zealand and responsible for initiation, enrolment and follow-up of the project in New Zealand. MM is the project lead in Germany and responsible for initiation, enrolment and follow-up of the project in Germany. DG, BB, LM and TT are members of the executive committee and have provided input into study design and execution. AF is also the

chief biostatistician for the project. All authors have critically reviewed the manuscript for content.

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Competing Interests statement

There are no competing interests to declare.

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Figure Legends

Figure 1. Schema of enrolment and assessment of outcomes. TXA: Tranexamic acid; GOSE: Glasgow Outcome Scale- Extended; SF-12: 12-item Short Form Survey

Figure 2. Analysis plan

Table 1. Inclusion and exclusion criteria

Inclusion criteria
· Adult patients (age ≥18 years)
· Injury through any mechanism
· Coagulopathy of Severe Trauma (COAST) score ≥3
· First dose of study drug can be administered within three hours of injury
· Patients to be transported to a participating trauma centre
Exclusion criteria
· Suspected pregnancy
· Nursing home residents
- Age<18 years

Table 2. The Coagulopathy of Severe Trauma (COAST) score

COAST score variable	Assessment	Result	Score
Entrapment (i.e. in vehicle)	Extraction of patient from vehicle or scene of injury requires use of cutting or lifting devices	Yes	1
Systolic blood pressure (mmHg)	Sphygmomanometer	<100 <90	1 2
Temperature (°C)	Tympanic temperature probe	<35 <32	1 2
Major chest injury likely to require intervention (e.g. decompression, chest tube)	In the opinion of pre-hospital clinician, there is likely chest injury sufficient to require a thoracostomy for pneumothorax or haemothorax	Yes	1
Likely intra-abdominal or pelvic injury	In the opinion of the pre-hospital clinician, there is likely to be injury to abdominal organs or to the pelvis.	Yes	1
Highest possible score			7

Table 3: Primary and secondary outcome measures

Primary outcome
Dichotomised GOSE at 6-months: the proportion of patients with a favourable outcome at six months (moderate disability or good recovery, GOSE scores 5-8), compared to those who have died (GOSE 1) or have severe disability (GOSE 2-4).
Secondary outcomes
1) Units of blood products used (packed red blood cells, fresh frozen plasma, platelets, prothrombin complex concentrate, rFVIIa, cryoprecipitate) in the first 24 hours. 2) Blood lactate concentration at patient arrival to hospital 3) Coagulation profile (INR, APTT, fibrinogen, platelet count) at a. hospital arrival b. end of treatment with study drug (i.e. immediately after administering the second dose of the study drug by 8-hour infusion) c. 24 hours after the first dose of study drug 4) Vascular occlusive events (DVT, PE, myocardial infarction, stroke) up until 28 days or hospital discharge (whichever occurs first) 5) Ventilator-free days in first 28 days 6) Mortality at: a. 24 hours b. 28 days c. 6 months 7) Proportion of deaths due to: a. Bleeding b. Vascular occlusion (pulmonary embolus, stroke or AMI) c. Multi-organ failure d. Brain / neurological injury 8) Cumulative incidence of sepsis up until 28 days or hospital discharge (whichever occurs first) 9) Quality of life (WHODAS 2.0 and EQ5D) at 6 months

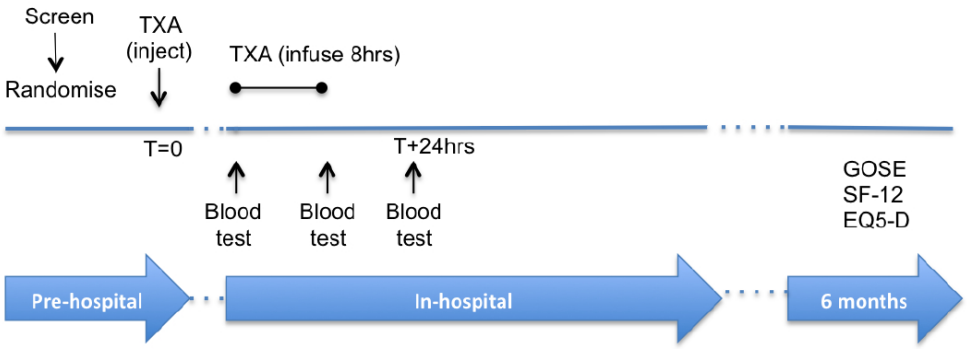

Figure 1. Schema of enrolment and assessment of outcomes. TXA: Tranexamic acid; GOSE: Glasgow Outcome Scale- Extended; SF-12: 12-item Short Form Survey

