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[1]Oxford University Hospitals NHS Foundation Trust, Nuffield Orthopaedic Hospital, Oxford, UK
[2]Centre for Trauma Sciences, Blizard Institute, Queen Mary University of London, London, UK
[3]NHS Blood and Transplant Clinical Trials Unit, Bristol, UK
[4]The University of Texas Health Science Center at Houston, Houston, TX, USA
[5]NHS Blood and Transplant Clinical Trials Unit, Cambridge, UK
[6]Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK
[7]Trauma Audit and Research Network, Salford Royal Hospital, Northern Care Alliance NHS Foundation Trust, Salford, UK
[8]Faculty of Health and Applied Sciences, University of the West of England, Bristol, UK
[9]Blizard Institute, Queen Mary University of London, London, UK
[10]NHS Blood and Transplant and Bart's Health NHS Trust, London, UK
[11]NHS Blood and Transplant and Oxford University Hospitals NHS Foundation Trust, John Radcliffe Hospital, Oxford, UK
[12]Radcliffe Department of Medicine, University of Oxford, Oxford, UK

[*]Corresponding author

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This article

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Abstract

Early high-dose cryoprecipitate to reduce mortality in adult patients with traumatic haemorrhage: the CRYOSTAT-2 RCT with cost-effectiveness analysis

Nicola Curry,[1] Ross Davenport,[2] Helen Thomas,[3] Erin Fox,[4] Joanne Lucas,[5] Amy Evans,[5] Efthalia Massou,[6] Rupa Sharma,[5] Shaminie Shanmugaranjan,[3] Claire Rourke,[5] Alice Newton,[3] Alison Deary,[5] Nikki Dallas,[5] Chloe Fitzpatrick-Creamer,[5] Jeanette M Podbielski,[4] Charles E Wade,[4] Antoinette Edwards,[7] Jonathan Benger,[8] Stephen Morris,[6] Bryan A Cotton,[4] James Piercy,[2] Laura Green,[9,10] Karim Brohi[2] and Simon Stanworth[11,12*]

[1]Oxford University Hospitals NHS Foundation Trust, Nuffield Orthopaedic Hospital, Oxford, UK
[2]Centre for Trauma Sciences, Blizard Institute, Queen Mary University of London, London, UK
[3]NHS Blood and Transplant Clinical Trials Unit, Bristol, UK
[4]The University of Texas Health Science Center at Houston, Houston, TX, USA
[5]NHS Blood and Transplant Clinical Trials Unit, Cambridge, UK
[6]Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK
[7]Trauma Audit and Research Network, Salford Royal Hospital, Northern Care Alliance NHS Foundation Trust, Salford, UK
[8]Faculty of Health and Applied Sciences, University of the West of England, Bristol, UK
[9]Blizard Institute, Queen Mary University of London, London, UK
[10]NHS Blood and Transplant and Bart's Health NHS Trust, London, UK
[11]NHS Blood and Transplant and Oxford University Hospitals NHS Foundation Trust, John Radcliffe Hospital, Oxford, UK
[12]Radcliffe Department of Medicine, University of Oxford, Oxford, UK

[*]Corresponding author simon.stanworth@nhsbt.nhs.uk

Background: Traumatic haemorrhage is common after severe injury, leading to disability and death. Cryoprecipitate, a source of fibrinogen, may improve outcomes for patients with traumatic haemorrhage.

Objective: To investigate the effects of early fibrinogen supplementation in the form of 3 pools (15 units, approximately 6 g of fibrinogen) of cryoprecipitate on 28-day mortality.

Design: A randomised, parallel-group, unblinded, multicentre, international trial and economic evaluation. Patients were randomised to either the intervention (early cryoprecipitate) or the comparator (standard major haemorrhage protocol) arm via opaque, sealed envelopes in the emergency department or the transfusion laboratory/blood bank. All analyses were performed on an intention-to-treat basis. A cost-effectiveness analysis was undertaken.

Setting: Twenty-five major trauma centres in the UK and one level 1 trauma centre in the USA.

Participants: Adults who had traumatic haemorrhage following severe injury requiring activation of the major haemorrhage protocol and had received a blood transfusion.

Intervention: Early cryoprecipitate – 3 pools (equivalent to 15 single units of cryoprecipitate or 6 g of fibrinogen supplementation), infused as rapidly as possible, within 90 minutes of arrival at hospital in addition to standard major haemorrhage protocol or standard major haemorrhage protocol only.

Main outcome measures: The primary outcome was all-cause mortality at 28 days. The secondary outcomes were all-cause mortality at 6 hours, 24 hours, 6 months and 12 months from admission; death from bleeding at 6 hours and 24 hours; transfusion requirements at 24 hours from admission; destination of participant at discharge; quality-of-life measurements (EuroQol-5 Dimensions, five-level version and Glasgow Outcome Scale) at discharge/day 28 and 6 months after injury; and hospital resource use up to discharge or day 28 (including ventilator-days, hours spent in critical care and inpatient stays).

Results: Eight hundred and five patients were randomised to receive the standard major haemorrhage protocol (control arm). Seven hundred and ninety-nine patients were randomised to receive an additional three pools of cryoprecipitate in addition to standard care (intervention arm). Baseline characteristics appeared well matched. Patients had a median age of 39 (interquartile range 26–55) years, and the majority (79%) were male. All-cause 28-day mortality (n = 1531 patients; intention to treat) was 25.3% in the intervention arm compared with 26.1% in the control arm (odds ratio 0.96; p = 0.74).

Limitations: There was variability in the timing of cryoprecipitate administration, with overlap between the treatment arms, limiting the degree of intervention separation.

Conclusions: There was no evidence that early empiric administration of high-dose cryoprecipitate reduced the risk of death in unselected patients with traumatic haemorrhage. There was also no difference in adverse events. The cost-effectiveness of the intervention was similar to that of standard care.

Future work: Research to evaluate if fibrinogen replacement is more beneficial for selected patients, for example those with low fibrinogen blood levels, is needed, as is further exploration of whether there is a difference in outcome according to mechanism of injury.

Trial registration: This trial is registered as ISRCTN14998314.

Funding: This award was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme (NIHR award ref: 15/57/02) and is published in full in *Health Technology Assessment*; Vol. 28, No. 76. See the NIHR Funding and Awards website for further award information.

Contents

List of tables

List of figures

List of supplementary material

Report Supplementary Material 1	Statistical Analysis Plan for 28-day outcomes
Report Supplementary Material 2	Statistical Analysis Plan for longer-term outcomes
Report Supplementary Material 3	Trial Case Report Form

Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/JYTR6938).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

List of abbreviations

AIS	Abbreviated Injury Score
CAG	Confidentiality Advisory Group
CRF	case report form
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
EQ-5D-5L	EuroQol-5 Dimensions, five-level version
FFP	fresh-frozen plasma
GOS	Glasgow Outcome Scale
HTA	Health Technology Assessment
HDU	high-dependency unit
ICU	intensive care unit
ISS	Injury Severity Score
ITT	intention to treat
MHP	major haemorrhage protocol
NIHR	National Institute for Health and Care Research
PAIR	Patient/Public Advisors for Injury Research
PPI	patient and public involvement
PPIE	patient and public involvement and experience
QALY	quality-adjusted life-year
RBC	red blood cell
SAP	statistical analysis plan
TARN	Trauma Audit and Research Network
TIC	trauma-induced coagulopathy
TMG	Trial Management Group
TSC	Trial Steering Committee

Plain language summary

Uncontrolled bleeding following injury is a leading cause of death and disability, killing over 12,000 people in the United Kingdom every year. People who have severe bleeding after injury often develop a problem with their clotting system that means that they tend to bleed more. One change after trauma is low levels of fibrinogen, a clotting protein normally circulating in the bloodstream. Fibrinogen acts as the 'glue' that holds a blood clot together. At low levels, blood clots do not form properly, and bleeding can continue. Cryoprecipitate is stored as a frozen type of blood component that is prepared from plasma after blood donation. It is rich in fibrinogen. This study investigated whether giving a high dose of cryoprecipitate transfusion as soon as possible after injury reduced death rates.

We studied people who required a blood transfusion following major injury due to trauma admitted at 26 hospitals in the United Kingdom and the United States of America. A total of 1604 people were allocated at random to one of two study groups. One group were given an early transfusion of high-dose cryoprecipitate in addition to standard treatments including other blood transfusions. The other group received the standard treatment alone.

Outcomes from 1531 participants were analysed. Among participants treated with the additional early cryoprecipitate, the death rate was 25.3% (192/760). In the standard treatment group, the death rate was 26.1% (201/771). There was no evidence that treating patients with early high-dose cryoprecipitate had an effect on the death rate. There were also no differences in side effects. The economic analysis shows that, overall, treatment costs and quality of life did not differ between patients who received early cryoprecipitate and patients who did not.

Scientific summary

Background

Worldwide, trauma accounts for 5.8 million deaths every year, equivalent to 1 death every 9 minutes, and is the leading cause of death in persons under the age of 44 years. Bleeding accounts for 40% of all injury-related deaths, many within hours of injury, and there is a high burden from major haemorrhage on both patients and the NHS.

Twenty-five per cent of all trauma patients have abnormal blood clotting, which causes higher rates of bleeding, major haemorrhage and a three- to fourfold increase in the risk of death. There are two main clotting abnormalities: low fibrinogen levels (hypofibrinogenaemia) and increased clot breakdown (fibrinolysis).

Cryoprecipitate is the current standard source of concentrated fibrinogen in the UK. Cryoprecipitate may improve outcomes for patients with traumatic haemorrhage by improving clot strength, reducing blood loss and, hence, increasing survival. This is supported by data from our pilot study (CRYOSTAT-1) that showed that the early replacement of fibrinogen with cryoprecipitate was able to rapidly restore fibrinogen levels and may reduce mortality rates from traumatic haemorrhage.

Objectives

We assessed the effects and cost-effectiveness of the early administration of high-dose cryoprecipitate to traumatic haemorrhage patients on death rates, transfusion requirements and adverse events.

Methods

The CRYOSTAT-2 trial was a randomised, parallel-group, unblinded, multicentre, international trial conducted in 25 major trauma centres in the UK and at one level 1 trauma centre in the USA. Adults who had traumatic haemorrhage following severe injury necessitating activation of the major haemorrhage protocol (MHP) and received a blood transfusion were eligible. (Standard MHPs in the UK include empiric cryoprecipitate in the second pack of blood components if a patient continues to bleed.)

Patients were randomly allocated to receive early high-dose cryoprecipitate (3 pools, equivalent to 15 single units of cryoprecipitate or 6 g of fibrinogen supplementation) in addition to the standard MHP or the standard MHP only. Fibrinogen levels were not required at randomisation.

The primary outcome was all-cause mortality at 28 days. The secondary outcomes were all-cause mortality at 6, 24 hours, 6 months and 12 months from admission; death from bleeding at 6 hours and 24 hours; transfusion requirements for red blood cells, platelets, fresh-frozen plasma and cryoprecipitate at 24 hours from admission; destination of participant at discharge; quality-of-life measurements (EuroQol-5 Dimensions, five-level version, and Glasgow Outcome Scale) at discharge/day 28 and 6 months after injury; and hospital resource use up to discharge or day 28 (including ventilator-days, hours spent in critical care and inpatient stays).

We assessed the cost-effectiveness of the early administration of high-dose cryoprecipitate in addition to the standard MHP compared with that of standard MHP only.

The original planned sample size was 1568 (later amended).

Results

Patients were allocated to early cryoprecipitate in addition to the MHP (*n* = 799) or to the MHP alone (*n* = 805). A total of 1604 patients were enrolled, of whom 1531 had outcome data available for analysis (intervention arm, *n* = 760; standard care arm, *n* = 771). Patients in both treatment arms were well matched on all baseline clinical characteristics, with a median age of 39 [interquartile range (IQR) 26–55] years; 79% were male. The median Injury Severity Score was 29 (IQR 18–43), consistent with major injury.

Overall, any cryoprecipitate was administered within the first 24 hours of arrival at hospital to 85% of patients in the intervention arm and 32% of patients in the standard care arm. By intention-to-treat analysis, 25.3% died in the intervention arm compared with 26.1% in the standard care arm [odds ratio (OR) 0.96; *p* = 0.74]. Mortality was also similar between the treatment arms at 6 and 24 hours. There were no differences between the treatment arms in secondary outcomes, including 24-hour transfusion requirements (other than cryoprecipitate) and safety outcomes (thrombotic).

Conclusions

Our findings do not support empiric fibrinogen supplementation for all trauma patients suspected of bleeding.

The study supports current MHP practices, whereby concentrated fibrinogen therapies such as cryoprecipitate are given often in the second 'MHP pack', or reactively in response to repeated monitoring for low fibrinogen concentrations.

Trial registration

This trial is registered as ISRCTN14998314.

Funding

This award was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme (NIHR award ref: 15/57/02) and is published in full in *Health Technology Assessment*; Vol. 28, No. 76. See the NIHR Funding and Awards website for further award information.

Chapter 1 Introduction

Trauma and major haemorrhage

Trauma is one of the biggest contributors to the global burden of disease, with over 5 million deaths each year, and is responsible for as many lost functional life-years as cardiovascular disease and cancer.[1] It is also one of the few conditions that is on the rise globally, as population growth, socioeconomic inequalities and climate change lead to increased road-, occupation-, violence- and conflict-related injuries. Approximately half of all trauma deaths are due to bleeding.[2] Bleeding can cause death rapidly from exsanguination and subsequently from the effects of insufficient blood supply to the heart, brain and other organs.[3]

Trauma-induced coagulopathy

Bleeding is complicated by a complex clotting disorder induced by injury and resuscitation, termed trauma-induced coagulopathy (TIC).[4] TIC reduces the ability of blood to form stable clots, and this leads to increased bleeding and impairs surgical attempts to stop the haemorrhage. Subsequent rebound changes can lead to increased clotting, a tendency to thrombose and further organ dysfunction.

Early intervention to stop bleeding and correct TIC has led to dramatic reductions in mortality over the last decade.[3] Since the discovery of TIC, approaches to resuscitation have changed completely. Most hospitals now have a major haemorrhage protocol (MHP) that is activated for patients who are suspected of having active bleeding.[5] This brings additional specialist resources and expertise to the patient. A new 'haemostatic resuscitation' paradigm focuses on rapid bleeding control and the targeted correction of coagulopathy.[6] This focuses on controlling bleeding and protecting the body's ability to form a clot. Clear fluids such as saline are no longer used, as they dilute the body's clotting factors. Instead, plasma is given alongside red blood cell (RBC) transfusions to replace lost blood volume.[7] Other agents are also used to prevent or treat different aspects of TIC. Tranexamic acid is given early to reduce clot breakdown.[8] Platelet concentrates are given, typically later in the bleeding course, to restore platelet numbers and function.[9] In addition, most protocols include some later replacement of fibrinogen, either with cryoprecipitate transfusions or with fibrinogen concentrates.[10,11]

Fibrinogen in trauma-induced coagulopathy

Fibrinogen is an essential pro-coagulant factor that is needed for stable clot formation and effective haemostasis.[11] Fibrinogen is rapidly lost in bleeding trauma patients. In TIC, it is consumed during clot formation and directly broken down through fibrinogenolysis.[12] Alterations in fibrinogen metabolism, including differential effects on synthesis and breakdown, also contribute to decreased fibrinogen availability.[13] Low fibrinogen levels on hospital admission have been found to be independently associated with in-hospital, 24-hour and 28-day mortality.[14] Studies have shown that patients with fibrinogen levels below 1 g/l have a greater than threefold increase in the odds of dying compared with those with normal fibrinogen concentrations of 1.5–3.5 g/l. European and other guidance recommend maintaining fibrinogen levels above 2 g/l during haemorrhage.[15,16] Therefore, the effective replacement of fibrinogen is important for managing TIC and preventing further bleeding and an increase in morbidity and mortality (*Figure 1*).

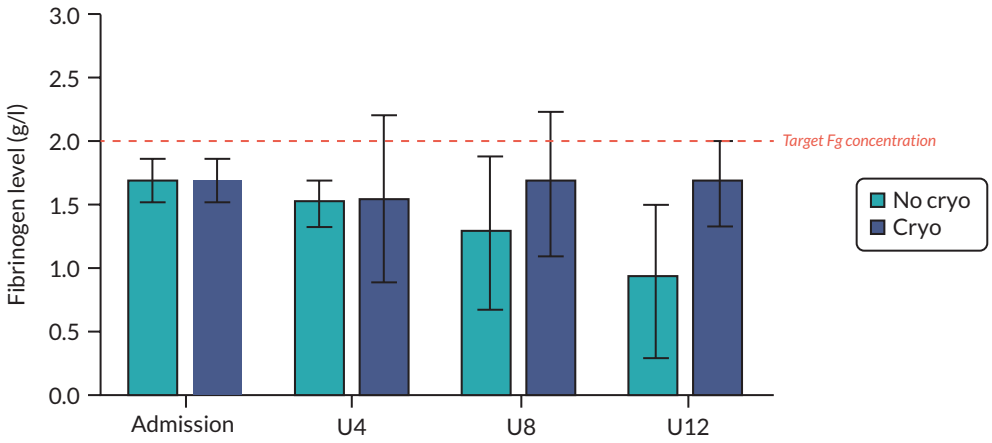

FIGURE 1 Effects of cryoprecipitate on fibrinogen levels following traumatic haemorrhage. Fg, fibrinogen.

Fibrinogen replacement

When treating bleeding disorders caused by low fibrinogen levels, there are two main options: cryoprecipitate and fibrinogen concentrate.[17] Cryoprecipitate is derived from fresh-frozen plasma (FFP) and contains several proteins, including fibrinogen, factor VIII, von Willebrand factor, factor XIII, fibronectin and alpha-2 antiplasmin, which may have additional effects on trauma haemorrhage.[18] Cryoprecipitate is typically pooled from five or six single plasma donations and undergoes two or three freeze–thaw cycles before being transfused. Variability in clotting factor levels in blood donors means that the fibrinogen concentration in cryoprecipitate can vary. Fibrinogen replacement is also available as a concentrate. Fibrinogen concentrate is a purified and standardised product that is often used in Europe. Fibrinogen concentrate is made by extracting fibrinogen from pooled plasma and then purifying and concentrating it. A systematic review comparing the efficacy of cryoprecipitate and fibrinogen concentrate found no difference in fibrinogen increment, transfusion requirement, thromboembolic events or bleeding across the four studies included.[19] In vitro and ex vivo studies have shown that these two products lead to similar, but not identical, improvements in clot structure and quality.[20] Currently, cryoprecipitate is the more frequently used replacement in the UK and the USA, while fibrinogen concentrate is favoured more in Europe.