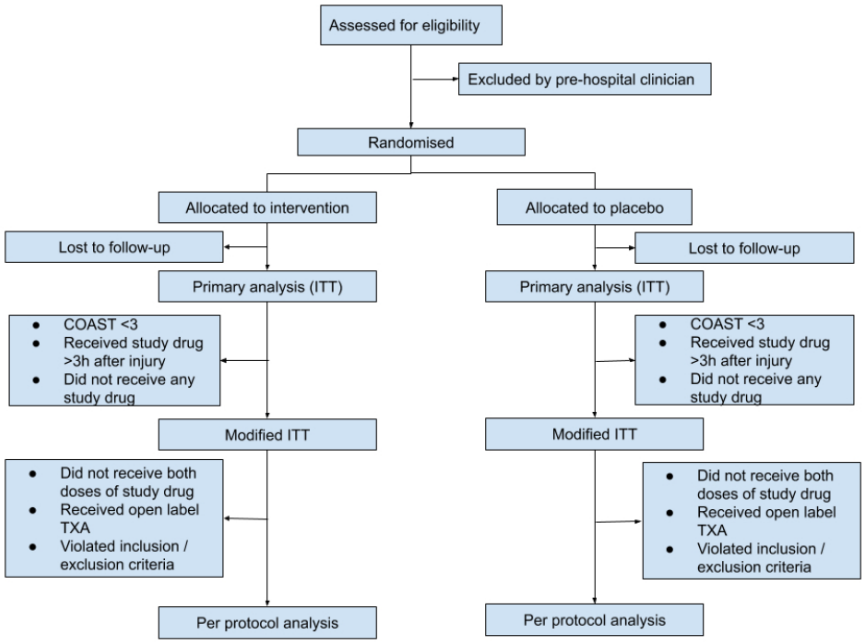

Figure 2. Analysis plan

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page Number on which item is reported
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	Online
Protocol version	3	Date and version identifier	Online
Funding	4	Sources and types of financial, material, and other support	13
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 and 13
	5b	Name and contact information for the trial sponsor	13
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-9
	6b	Explanation for choice of comparators	4-9
Objectives	7	Specific objectives or hypotheses	8-9 and Table 3
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 5 and Table 1
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	7
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-9

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Page 10 and Figure 2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page 11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	NA
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6-7
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9-10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	12

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12-13
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	12
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	12
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	12
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12-13
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Online

	31b	Authorship eligibility guidelines and any intended use of professional writers	Online
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Online
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Protocol for a multicentre pre-hospital randomised controlled trial investigating tranexamic acid in severe trauma: The PATCH-Trauma trial

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Protocol for a multicentre pre-hospital randomised controlled trial investigating tranexamic acid in severe trauma: The PATCH-Trauma trial

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Trial registration: ClinicalTrials.gov Identifier NCT02187120

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Abstract

Introduction: Haemorrhage causes most preventable pre-hospital trauma deaths and about a third of in-hospital trauma deaths. Tranexamic acid (TXA), administered soon after hospital arrival in certain trauma systems, is an effective therapy in preventing or managing acute traumatic coagulopathy. However, delayed administration of TXA appears to be ineffective or harmful. The effectiveness of pre-hospital TXA, incidence of thrombotic complications, benefit versus risk in advanced trauma systems, and the mechanism of benefit remain uncertain.

Methods and analysis: The Pre-hospital Anti-fibrinolytics for Traumatic Coagulopathy and Haemorrhage (The PATCH-Trauma Study) is comparing TXA, initiated pre-hospital and continued in hospital over 8 hours, with placebo in patients with severe trauma at risk of acute traumatic coagulopathy. We present the trial protocol and an overview of the statistical analysis plan. There will be 1316 patients recruited by pre-hospital clinicians in Australia, New Zealand and Germany. The primary outcome will be the eight-level extended Glasgow outcome scale (GOSE) at 6 months after injury, dichotomised to favourable (GOSE 5-8) and unfavourable (GOSE 1-4) outcomes, analysed using an intention-to-treat (ITT) approach. Secondary outcomes will include mortality at hospital discharge and at 6 months, blood product usage, quality of life and the incidence of pre-defined adverse events.

Ethics and Dissemination: The study was approved by The Alfred Hospital Research and Ethics Committee in Victoria and also approved in New South Wales, Queensland, South Australia, Tasmania and the Northern Territory. In New Zealand, Northern A Health and Disability Ethics Committee provided approval. In Germany, Witten/Herdecke University has provided ethics approval. The PATCH-Trauma Study aims to provide definitive evidence of the effectiveness of prehospital TXA, when used in conjunction with current advanced trauma care, in improving outcomes after severe injury.