Empiric therapy versus guided therapy

One key concern with fibrinogen therapy in traumatic haemorrhage is that the time interval between identifying low fibrinogen levels and administering the replacement may be too long for the replacement to exert an effect. In our national study of existing MHPs, on average, patients received their first cryoprecipitate 3 hours after admission to hospital.[10] We know that a large proportion of bleeding trauma patients will have died by this point. Others may have developed such a profound coagulopathy that treatment is likely to be ineffective, and failure to stop or reduce haemorrhage by that point may lead to irreversible cell and organ damage.

Most hospitals in England and around the world will guide fibrinogen therapy using laboratory-based assays of fibrinogen activity. However, these assays are slow to be processed, and the results are usually not available for at least 1 hour after sampling. Point-of-care assessments of fibrinogen levels are not widely available, and so some protocols suggest administering fibrinogen products empirically. These products are usually given later during bleeding, for example after 8 or 10 units of RBC transfusions have been given.[3] The question remains whether the early administration of fibrinogen to all at-risk patients will be of benefit in reducing death rates and other outcomes after traumatic haemorrhage.

Studies of small clinical trials of fibrinogen supplementation have suggested a benefit to replacing fibrinogen, although they have not been powered for a primary mortality end point. We studied the potential for cryoprecipitate in the CRYOSTAT-1 feasibility trial (ISRCTN55509212),[21] which provided pilot data for CRYOSTAT-2. This trial demonstrated that it was feasible to deliver cryoprecipitate within 90 minutes of admission and suggested that early cryoprecipitate therapy maintained blood fibrinogen levels during resuscitation, which may lead to reduced mortality. Other pilot studies have used fibrinogen concentrate. FiiRST (NCT02203968),[22] RETIC (NCT01545635)[23] and E-FIT1 (ISRCTN67540073)[24] set coagulation results as the main end points. These trials have demonstrated that early infusion of supplemental fibrinogen leads to an increase in plasma fibrinogen concentration. The European prehospital trial FIinTIC (NCT01475344) found that physicians were able to administer fibrinogen concentrate in the field, resulting in an improved coagulation profile of the patient on arrival at the hospital.[25]

Overall study objective

Based on the results of CRYOSTAT-1 and these other studies, we postulated that patients thought to have active haemorrhage would benefit from the early empiric administration of cryoprecipitate as soon as possible after admission to hospital. Early administration would treat those who presented with low fibrinogen levels and provide enough reserve fibrinogen such that levels would not fall to critical levels during haemorrhage. We therefore hypothesised that early empiric cryoprecipitate administration would improve outcomes following traumatic haemorrhage and reduce medium- and long-term mortality.

Chapter 2 Methods

Trial design

CRYOSTAT-2 was a randomised, parallel-group, unblinded, multicentre, international trial evaluating the effects of early high-dose cryoprecipitate in adult patients with major trauma haemorrhage requiring MHP activation. The trial is registered at ISRCTN, with reference number ISRCTN14998314 (https://doi.org/10.1186/ISRCTN14998314),[26] Sections of this chapter are based on the trial protocol published in *Transfusion Medicine*,[27] and the original study protocol document,[28] available from the National Institute for Health and Care Research (NIHR) Funding and Awards site.

Approvals

The Medical Research and Ethics Committee and Health Research Authority reviewed the protocol and supporting documents for the CRYOSTAT-2 trial and provided a favourable ethics opinion on 26 May 2017 (Research Ethics Committee reference 17/SC/0164).

Six substantial amendments and eight non-substantial amendments were approved during the project, as detailed in *Table 1*.

The Confidentiality Advisory Group (CAG) reviewed the application and supporting documents for Section 251 support to process confidential patient information without consent and provided approval on 28 January 2020 (CAG reference 19/CAG/0161).

Participants (inclusion and exclusion)

Patients were eligible for this trial if:

1. The patient was judged to be an adult, was aged ≥ 16 years in the UK (or according to local guidance) and had sustained severe traumatic injury.
2. The patient was deemed by the attending clinician to have active haemorrhage.

And required:

3. Activation of the local MHP for the management of severe blood loss.

And had started or *had received*:

4. At least one unit of any blood component.

Patients were not eligible for this trial if they fulfilled one or more of the following criteria:

1. They had been transferred from another hospital.
2. The trauma team leader deemed the injuries incompatible with life.
3. More than 3 hours had elapsed from the time of injury.

TABLE 1 Ethics approvals

Amendment number	Date of approval	Comments
Substantial 02	10 September 2018	Temporary halt at a participating site following a serious breach of the protocol
Substantial 03	28 November 2018	Restart at a participating site following a serious breach of the protocol
Substantial 04	31 January 2020	Application to the CAG seeking Section 251 support to enable linkage of participant identifiable data from a subset of patients from whom it was not possible to collect signed, informed consent. This was to provide information to NHS Digital and TARN for patient matching
Substantial 05	3 April 2020	Public-facing study poster
Substantial 06	14 June 2021	Extension to the study approved by funder and sponsor. Approval for sites in Northern Ireland
Substantial 07	5 May 2022	Extending the number of participants for whom we used Section 251 support for to collect data where appropriate and in line with conditions of CAG support. The NIHR and sponsor agreed that it would be possible to recruit more patients in the UK to make up for the shortfall in expected US patients due to COVID-19. Updates to the statistical section of the protocol including the per-protocol analysis population and updates to administrative sections
Non-substantial 01	31 August 2017	Additions and changes to principal investigators at participating sites
Non-substantial 04	2 September 2019	Approval for sites in Wales. Additions and changes to principal investigators at participating sites
Non-substantial 05	6 April 2020	Non-notifiable amendment: temporary pause in recruitment due to COVID-19, approved by the sponsor
Non-substantial 06	1 May 2020	Non-notifiable amendment: reopening to recruitment due to COVID-19, approved by the sponsor
Non-substantial 07	29 May 2020	Change of principal investigator at participating site
Non-substantial 08	29 June 2020	Change in recruitment end date
Non-substantial 09	19 April 2021	Change in recruitment end date definition from a date to until the target number of participants is reached
Non-substantial 10	7 October 2021	Increase in sample size due to a larger number of participants exiting the study than expected

TARN, Trauma Audit and Research Network.

Consent

Patients with major trauma haemorrhage have a life-threatening injury. On arrival at the emergency department, patients are usually unconscious, and those who are not are usually in pain, in distress and/or under the influence of medication. Patients were enrolled into the study using an 'emergency waiver of consent', whereby the treating senior clinician (the trauma team leader) assessed the patient for eligibility and made the decision whether or not to enter them into the trial. This is an established method of enrolling patients without capacity into emergency medicine trials.

UK law allows patients who need emergency treatment and lack capacity to consent to have a 'consultee', who can recommend whether the participant would like to continue in or would object

to being in the trial. This consultee can be the treating clinician who is not part of the research team (a professional consultee) or a relative/friend (a personal consultee). This study recommended that a professional consultee be sought in the first instance to allow the participant to move from the emergency waiver to consultee declaration and remain in the study until such time that a personal consultee or the participant could be approached about the study. The aim of the consent process in this trial was always to obtain informed signed consent from participants. The parents/legal guardians of participants who were found to be below 16 years of age after the point of entry were approached as personal consultees. See *Appendix 1*, *Figure 11*, for an overview of the consent procedure used in the UK.

Participants enrolled at international sites were subject to the regional or national ethical code of practice for conducting research in incapacitated adults.

There were occasions where a participant died soon after their arrival at hospital, and there had been no opportunity for contact between the research team and a personal consultee. In these situations, it was accepted that approaching the consultee to ask their opinion was likely to be distressing and without benefit. Families of bereaved participants were not contacted by the research team after the participant's death to obtain personal consultee advice. In these cases, advice from a professional consultee was sought so that data collection could be completed at site. Recruiting hospitals were informed that participation in the trial should be disclosed if a coroners' court hearing was convened. This process was agreed after receiving advice from the Research Ethics Committee.

The COVID-19 pandemic began during this trial. This made the consent process more complex because of COVID-19-related restrictions in hospitals, particularly when participants were on a COVID-19 ward where no visitors or staff visits were allowed. It was agreed that initial verbal consent could be taken from COVID-19-positive individuals or those on restricted wards in hospital if this was documented appropriately in the medical notes. When it was safe to do so, the participant was approached to sign an informed consent form. If the participant had been discharged, they were contacted at home by telephone or by post. Consent was obtained using an electronic form or via a physical form returned to the hospital. This process was also followed when seeking consultee declarations during this time. The PANDO application[30] was used at some participating sites to electronically transfer patient-signed informed consent forms from COVID-19-restricted wards to the research team.