Trial registration: ClinicalTrials.gov Identifier NCT02187120

Keywords: Antifibrinolytic, Wounds and Injuries; Haemorrhage; Tranexamic acid; Coagulopathy; Trial; Protocol; Trauma; Bleeding; Resuscitation

Strengths and limitations of this study

- A double blinded randomised controlled design will minimise bias of the results.
- Delivery of the initial study drug in the pre-hospital phase of trauma care will provide level I evidence on pre-hospital use of tranexamic acid for trauma.
- The primary outcome is patient-centric being favourable functional status at 6-months after injury.
- Pre-specified secondary outcome measures are designed to investigate potential mechanism of actions of tranexamic acid in injured patients.
- The study is enrolling patients from Australia, New Zealand and Germany and results may not be generalisable to all trauma systems.

Introduction

Every year, over 5 million people die from injury worldwide.[1] In Australia injuries result in approximately 2,500 deaths per year, 5,000 survivors who are severely disabled, and 25,000 survivors who bear other long-term disabilities.[2] Acute haemorrhage is directly responsible for most preventable pre-hospital trauma deaths and about a third of in-hospital trauma deaths.[3] Haemorrhage and its management, often involving massive blood transfusion, also contribute to multi-organ failure leading to later mortality and morbidity.[4,5]

Normal circulatory homeostasis, ensuring both tissue perfusion and rapid plugging of damaged vessels to minimise bleeding, depends on a complex system of concurrent clot formation and clot breakdown (fibrinolysis). Following severe haemorrhage and tissue damage, many patients develop pathological hyper-fibrinolysis and a measurable acute traumatic coagulopathy (ATC). Patients with ATC are up to 8 times more likely to die within the first 24 hours than trauma patients without coagulopathy.[6,7] Acute traumatic coagulopathy on admission is also associated with a higher risk of development of acute renal injury, multiple organ failure, fewer ventilator-free days, and longer stay in the intensive care unit (ICU) and hospital.[8]

Hyperfibrinolysis is the consequence of raised levels of tissue-type plasminogen activator (t-PA) causing excessive plasminogen activation of the fibrin surface and subsequent fibrin dissolution. Mechanistically, plasminogen binds to exposed lysine residues located on the fibrin surface. Once bound to fibrin, plasminogen partially unfolds becoming more accessible to tPA allowing plasmin to be generated. Tranexamic acid (TXA) is a lysine analogue that

competitively inhibits the binding of plasminogen to fibrin thereby sparing fibrin from plasmin-mediated fibrinolysis.[9] Many studies in elective surgery have demonstrated TXA reduces blood transfusion requirements.[10] The most significant study of TXA in trauma care was the Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage-2 (CRASH-2) trial, which measured the effects of TXA administered in hospital on death, vaso-occlusive events, and the receipt of blood transfusion in trauma patients at risk of significant haemorrhage.[11] The trial found that TXA was associated with significantly reduced deaths due to bleeding and all-cause mortality (RR 0.91; 95% CI: 0.85-0.97; p=0.0035), an effect that varied inversely with time to treatment. The researchers further found that the beneficial effects were seen when TXA was administered within 3 hours of injury, with potential for harm when administered after 3 hours.[12]

CRASH-2 was the largest randomised controlled trial enrolling patients in the early stages of trauma resuscitation, and its findings have influenced trauma care worldwide. It has also engendered considerable debate, however, and the following issues have prompted calls for further trials prior to indiscriminate application of this therapy in advanced trauma systems:[13-20]

1. Timing of intervention: The interpretation of the effects of tranexamic acid was complicated by an apparent increase in the risk of death due to bleeding if TXA was administered 3 hours or more following injury.[21] More detailed analysis of the timing of treatment suggested that while TXA was administered after hospital arrival, there appeared to be homogeneous improvement in outcomes with early administration of TXA.[22] This suggests that pre-hospital therapy may be of benefit, but this hypothesis has not yet been adequately explored.[23]

2. Generalisability: Almost all patients in CRASH-2 were in low-income and middle-income countries where pre-hospital care was limited, blood components were uncommonly used, and where injury mortality was high.[24] Seventy-four percent of the CRASH-2 patients were enrolled in Columbia, Ecuador, Georgia, Nigeria, Egypt and India; only 340 (1.7%) patients were from Australia, New Zealand, USA, Canada, Western Europe or the UK, where trauma system improvements have greatly reduced injury mortality and improved functional recovery. Subgroup analyses of CRASH-2 have not addressed this limitation.[21,22,25] In regions with advanced trauma care systems, where preventable trauma deaths have been reduced through other means, it is unclear whether the same risk-benefit ratio of TXA applies. If the number of trauma deaths that could be prevented by use of TXA is fewer, it is possible that

the incidence of adverse effects (such as vascular occlusive events) will unfavourably shift the balance of benefit and harm.[26] Furthermore, it is uncertain whether TXA administered in the pre-hospital setting alongside current advanced pre- and in-hospital trauma care including routine blood product use adds additional benefit.[27,28]

3. Effect size: CRASH-2 enrolled patients if they were 'at risk of significant haemorrhage', defined as a systolic blood pressure < 90mmHg or heart rate >110/min or both, or at clinician discretion. These measures are neither sensitive nor specific for haemorrhage or coagulopathy. It is possible these criteria decreased the proportion of patients who had hyperfibrinolysis and who could have benefitted from TXA, while exposing patients without ATC or significant bleeding to potential pro-coagulant harm.

4. Assessment of potential adverse events: A potential concern relates to altering the delicate balance between thrombogenic and thrombolytic mechanisms in favour of systemic thrombosis, resulting in venous or arterial thromboembolism, ischaemic heart disease, or stroke. In CRASH-2, patients receiving TXA were not diagnosed with such vascular occlusive events more often than those who received placebo, and the overall incidence was lower than observed in other trauma cohorts.[29] This is at odds with a number of observational studies, in which TXA administration seemed to be an independent risk factor for venous thromboembolism, casting doubt on this finding.[20,30,31] Seizures, a known risk of high-dose TXA, did not seem to be a significant problem in the CRASH-2 study.[32]

5. Mechanism of benefit: An understanding of the mechanisms by which TXA may improve outcomes could assist in tailoring therapy to those who may benefit, while identifying sub-groups at risk of adverse events. Plasmin has roles unrelated to fibrinolysis (probably influencing inflammation, immunity, neurological function, and neuropathic pain) that may be blocked by TXA.[33] However, there was no detailed analysis of the immunomodulatory or haemostatic effects of TXA in CRASH-2. Indeed, the mechanism of mortality benefit observed in CRASH-2 was unclear, as there was no difference in transfusion requirements between TXA and placebo groups, and neither sepsis nor neurological outcomes were specifically reported.

Methods and Analysis

Design: PATCH-Trauma is an international, multi-centre, double-blind, randomised, placebo-controlled trial that aims to determine the benefits and harms of initiating TXA treatment in the pre-hospital setting for severely injured patients at high risk of developing

ATC.

Participants: Injured adult patients being transported by ambulance to major trauma services in three countries (Australia, New Zealand and Germany) are eligible for inclusion if assessed as being at high risk of ATC and if the first dose of study drug can be administered within 3 hours of injury. Details of eligibility are listed in Table 1.

COAST Assessment: The validated, five-item Coagulopathy of Severe Trauma (COAST) score is used to assess whether each patient is at high risk of acute traumatic coagulopathy (Table 2).[34-36] COAST is a score that can be easily and rapidly applied in the field by trained paramedics. Patients with COAST scores ≥ 3 are eligible for enrolment. Patients may be assessed for eligibility at any time in the pre-hospital setting.

Randomisation and Blinding: Trial packs are prepared by an independent pharmaceutical packaging company (PCI Pharma Services for Australia and New Zealand, Pharmacy University of Nuremberg Erlangen for Germany) with either TXA or placebo using a computer-generated sequence provided by a statistician at Monash University, Department of Epidemiology and Preventive Medicine. Packs are consecutively numbered, opaque, foil parcels with a tamper proof seal. Randomisation sequence is stratified for each state and country participating in the study. The pleiotropic activity of TXA, separate to its anti-fibrinolytic effect, may have disproportionate effects on patients with traumatic brain injury (TBI).[34] Therefore, patients are additionally being stratified by the presence of severe traumatic brain injury defined by a Glasgow Coma Scale (GCS) < 9 at the time of randomisation. All trial personnel, including the follow-up assessors and participants, are blinded to treatment allocation. Unblinding of the treatment assignment can only occur in the unlikely event of an emergency in which the appropriate treatment of the patient requires knowledge of the study drug.

Study interventions: Two 10 ml ampoules containing either 1000 mg TXA or 0.9% sodium chloride (NaCl) are in each trial pack, labelled with a unique study ID number. The attending clinicians deliver one dose of the trial drug intravenously to the patient as a bolus (over 10 minutes) as soon as practicable after initial assessment of the patient, and before the patient reaches hospital. Upon arrival to the Emergency Department of participating hospitals, the second 10 ml ampoule in the trial pack is added to one litre of 0.9% NaCl and infused over 8

hours (Figure 1). Study medications are ceased permanently for any serious adverse event such as seizure, cardiac arrest or anaphylaxis, and also in the setting of an exclusion criterion being discovered, e.g. positive urine or blood pregnancy test or when a 'Not for active treatment' directive becomes apparent or the participant declines further participation in the study. Ultimately the patient and treating clinician have the right to decide whether to discontinue treatment.