It became apparent shortly after the trial began that, for a subset of participants, research staff were at times not able to start or complete the consent process. The reasons for this included:

- patients unexpectedly being discharged (overnight or weekends)
- patients unexpectedly self-discharging (including absconding from authorities)
- participants being rapidly discharged to police custody or returned to the custody of His Majesty's Prison Service
- participants being rapidly transferred to mental health trusts under section
- participants having been repatriated to a non-participating hospital or residential nursing care home or rehabilitation centre
- participants providing false details or refusing to give any details to hospital staff
- participants being homeless and having no listed general practitioner
- participants in hospital being abusive, aggressive or violent, and whom the research team had been advised not to approach
- participants who would have been extremely distressed if contacted due to the nature of their trauma (e.g. if they had been in an accident in which a loved one had died)
- participants who never regained capacity due to the nature of their injuries (brain injury or coma)
- participants having considerable language difficulties where it was not possible to provide an NHS translator or to ask a family member to translate information about the trial.

To enable follow-up data to be collected for these participants, we applied to the HRA for Section 251 support via the CAG, and this was granted.

The participant or their consultee was free to withdraw their consent or change their opinion about participating in the trial at any time. Participants were withdrawn with or without permission for follow-up data collection. If participants withdrew and did not provide permission for continued data collection, data collected up to the point of withdrawal were retained. Although the participant was not required to give a reason for withdrawing consent, a reasonable effort was be made to establish this reason while fully respecting the participant's rights.

Randomisation

The allocation sequence was produced by the trial statistician using SAS® statistical software (SAS Institute Inc, Cary, NC, USA). The allocation sequence had a varying block size that was not disclosed and was stratified by centre. Participants were allocated in a 1 : 1 ratio to the intervention (early cryoprecipitate + standard MHP) or standard care (standard MHP) arm. Allocation cards were prepared and placed in sequentially numbered opaque envelopes, 100% QA checked and sealed with tamperproof tape. Each envelope contained a randomisation number and the allocated treatment and were opened at sites in sequential order. Envelopes were released by the Clinical Trials Unit (CTU) in small batches sufficient to support projected recruitment and replace used envelopes. Envelopes were securely stored in a locked cupboard at each site, access to which was controlled by the research team. In February 2020, an issue was identified with the creation of the allocation sequence, such that there was a tendency for one arm to appear first more often in each block in the early part of the randomisation list, leading to concerns about a small imbalance by the end of the trial. A revised list was created and used when issuing new randomisation envelopes from that point on.

Randomisation took take place in the emergency department or the transfusion laboratory/blood bank, as agreed with the participating hospital. The recruiting staff completed an enrolment log each time an envelope was taken for use, and signed and dated the envelope to confirm that the next available and lowest numbered envelope of the batch had been taken, was unopened and bore no evidence of tampering. The participant's initials, date of birth and hospital number were also written on the envelope prior to opening (if the initials and date of birth were not known, the unique identifiers used at the participating hospital for unknown patients were used). The correct and sequential use of envelopes was strictly audited by the site research team and CTU staff at site monitoring visits.

If the randomised intervention differed from that which the participant received, a reason for this was requested. These processes allowed for clear and regular auditing of the randomisation process through comparison with the randomisation list held by the statistician. At the end of recruitment, sites returned the randomisation envelopes to the CTU, with participant details obscured.

This was an unblinded trial. As the study control arm was standard care (MHP), it was not possible to blind the intervention of early cryoprecipitate as there was no comparative transfusion of a placebo. Members of the trauma team in emergency department were therefore aware of the treatment arm to which the participant had been randomised. However, the risk to trial integrity was minimised, given that the primary outcome of 28-day mortality was a hard end point.

Trial intervention

The intervention was 3 pools of cryoprecipitate (equivalent to 15 single units of cryoprecipitate or 6 g of fibrinogen supplementation), infused as rapidly as possible, within 90 minutes of arrival at hospital. The intervention was given in addition to the standard MHP.

The comparator was standard MHP only. The standard treatment of major traumatic haemorrhage involves administering RBCs, FFP and platelets. Each participating site followed its local standardised MHP that aligned with the current accepted best practice for transfusion therapy, that is damage control resuscitation, the use of tranexamic acid and the empiric (automatic and unguided) delivery of RBCs, FFP and platelets. The MHP comprises a balanced resuscitation with blood products and was standardised as much as possible across participating sites; however, some degree of variation was inevitable and pragmatic, reflecting actual clinical practice. The transfusion products given vary to some extent from the target ratio according to blood product availability and the participant's ongoing clinical condition.

Early cryoprecipitate (3 pools = 6 g of fibrinogen) was stored in its frozen state and defrosted in accordance with the local standard operating procedures for each blood bank/transfusion laboratory. In the UK, these procedures will be in accordance with the national guidelines.[31] The cryoprecipitate was made available to the emergency department as quickly as possible. The study team provided trial-specific, yellow-labelled bags for the intervention to differentiate trial cryoprecipitate from any cryoprecipitate given as standard of care. As an alternative, and depending on local approval for use, pre-thawed cryoprecipitate was also permitted during the trial. The early cryoprecipitate was administered as rapidly as possible via an intravenous line and in accordance with local practice. The cryoprecipitate was not mixed with platelets prior to infusion.

There were no restrictions on treatments that could be given during this trial, as long as the treatments were part of standard care and were not administered as part of another trial [unless authorised by the Trial Management Group (TMG) or delegated co-investigator].

Sites

This study was conducted in participating major trauma centres in the UK and the USA. The list of study sites is in *Appendix 2*, *Table 17*.

Data collection

Screening data

Site research teams collected data in a screening log to allow an assessment of the proportion of eligible patients recruited and the reasons why eligible patients were not recruited to CRYOSTAT-2. This log recorded data for all patients considered eligible for enrolment in the trial and included age, sex, inclusion/exclusion criteria, and other reasons for non-enrolment.

Outcome data

Once patients were randomised into CRYOSTAT-2, data were collected on paper case report forms (CRFs) by the local research team, and these were posted to the CTU at day 28, discharge or death, for data entry into the MACRO database. Background data (participant characteristics) were collected, including participant age, participant sex, mechanism of injury and injury type. Clinical data were also collected, which included vital signs on arrival at the emergency department (systolic blood pressure, heart rate and Glasgow Coma Scale), blood components given (pre-hospital, in the emergency department and 24 hours from arrival in the emergency department) and cryoprecipitate administration.

At day 28, discharge or death, the Injury Severity Score (ISS), EuroQol-5 Dimensions, five-level version (EQ-5D-5L) and Glasgow Outcome Scale (GOS), hospital stay, consent status, and discharge and mortality status of participants were collected on the CRF. Patient-reported outcome measures are routinely collected from eligible patients at all major trauma centres across the UK during the first hospital admission and at 6 months from injury as part of an ongoing (Trauma Audit and Research Network (TARN) project.

Follow-up data

Data on participants' quality of life at 6 months post admission were collected through linkage with TARN for participants with informed consent in place. Data on participants' survival status up to 1 year post admission were collected through linkage with NHS Digital for participants with patient informed consent in place or those covered by Section 251 approval.

Monitoring

CRYOSTAT-2 was assessed as moderate risk; therefore, visits were conducted twice per year at each site. Investigators and their institutions provided direct access to source data for monitoring, auditing and regulatory inspections. We planned to monitor 20% of UK participants through on-site source data verification, but from March 2020, owing to restrictions during the COVID-19 pandemic, as most sites had been visited multiple times monitoring was conducted remotely, with site research teams using a checklist to reconfirm key data. We monitored 30% of UK participants on site. Key data were monitored centrally on a bi-monthly basis as part of the TMG report. This included recruitment, withdrawals, serious adverse events, data queries and completion and consent.

Outcome measures

Primary outcome measures

The primary outcome measure was all-cause mortality at 28 days.

Secondary outcome measures

Secondary outcome measures were all-cause mortality at 6 hours, 24 hours, 6 months and 12 months from admission; death from bleeding at 6 and 24 hours; transfusion requirements for RBC, platelets, FFP and cryoprecipitate at 24 hours from admission; destination of participant at discharge; quality-of-life measurements (EQ-5D-5L and GOS) at discharge/day 28 and 6 months after injury; and hospital resource use up to discharge or day 28 (including ventilator-days, hours spent in critical care and inpatient stays).

Adverse events

Data on symptomatic thrombotic events (venous thromboembolism and arterial thrombotic events), death and serious transfusion-related adverse reactions were collected from randomisation up to day 28 or discharge. All serious adverse events were reviewed by the chief investigators or delegated clinical members of the TMG.

Changes to the protocol

Table 2 summarises the changes made to the protocol throughout the lifespan of the trial.

Sample size

The CRYOSTAT-2 study was designed to detect an absolute mortality difference of 7% from a baseline mortality rate of 26%, that is a reduction to 19%. The baseline mortality was based on the feasibility study CRYOSTAT-1, which reported a 28% mortality rate; the national epidemiological study of trauma transfusion practice, which reported a 39% mortality rate among patients receiving ≥ 10 units of RBC in 24 hours (classified as having 'massive haemorrhage'); and the PROPPR study of bleeding trauma

TABLE 2 Changes to the protocol

Version	Author	Date	Reason for revision
2.0	TMG	3 July 2019	Clarification of consent processes for England and Wales. Clarification of continued follow-up data in accordance with General Data Protection Re gulation and CAG approval
3.0	TMG	25 March 2021	Change in planned study duration. Addition of Northern Ireland specific study processes. Addition of verbal and electronic consent of personal consultees and participants where obtaining a signed copy of the personal consultee declaration form or participant informed consent form would put staff and/or participants at risk of contracting COVID-19. Addition of the use of the PANDO application to transfer consultee declaration form and participant informed consent forms
3.1	TMG	5 October 2021	Sample size changed to 1600; changes to the statistics section to reflect this
4.0	TMG	15 February 2022	To reflect that ISSs will be collected from TARN to ensure consistency with nationally reported scores. Additional data collection of baseline quality-of-life data from TARN where the research team have not been able to collect it in hospital

patients conducted at level 1 trauma centres in North America, which had a baseline mortality rate of 26%.