<<Insert Figure 1 here>>

Concomitant care: Initial assessment and treatment of seriously injured patients follows usual practice. Pre-hospital clinicians attending the scene continue to resuscitate patients as per their usual ambulance service guidelines. Following arrival at hospital standard procedures for trauma reception and resuscitation are followed. Specifically, while the trial investigators, including those at each participating site, have confirmed equipoise about the benefit and harms of TXA in these patients and settings, open label administration of TXA is allowed at clinician discretion, and data on such administration is collected for analysis.

Outcomes: Details of all outcome measures are listed in Table 3. A purpose-built website with an electronic case report form is used for data collection at participating sites. All data are collected by trained research site staff directly from clinical source data. Trained assessors, blinded to the intervention, also collect data on the primary outcome measure at 6-months after injury. A study monitor from the Australian and New Zealand Research Centre, Monash University undertakes site visits and remote checks for study compliance, accuracy and completion of data collection.

Functional Recovery (the Primary outcome) is measured using the dichotomised Glasgow Outcome Scale Extended (GOSE) conducted by telephone interview 6-months after injury. GOSE is dichotomised into "unfavourable outcome" (GOSE 1-4), and "favourable outcome" (GOSE 5-8). A medium-term functional outcome measure incorporating death and disability, rather than a shorter-term measure such as hospital-based mortality, was chosen. The quality of recovery (rather than just survival) after trauma is increasingly understood to be an important research outcome, as many injured patients who survive have long-term disability and are dependent on high levels of care. In addition, plasmin is known to affect immune system and neurological function as well as coagulation, and recent trials in traumatic brain injury have found outcomes assessed at the time of hospital discharge correlated poorly with

long-term functional outcomes and, in at least one study, incorrectly predicted the direction of effect.[35]

Blood product usage (Secondary outcome 1), **ventilator-free days (Secondary outcome 5)** and **quality of life measures (Secondary outcome 9)** are recorded on case report forms using the appropriate tools.

Assessment for coagulopathy and acidemia (Secondary outcomes 2 and 3): Coagulation tests (INR, aPTT and fibrinogen levels) and full blood examinations including platelet counts are conducted for all patients as part of standard practice shortly after arrival to an Emergency Department. Laboratory analysis of venous blood lactate is also performed. Additional blood samples are collected at the end of the 8-hour infusion of the study drug, and 24 hours after the pre-hospital dose of study drug.

Assessment for venous thromboembolism (Secondary outcome 4): To minimise the potential for selective outcome bias, all participants in a subgroup of centres undergo bilateral compression Doppler ultrasound between 5 to 7 days post-injury to examine for proximal lower limb deep venous thromboses (DVTs). In all centres, where there is clinical suspicion of DVT or pulmonary embolism (PE), clinicians further investigate patients to confirm diagnosis. Results of any additional relevant diagnostic imaging are recorded. The incidence of DVT will be reported for the total study sample and in addition, among the sub-group of centres where routine Doppler ultrasound is protocolised.

Assessment for cause of death (Secondary outcome 7): In addition to all-cause death at 24-hours, 28-days and at 6-months (**Secondary outcome 6),** among patients that die within 6 months the primary cause of death is categorised as: death due to bleeding; death due to vascular occlusion (including pulmonary embolism, stroke or acute myocardial infarction); death due to multi-organ failure that is not a direct result of bleeding or vascular occlusion; death due to brain and/or neurological injury; or death due to another cause not classified. The principal investigator at each site is responsible for reporting the cause of death.

Assessment for sepsis (Secondary outcome 8): The cumulative incidence of sepsis will be collected up to 28 days or hospital discharge, whichever occurs first. Sepsis will be defined as: 1) Clinical suspicion or confirmed infection ≥48 hours after hospital admission; and 2) at least two criteria for systemic inflammatory response syndrome; and 3) commencement of antibiotics, or change to the current antibiotic regimen.

Sub-group analyses: The overall sample will be sub-grouped by the following variables and the effect of the intervention assessed: age dichotomised to ≥ 50 years; time from injury to first dose; first valid recorded systolic blood pressure categories (≤ 75, 76-89, ≥ 90 mmHg); mechanism of trauma (penetrating, blunt, burns) and baseline GCS < 9.

Statistical analysis: The analysis and reporting of the results will follow the CONSORT guidelines.[37] Baseline characteristics will be tabulated by using appropriate summary statistics. Principal analysis of the primary outcome will be by intention-to-treat (ITT), including all randomised patients.

A modified intention to treat supporting analysis will also be presented that excludes patients who did not receive the study intervention after being randomised, or who were not eligible for randomisation. In addition, a per-protocol analysis will be presented for patients who satisfied all inclusion / exclusion criteria, received both doses of the study drug and who did not receive any open-label TXA (Figure 2). All secondary endpoints will be analysed using the ITT population only. A nominal two-tailed 5% significance level will be employed.

<<Insert Figure 2 here>>

The primary outcome will be compared between treatment groups using a risk ratio (95% confidence interval), and p-value estimated by a log-binomial regression model. If model convergence is not achieved, then Poisson regression with robust standard errors will be applied. Supplementary analyses will adjust for the randomisation stratification variables. If the proportion of patients missing the primary outcome exceeds 5%, multiple imputation using chained equations will be employed using relevant baseline and post-baseline variables in the imputation models, constructed separately for each treatment arm. Post-hoc adjustment for any variables exhibiting substantial imbalance across treatment arms at baseline will be performed and regarded as sensitivity analyses. Assessment of heterogeneity of treatment effect across pre-specified subgroups will incorporate interaction term(s) in the regression models.

Binary secondary outcomes will also be analysed using log-binomial regression. Analysis of outcomes with approximately symmetric distributions will be analysed using linear

regression to estimate the difference in means between treatment arms together with 95% CIs and p-values. Analysis of skewed outcomes and ventilator-free-days will be analysed using quantile (median) regression, reporting the difference in medians between treatment arms together with 95% CIs and p-values. Additional analyses of binary outcomes at 28 days will be performed to take into account the competing risk of death using cumulative incidence functions, and similarly for analyses of causes of death at 6 months. For analysis of quality of life outcomes at 6 months, a value of 0 will be imputed for the EQ5D summary and VAS score for patients not alive at 6 months[38] and for WHODAS, in the absence of published guidelines for addressing mortality a score of 61 will be imputed, placing death as worse than the maximum scale score of 60. Supplementary analyses of these quality of life endpoints will use inverse probability of death weighting rather than imputation of values to accommodate truncation by death. A detailed statistical analysis plan will be finalised prior to locking of the trial database and unblinding of treatment codes, and will be posted on the PATCH-Trauma study web site.

Sample Size: Targeting 90% power to detect an increase in a favourable GOSE outcome (scored 5-8) from 60% to 69% with TXA this study would require 592 patients in each arm (1184 total) with a two-sided 5% significance level. In a protocol amendment (PATCH Protocol ANZIC-RC/Version 1.6 03 Feb 2020) accommodation for a 10% loss to follow-up, the required sample size was increased to 658 patients in each arm (1316 total).

This sample size is based on a conservative interpretation of results of the CRASH-2 study, in which the early mortality reduction was 13% and reduction of death due to bleeding was 32-39%. The PATCH study could be expected to observe a similar or greater effect of TXA because (1) it is enrolling only patients likely to be bleeding and coagulopathic, and (2) intervention to be within one hour, and often less than 30 minutes of injury. Because patients in PATCH are bleeding and coagulopathic (factors strongly associated with early haemorrhagic deaths and late deaths due to single- or multi-organ failure) and because patients with isolated head injury are excluded by COAST≥3, the relevant end point from CRASH-2 to guide the expected effect size is the effect on death due to bleeding rather than all-cause mortality.

On the other hand, the observed effect of TXA in the PATCH study might be reduced because (1) given that high velocity blunt injury mechanism is responsible for most major trauma in Australia and New Zealand, some included multiply-injured patients will have

unsurvivable brain injury; and (2) hospital-based clinicians will be aware that patients were enrolled in the study, and may know that a high proportion of enrolled patients will have ATC. With that knowledge, hospital clinicians may adjust their management to improve the underlying coagulopathy, hence the death/disability rate in the control group may be less than currently estimated (54%).

Data and safety monitoring, and interim analyses: Two planned interim safety analyses for potential harm have been performed by the independent data and safety monitoring committee (DSMC) at 25% and 50% patient enrolment. Both analyses examined in-hospital and 28-day mortality using the Haybittle-Peto conventional 3-standard deviation threshold of a standardised statistic (i.e. $|Z_k|>3$) calculated from a normal approximation to the difference in mortality proportions. Based on the observed effects of the study drug and adherence to the study protocol in these analyses, the members of the DSMC were unanimous in recommending to the management committee continuation of the study to full enrolment.

Patient and public involvement: A patient representative (AB) is part of the investigator group and provided input into the study design from prior to first enrolment.

Ethics and dissemination

This study is endorsed by the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS-CTG). The study is performed in accordance with the ethical principles of the Declaration of Helsinki (June 1964 and amended 1975, 1983, 1989, 1996, 2000, 2008 and Note of Clarification 2002 and 2004), ICH GCP Notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with Therapeutic Goods Administration comments, the NHMRC National Statement on Ethical Conduct in Research Involving Humans (March 2007); the New Zealand Interim Good Clinical Research Practice Guidelines (Volume 2 1998 and Volume 3 2000) and ICH GCP Notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95).