CRYOSTAT-2 used 90% power to detect a reduction in 28-day all-cause mortality of 7% using a 5% level of significance and a two-tailed test. An initial blinded analysis after the first 300 participants had been recruited and followed up to 28 days was used to reassess sample size requirements and recruitment rates, and at the request of the Data Monitoring Committee (DMC) this was repeated after 750 participants had been recruited.

A group sequential design was used to allow for the DMC reviewing the primary outcome for evidence of harm or benefit (but not futility) after 500 and 1000 participants had been followed up for 28 days. The design used O'Brien–Fleming stopping guidelines[29] determined at the study design stage to ensure an overall Type I error of 5% at the end of the trial. O'Brien–Fleming guidelines were used because of the low chance of terminating the trial at early interim analysis, and because of the minimal change to the alpha used at final analysis. The stopping guidelines were used to help guide the DMC's decision-making alongside other safety data available to the committee. Allowing for the interim analyses in this way, the required sample size to meet specified power requirements was 1530 participants in total. This was initially increased by 2.5% to allow for dropout, but as dropout was higher than anticipated this was later increased to 4.4%, resulting in a total of 1600 participants.

Statistical methods and analysis plan

The Statistical Analysis Plans (SAPs) for 28-day outcomes and for longer-term outcomes are available in *Report Supplementary Material 1* and *2*. All analyses were on an 'intention-to-treat' (ITT) basis and included all randomised participants (including those randomised in error) for whom values of a response variable were obtained, analysed according to randomised group. All analyses were two-sided and the significance level was 5%.

The primary outcome, all-cause mortality at 28 days from arrival at hospital, was determined as the proportion of participants in each treatment arm who died within 28 days. The odds ratio (OR) for death within 28 days [with 95% confidence interval (CI) and *p*-value for the treatment arm term] was presented, and adjusted for centre using a marginal model, and this was the primary analysis of the outcome. This was supplemented by logistic regression analysis so that account could be taken of any prespecified factors that might have differed between the treatment arms and had a statistically

significant association with 28-day mortality. Mortality rates according to timing of cryoprecipitate administration were also analysed, using categories of ≤ 45 minutes, 46–60 minutes, 61–90 minutes and > 90 minutes from arrival at hospital. Mortality rates among those who did or not receive cryoprecipitate in the cryoprecipitate arm were also analysed.

As no placebo was used in the study, a per-protocol analysis that excluded patients who did not receive trial treatment would differentially exclude those in the intervention arm. Per-protocol analysis therefore focused on the cohort of patients who could have benefitted from the intervention and excluded only protocol deviations unrelated to the details of cryoprecipitate administration, randomisations in error, those who died within 90 minutes of admission and those who did not receive any blood products after arrival at hospital (an indication that they had already stopped bleeding). A per-protocol analysis was conducted for all mortality end points up to 28 days (6 hours, 24 hours and 28 days), transfusion requirements, hospital stay and thrombotic events.

Multiple imputation based on full conditional specification was used to impute values of potential risk adjustment factors. The set of variables used in the multiple imputation model was specified in the SAP and included the primary outcome variable. Primary and secondary outcome measures were not imputed, and these were treated as missing data. The methods used for the analysis of secondary outcomes in the form of proportions were similar to those described for the primary outcome. Survival times and rates were estimated using the Kaplan–Meier method and compared using Cox proportional hazards regression. Transfusion requirements were summarised as the median and interquartile range (IQR) of the number of units administered from injury to 24 hours post arrival at hospital, and the mean products transfused per participant per hour over the first 24 hours compared between the arms. Hospital stay, critical care stay and ventilator-days were estimated using a competing risks analysis,[32,33] with discharge/extubation as the event and death as the competing risk.

The number of symptomatic thrombotic events up to day 28 were presented overall and by treatment arm. In particular, the number of venous thromboembolisms (pulmonary embolism, deep-vein thrombosis) and arterial thrombotic events (myocardial infarction, stroke) were calculated.

Subgroup analyses

The primary outcome analysis was repeated to assess the heterogeneity of treatment effects for the following subgroups:

a. UK participants versus non-UK participants
b. head Abbreviated Injury Score (AIS) < 4 versus ≥ 4
c. participant sex
d. participant age < 70 versus ≥ 70
e. injury type, blunt versus penetrating.

The secondary outcome analysis of 6- and 24-hour mortality was repeated for subgroup analysis (b), head AIS < 4 versus ≥ 4.

Economic evaluation methods

An economic analysis model was developed to analyse the cost-effectiveness of early cryoprecipitate plus standard of care versus standard of care alone from an NHS and Personal Social Services perspective. Full details of the methods and results are provided in *Chapter 4*.

Patient and public involvement

The principles set out by the INVOLVE advisory group (active until 2020) were used to guide our approach to patient and public involvement and experience (PPIE) engagement. The research team also built on their pre-existing patient and public involvement (PPI) links that had been set up prior to the start of the feasibility study, CRYOSTAT-1, in 2012. The initial focus of CRYOSTAT-2 PPIE was to engage with patient and public stakeholders to inform the design of the study. Advertising documents (posters/e-mails/website adverts) were sent out both to patients who had previously been injured and to all the lay members of one participating site's trust mailing list to ask for interested volunteers to join a meeting to discuss the study. In total, 2 face-to-face meetings were held (2014, 2016) and 1 survey was distributed to 50 members of the public, asking for views about 2 important trial design questions: what they felt would be the most relevant outcome to test in the proposed CRYOSTAT-2 study (e.g. survival, functional status, or other) and what their views were about consenting participants to a study for which most eligible patients lacked capacity.

Following the second meeting, which specifically focused on consent, in 2016 a dedicated PPI group Patient/Public Advisors for Injury Research (PAIR) was formed to support CRYOSTAT-2 trial development. This group provided ongoing support to the CRYOSTAT-2 trial in the following ways: (1) most importantly, they helped the study team shape the trial design with regard to the primary end point and most acceptable method of gaining consent; (2) the group nominated a member to sit on the Trial Steering Committee (TSC) and this member actively contributed to each TSC meeting throughout the study (a second, more experienced PPI representative was also invited to sit on the TSC); (3) the PAIR group collectively co-wrote the plain language summary for the application to the NIHR Health Technology Assessment (HTA) programme as well as the CRYOSTAT-2 trial protocol and will continue to help with the dissemination of information; (4) the group helped to draft and subsequently edited the patient-facing trial documents such as the patient/patient representative information leaflets and consent/assent forms; and (5) the TSC members helped to develop the NIHR HTA funding application as an integral part of the research team. We will ask the PAIR group for assistance in disseminating the results of this study more widely through social media and patient forums.

Chapter 3 Results

Recruitment and baseline results

The first patient was enrolled on 23 August 2017 and the last patient was enrolled on 2 November 2021. Recruitment was stopped temporarily between 6 April 2020 and 1 May 2020 due to the COVID-19 pandemic. Trial-specific data collection continued until 1 December 2021 in the UK and until 5 July 2022 in the USA. Central data linkage for mortality continued until 27 May 2022 in the UK.

The original planned sample size was 1568, later amended to 1600. A planned sample size re-estimation was conducted after 300 participants had been randomised and repeated after 750 participants had been randomised following a DMC request. In both cases, the committee recommended that the study continue with the original sample size. The final sample size was subsequently increased to 1600 after the TMG reviewed lost to follow-up rates. Two pre-planned interim analyses for harm or benefit after the recruitment of 500 and 1000 participants were conducted using data on 578 and 1027 participants, respectively. In both cases, the test statistic did not cross the O'Brien–Fleming early stopping boundary, and the DMC recommended that the trial continue to the full sample size. Due to delayed randomisation notifications, recruitment closed after the recruitment of 1604 participants. In total, 1555 participants were recruited across 25 UK centres, and 49 participants were recruited in one US centre (see *Appendix 2*, *Table 17*).

The Consolidated Standards of Reporting Trials diagram is shown in *Figure 2*. A total of 9036 patients were assessed for eligibility, of whom 2756 (31%) were found to be eligible for the study; 1604 (58%) of these 2756 patients were randomised. The most common reason for not randomising eligible patients was that the research team was unavailable for patients presenting at sites out of hours.

The 1604 patients were randomly assigned to receive either early cryoprecipitate in addition to the standard MHP (n = 799, 49.8%) or the standard MHP alone (n = 805, 50.2%).

Sixty-nine participants were randomised in error (intervention arm, n = 29; standard care arm, n = 40), having found to be ineligible for the study after randomisation, most commonly because they had not received at least one unit of any blood component prior to randomisation. All patients randomised in error were included in the ITT analysis if they had primary outcome data.

A total of 88 patients (intervention arm, n = 50; standard care arm, n = 38) withdrew consent after randomisation, but, of these, primary outcome data were missing for only 50 (intervention arm, n = 29; standard care arm, n = 21). For the remaining 38 patients, primary outcome data were available due to either the timing of withdrawal or the participants' agreement to continued data collection after withdrawal.

Primary outcome data were missing for a further 23 participants (intervention arm, n = 10; standard care arm, n = 13) for whom no follow-up data were available at all, or available only beyond day 24 (as the 28-day follow-up form had a reporting window of ± 4 days patients reported alive at day 24 were assumed alive at day 28 as specified in the SAP).

Baseline characteristics were similar in both arms (*Table 3*). Seventy-nine per cent of participants were male and the median age was 39 years (IQR 26–55 years). Sixty-four per cent of patients sustained a blunt injury, 26% had a head AIS ≥ 4 and the median ISS was 29 (IQR 18–43). Forty-three per cent were administered a blood component and 79% were administered tranexamic acid prior to hospital arrival.

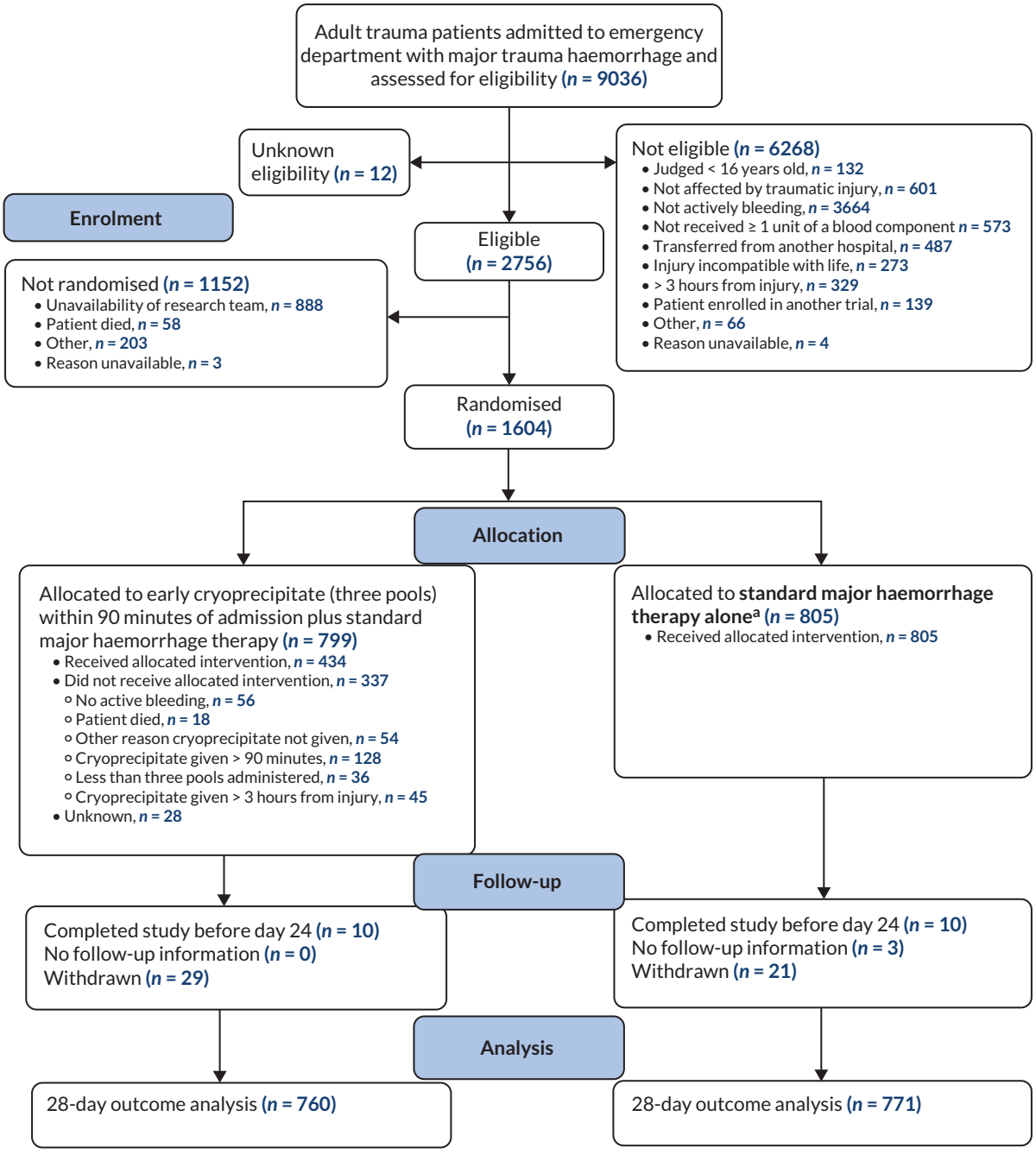

FIGURE 2 Summary of trial entry, randomisation and treatment. a, Standard major haemorrhage therapy: empiric high ratio RBC, FFP and platelet transfusions.

As expected in the absence of a placebo, protocol deviations were more common in the intervention arm. One patient was transfused the wrong component in error and a further 337 of the 799 patients (42%) in the intervention arm did not receive the full intervention per protocol. Of those 337 patients, 128 did not receive any early cryoprecipitate (16% of those randomised to early cryoprecipitate) because the patient had died, no active bleeding was identified at the time, or it was reported that haemostasis or correction of coagulopathy had been achieved. Other reasons for protocol deviations were administering cryoprecipitate more than 90 minutes after admission (e.g. due to delayed activation of the MHP), administering fewer than three pools of cryoprecipitate or administering cryoprecipitate more than 3 hours after injury.

TABLE 3 Baseline characteristics: data are number/total number (%) for categorical variables and median (IQR) for continuous variables

Characteristic	Standard care arm (*n* = 805)	Intervention arm (*n* = 799)	Overall (*n* = 1604)
Male	633/796 (80)	618/785 (79)	1251/1581 (79)
Age (years)	40 (26–55)	38 (25–55)	39 (26–55)
Time from injury to admission to emergency department (minutes)	77 (55–100)	75 (55–99)	76 (55–100)
Time from admission to randomisation (minutes)	14 (7–27)	15 (7–28)	15 (7–27)
Injuries and physiology at admission to emergency department			
Blunt injury	519/796 (65)	495/785 (63)	1014/1581 (64)
ISS	29 (18–43)	29 (17–43)	29 (18–43)
Head AIS ≥ 4	191/664 (29)	157/665 (24)	348/1329 (26)
Systolic blood pressure (mmHg)	103 (83–126)	102 (84–124)	103 (83–125)
Systolic blood pressure < 90 mmHg	250/738 (34)	230/724 (32)	480/1462 (33)
Heart rate (per minute)	108 (88–127)	108 (88–126)	108 (88–127)
In cardiac arrest	17/735 (2)	12/717 (2)	29/1452 (2)
Glasgow Coma Scale score	13 (3–15)	14 (3–15)	14 (3–15)
Pre hospital			
Administered any blood components	348/795 (44)	323/783 (41)	671/1578 (43)
RBC (units)	0 (0–2)	0 (0–2)	0 (0–2)
FFP (units)	0 (0–1)	0 (0–1)	0 (0–1)
Crystalloids (ml)	0 (0–250)	0 (0–250)	0 (0–250)
Colloids (ml)	0 (0–0)	0 (0–0)	0 (0–0)
TXA administered	639/796 (80)	615/783 (79)	1254/1579 (79)

TXA, tranexamic acid.

Note
Summary of missing data: data on all characteristics were missing for 23 participants. In addition, ISS, cardiac arrest and blood pressure were missing for 246, 129 and 119 participants, respectively. There was a small number of missing data for other items.

Four patients in the standard care arm had protocol deviations. Two were randomised when recruitment at the site was paused due to COVID-19-related pressures, one was randomised when human error resulted in production of the randomisation envelope that showed the incorrect treatment, and one patient was randomised twice [in the emergency department and intensive care unit (ICU), randomised to the same arm, only one set of data was collected and analysed].

Eighty-five per cent of those in the intervention arm and 32% of those in the standard care arm received cryoprecipitate within the first 24 hours of arrival at hospital. Sixty-eight per cent of participants in the intervention arm received it within 90 minutes of arrival at hospital, compared with 9% in the standard care arm ($p < 0.0001$; *Figure 3*). Median (IQR) time to first cryoprecipitate (among those who received it) was 68 (53–85) minutes in the intervention arm and 120 (79–184) minutes in the standard care arm.