The study was approved by The Alfred Hospital Research and Ethics Committee project ID HREC/13/Alfred/9 (Local Reference: Project 214/13). The study is also approved in other Australian states and their respective ethics committee. Specifically, New South Wales (2019/ETH00262), Queensland (HREC/14/QRBW/501), South Australia (490.14 - HREC/15/SAC/14), Tasmania (Project ID 14471), Northern Territory, (Reference ID 2016–1683). In New Zealand, Northern A Health and Disability Ethics Committee provided

approval with project reference 14/NTA/123/AM11. In Germany, Witten/Herdecke University has provided ethics approval, project reference F-48/2020.

This study constitutes emergency research. Consistent with Principle 29 of the Declaration of Helsinki, patients who have suffered major trauma and are unable to provide informed consent are nonetheless entitled to participate in clinical research. In Australia, the NHMRC Statement makes provision for delayed and/or waiver of consent in time-critical interventions within the emergency or critical care setting. The study is performed in each centre where there is also a legal framework allowing for delayed and/or waiver of consent for research in emergency situations. Justifications for deferred/waived consent in this trial include the requirement for treatment to be administered as quickly as possible for maximum efficacy, and the perceived low risk of TXA.

Serious adverse events and suspected unexpected serious adverse reaction are reported within 24 hours of identification by telephone or email to the local principal investigator and the coordinating centre. However, consistent with the advice of Cook et al., adverse events already defined and reported as study outcomes (mortality, vascular occlusive events) will not be labelled and reported a second time as serious adverse events.[39]

Conclusions

Death from major trauma is common and disproportionately affects young adults. Early management with TXA has the potential to reduce haemorrhage and improve outcomes. The benefit of pre-hospital TXA in advanced trauma systems, when administered in conjunction with pre- and in-hospital care that includes blood products, rapid angio-embolisation and/or surgery, and early access to specialised critical care and rehabilitation, is currently uncertain. The PATCH-Trauma RCT aims to provide definitive guidance for clinicians on the utility of TXA during resuscitation after trauma.

Authors' contributions

RG, BM and SB initiated the research and with AF and MR, obtained initial funding. VP was the project co-ordinator and contributed to the design, initiation and patient recruitment in all sites. CM is the project lead for New Zealand and responsible for initiation, enrolment and follow-up of the project in New Zealand. MM is the project lead in Germany and responsible for initiation, enrolment and follow-up of the project in Germany. DG, BB, LM and AT are members of the executive committee and have provided input into study design and

execution. AF is also the chief biostatistician for the project. All authors have critically reviewed the manuscript for content.

Funding Statement

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Competing Interests statement

There are no competing interests to declare.

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Figure Legends

Figure 1. Schema of enrolment and assessment of outcomes. TXA: Tranexamic acid; GOSE: Glasgow Outcome Scale- Extended; SF-12: 12-item Short Form Survey

Figure 2. Analysis plan

Table 1. Inclusion and exclusion criteria

Inclusion criteria
· Adult patients (age ≥18 years)
· Injury through any mechanism
· Coagulopathy of Severe Trauma (COAST) score ≥3
· First dose of study drug can be administered within three hours of injury
· Patients to be transported to a participating trauma centre
Exclusion criteria
· Suspected pregnancy
· Nursing home residents
- Age<18 years

Table 2. The Coagulopathy of Severe Trauma (COAST) score

COAST score variable	Assessment	Result	Score
Entrapment (i.e. in vehicle)	Extraction of patient from vehicle or scene of injury requires use of cutting or lifting devices	Yes	1
Systolic blood pressure (mmHg)	Sphygmomanometer	<100 <90	1 2
Temperature (°C)	Tympanic temperature probe	<35 <32	1 2
Major chest injury likely to require intervention (e.g. decompression, chest tube)	In the opinion of pre-hospital clinician, there is likely chest injury sufficient to require a thoracostomy for pneumothorax or haemothorax	Yes	1
Likely intra-abdominal or pelvic injury	In the opinion of the pre-hospital clinician, there is likely to be injury to abdominal organs or to the pelvis.	Yes	1
Highest possible score			7