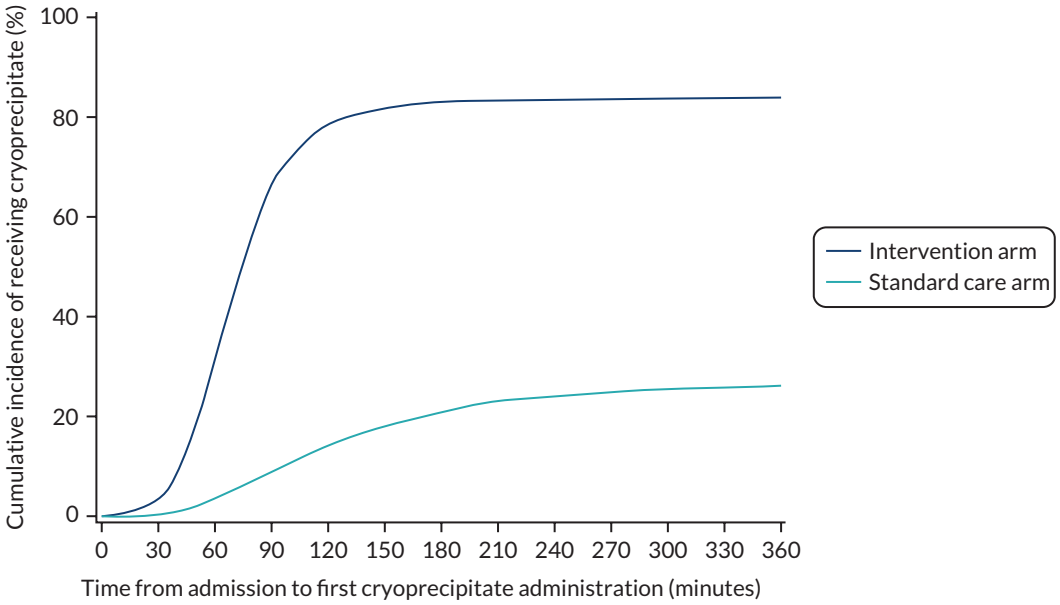

FIGURE 3 Cumulative incidence curve of time from admission to first cryoprecipitate administration (including all patients) by treatment arm.

Primary outcome

We obtained primary outcome data for 760 patients in the intervention arm (95%) and 771 participants (96%) in the standard care arm. Patients discharged from hospital prior to 28 days were assumed alive at 28 days, together with anyone reported alive at day 24 or later.

Table 4 presents the ITT analysis of the primary outcome. In the intervention arm, 25.3% died within 28 days of admission compared with 26.1% in the standard care arm. The OR was 0.96 (95% CI 0.75 to 1.23) for 28-day mortality for early cryoprecipitate versus standard MHP, with a *p*-value of 0.7406 for the difference between the arms. The relative risk was 0.97 (95% CI 0.81 to 1.17).

After risk adjustment for statistically significant patient factors (see *Appendix 2*, *Table 20*, *Figures 11* and *12*, for the details of this model), the OR for mortality was 1.15 (95% CI 0.93 to 1.42). *Figure 4* presents an unadjusted Kaplan–Meier plot of survival to 28 days by treatment arm.

Similar results were obtained in a per-protocol analysis (those excluded from the per-protocol analysis are summarised in *Appendix 2*, *Table 21*). In the per-protocol analysis, 23.1% of those in the intervention arm and 22.5% in the standard care arm died within 28 days of admission (OR 1.03, 95% CI 0.77 to 1.37; $p = 0.8272$). The relative risk was 1.02 (95% CI 0.82 to 1.27). After adjustment for significant participant factors (as per ITT analysis), the OR was 1.24 (95% CI 1.00 to 1.55).

Similar results were obtained from other sensitivity analyses, including an ITT analysis unadjusted for centre (OR 0.96, 95% CI 0.76 to 1.21) and a sensitivity analysis that assumed that 2% of those discharged died before day 28 (OR 0.95, 95% CI 0.75 to 1.21). A forest plot is presented in *Appendix 2*, *Figure 13*.

The 28-day mortality rate ranged between 16.5% and 34.4% according to when early cryoprecipitate was given (see *Table 5* and *Figure 5*). Those given early cryoprecipitate 61–90 minutes after admission had significantly lower 28-day mortality than all those in the standard arm ($p = 0.0093$). Differences between the standard care arm and the other categories of cryoprecipitate timing were non-significant. *Figure 6* presents a plot showing the effect of the timing of first cryoprecipitate administration on the

TABLE 4 Primary outcome

Outcome	Standard care arm (*n* = 805)	Intervention arm (*n* = 799)	Overall (*n* = 1604)	*p*-value
Participants who died on or before day 28 from admission, *n*/*N* (%)	201/771 (26.1)	192/760 (25.3)	393/1531 (25.7)	
Relative risk[a] (95% CI)	0.97 (0.81 to 1.17)			
OR[b] (95% CI)	0.96 (0.75 to 1.23)			0.7406
OR also adjusted for participant factors[c] (95% CI)	1.15 (0.93 to 1.42)			
Participants for whom 28-day vital status was not available from any source, *n*/*N* (%)	34/805 (4.2)	39/799 (4.9)	73/1604 (4.6)	

a Intervention arm relative to standard care arm, adjusted for centre.
b Intervention arm relative to standard care arm, adjusted for centre; *p*-value for treatment term in mixed logistic regression model.
c Intervention arm relative to standard care arm adjusted for centre and significant participant factors.

Notes
Participants for whom 28-day vital status was not available were not included in this analysis. No participants were excluded for other reasons.
Shaded cells are used where the metric is not relevant or where a formal hypothesis test was not planned in the SAP and therefore a *p*-value is not presented.

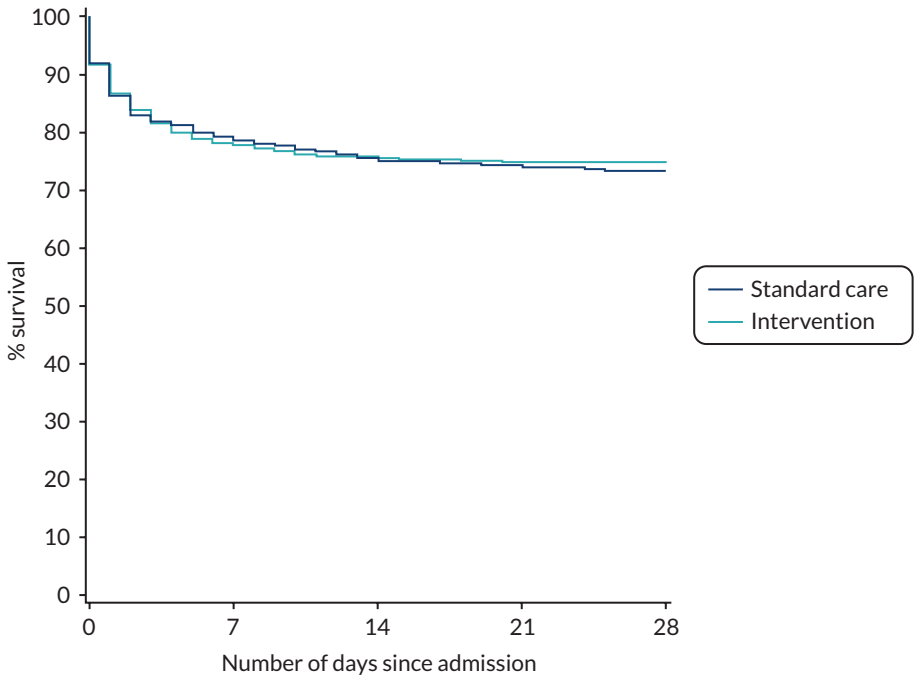

FIGURE 4 Kaplan–Meier survival plot up to 28 days from admission by treatment arm.

odds of 28-day mortality after adjustment for patient factors described in *Appendix 2*, *Table 20*. The timing term was fitted as a restricted cubic spline as there was evidence of non-linearity. The plot demonstrates the U-shaped relationship also seen in *Table 5*.

In a post hoc analysis, the baseline characteristics of participants who were given cryoprecipitate at different times were examined (see *Appendix 2*, *Table 18*), and those given cryoprecipitate early were

TABLE 5 All-cause mortality at 28 days in the standard arm and in the early cryoprecipitate arm by timing of first cryoprecipitate dose

Cryoprecipitate administered at	Mortality rate, *n*/*N* (%)	Relative risk (95% CI)[a]	OR (95% CI)[a]	*p*-value[b]
Standard care arm	201/771 (26.1)	1.00	1.00	
Intervention arm ≤ 45 minutes from admission	33/96 (34.4)	1.29 (0.94 to 1.77)	1.45 (0.91 to 2.31)	0.1195
Intervention arm 46–60 minutes from admission	42/144 (29.2)	1.11 (0.84 to 1.48)	1.16 (0.78 to 1.73)	0.4550
Intervention arm 61–90 minutes from admission	44/267 (16.5)	0.65 (0.46 to 0.91)	0.57 (0.38 to 0.87)	0.0093
Intervention arm > 90 minutes from admission	31/123 (25.2)	1.00 (0.71 to 1.41)	1.00 (0.62 to 1.60)	0.9870

a Cryoprecipitate administered in the time period relative to standard arm overall, adjusted for centre.
b Wald test *p*-value from logistic regression model, adjusted for centre.

Note
Participants for whom 28-day vital status was not available were not included in this analysis, in addition to 130 participants excluded due to missing timing of cryoprecipitate.