Table 3: Primary and secondary outcome measures

Primary outcome
Dichotomised GOSE at 6-months: the proportion of patients with a favourable outcome at six months (moderate disability or good recovery, GOSE scores 5-8), compared to those who have died (GOSE 1) or have severe disability (GOSE 2-4).
Secondary outcomes
1) Units of blood products used (packed red blood cells, fresh frozen plasma, platelets, prothrombin complex concentrate, rFVIIa, cryoprecipitate) in the first 24 hours. 2) Blood lactate concentration at patient arrival to hospital 3) Coagulation profile (INR, APTT, fibrinogen, platelet count) at a. hospital arrival b. end of treatment with study drug (i.e. immediately after administering the second dose of the study drug by 8-hour infusion) c. 24 hours after the first dose of study drug 4) Vascular occlusive events (DVT, PE, myocardial infarction, stroke) up until 28 days or hospital discharge (whichever occurs first) 5) Ventilator-free days in first 28 days 6) Mortality at: a. 24 hours b. 28 days c. 6 months 7) Proportion of deaths due to: a. Bleeding b. Vascular occlusion (pulmonary embolus, stroke or AMI) c. Multi-organ failure d. Brain / neurological injury 8) Cumulative incidence of sepsis up until 28 days or hospital discharge (whichever occurs first) 9) Quality of life (WHODAS 2.0 and EQ5D) at 6 months

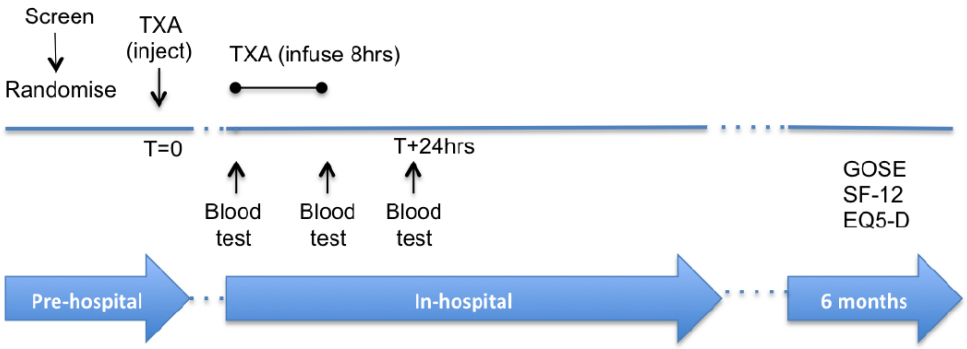

Figure 1. Schema of enrolment and assessment of outcomes. TXA: Tranexamic acid; GOSE: Glasgow Outcome Scale- Extended; SF-12: 12-item Short Form Survey

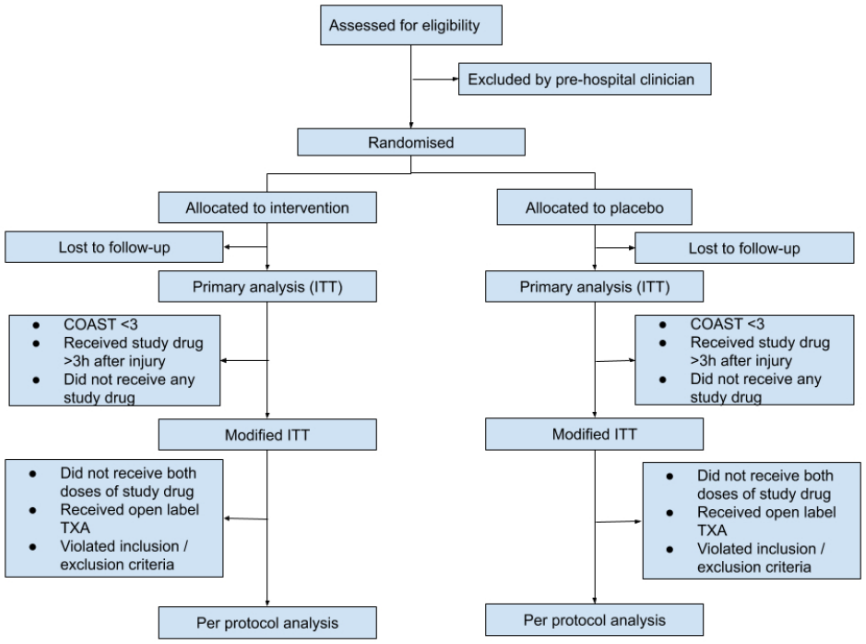

Figure 2. Analysis plan

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page Number on which item is reported
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	Online
Protocol version	3	Date and version identifier	Online
Funding	4	Sources and types of financial, material, and other support	13
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 and 13
	5b	Name and contact information for the trial sponsor	13
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-9
	6b	Explanation for choice of comparators	4-9
Objectives	7	Specific objectives or hypotheses	8-9 and Table 3
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 5 and Table 1
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	7
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-9

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Page 10 and Figure 2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page 11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	NA
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6-7
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9-10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	12

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12-13
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	12
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	12
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	12
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12-13
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Online

	31b	Authorship eligibility guidelines and any intended use of professional writers	Online
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Online
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.