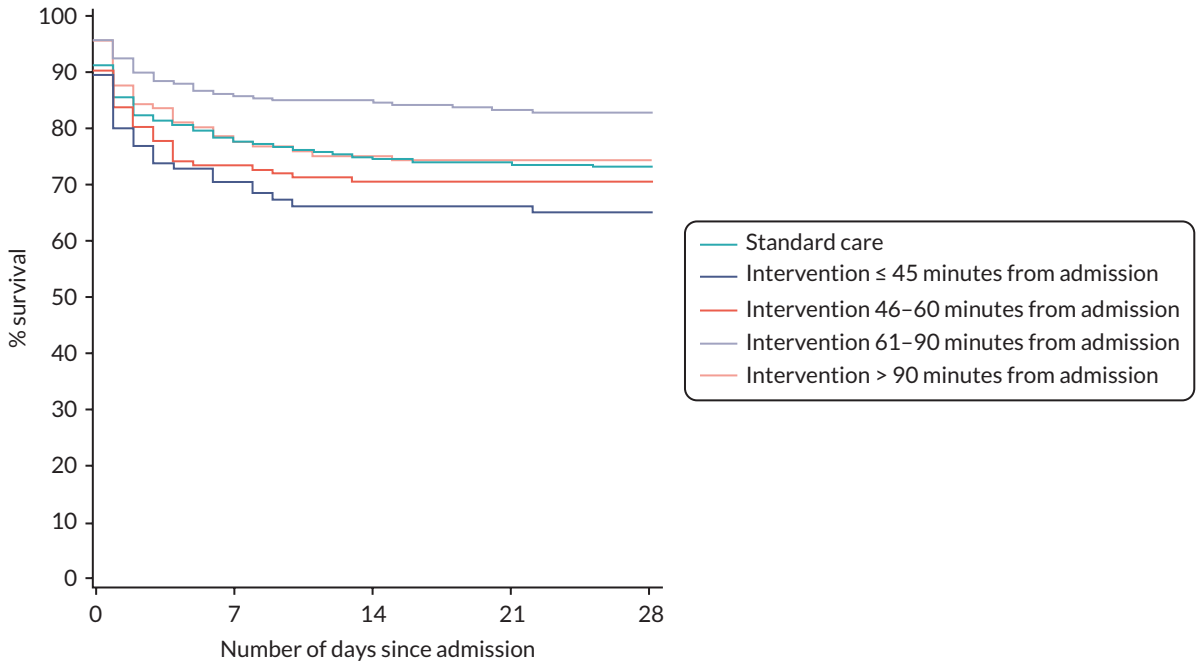

FIGURE 5 Kaplan–Meier survival plot up to 28 days from admission by treatment arm and time of first cryoprecipitate dose.

found to be more severely injured and shocked on admission. As there was no placebo, there is no equivalent 'timing' in the standard arm, and so a comparison can only be made against the whole standard MHP group, rather than with a similarly severely injured subgroup.

Appendix 2, *Table 22* presents the 28-day mortality rate for those in the standard care arm compared with those in the intervention arm who did or did not receive early cryoprecipitate. The 28-day mortality rate was 31.7% among those in the intervention arm who did not receive early cryoprecipitate and

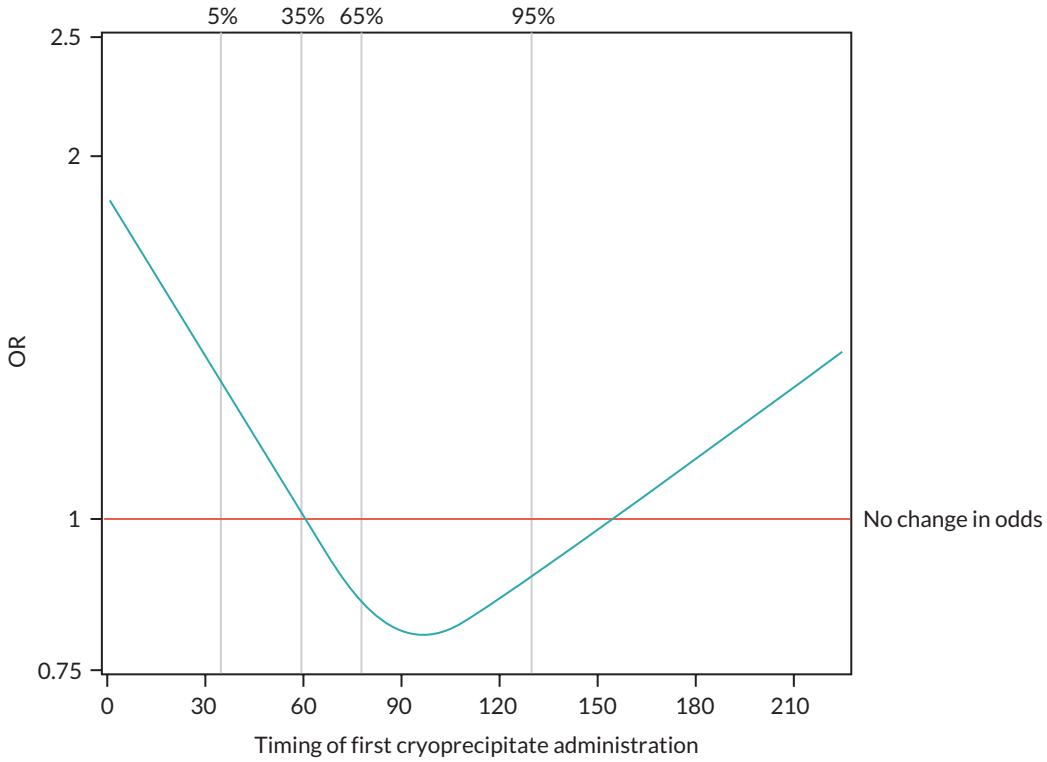

FIGURE 6 Effect of timing of first cryoprecipitate administration on 28-day mortality, relative to a baseline participant with first cryoprecipitate administration at 60 minutes, after adjustment for Glasgow Coma Scale score, ISS, participant age and systolic blood pressure (vertical lines indicate the distribution of the data and where the knots were applied for the restricted cubic spline).

24.0% among those who did. There were no statistically significant differences compared with the standard care arm. However, *Appendix 2*, *Figure 14*, demonstrates that in the group who did not receive early cryoprecipitate there were many very early deaths, indicating that the higher mortality rate may be because participants died before cryoprecipitate could be administered. This was confirmed when the analysis was repeated on the per-protocol cohort, from which early deaths were excluded (23.3% mortality among those in the intervention arm who did not receive early cryoprecipitate and 23.1% among those who did).

Table 6 presents the cause of death for the 393 participants who died within 28 days. The primary cause of death in both arms was traumatic brain injury (37%), followed by uncontrolled bleeding (22%).

Subgroup analysis

There was no evidence of a differential effect of early cryoprecipitate on 28-day mortality for four of the five prespecified subgroup analyses: UK versus non-UK participants, head AIS < 4 versus ≥ 4, participant sex, and participant age < 70 versus ≥ 70 years (see *Appendix 2*, *Tables 23–26* and *Figures 15–18*). However, there was evidence of a differential effect according to whether the participant's injury was blunt or penetrating (see *Table 7* and *Figure 7*). For penetrating injuries, early cryoprecipitate increased the odds of death compared with those who received only the standard MHP (OR 1.74, 95% CI 1.20 to 2.51). For blunt injuries, early cryoprecipitate decreased the odds of death, but this was not statistically significant (OR 0.82, 95% CI 0.62 to 1.09). There were no apparent differences in baseline characteristics between the two subgroups (see *Appendix 2*, *Table 19*). Head AIS < 4 versus ≥ 4 also did not have a differential effect on 6- or 24-hour mortality. Subgroup analysis results are also presented in the forest plot in *Appendix 2*, *Figure 13*.

TABLE 6 Causes of death for all-cause mortality at 28 days: *n*/*N* (% of those who died)

Cause of death	Standard care arm, *n*/*N* (% of those who died) (*N* = 805)	Intervention arm, *n*/*N* (% of those who died) (*N* = 799)	Overall, *n*/*N* (% of those who died) (*N* = 1604)
Total deaths within 28 days, *n*/*N* (% of those randomised)	201/771 (26)	192/760 (25)	393/1531 (26)
Multiorgan failure	26/201 (13)	21/192 (11)	47/393 (12)
Multiple injury	38/201 (19)	31/192 (16)	69/393 (18)
Myocardial infarction	0/201 (0)	3/192 (2)	3/393 (1)
Pulmonary embolism	1/201 (0)	0/192 (0)	1/393 (0)
Sepsis	4/201 (2)	0/192 (0)	4/393 (1)
Stroke	0/201 (0)	5/192 (3)	5/393 (1)
Traumatic brain injury	78/201 (39)	67/192 (35)	145/393 (37)
Uncontrolled bleeding	41/201 (20)	46/192 (24)	87/393 (22)
Other	13/201 (6)	19/192 (10)	32/393 (8)
All	201/201 (100)	192/192 (100)	393/393 (100)

TABLE 7 All-cause mortality at 28 days by treatment arm: blunt vs. penetrating injury type

Outcome	Blunt		Penetrating	
	Standard care arm (*N* = 519)	Intervention arm (*N* = 495)	Standard care arm (*N* = 277)	Intervention arm (*N* = 290)
Participants who died on or before day 28 from admission, *n*/*N* (%)	174/500 (34.8)	147/483 (30.4)	27/271 (10.0)	45/277 (16.2)
Relative risk[a] (95% CI)	0.88 (0.72 to 1.06)		1.62 (1.17 to 2.23)	
OR[a] (95% CI)	0.82 (0.62 to 1.09)		1.74 (1.20 to 2.51)	
p-value for subgroup[a]	0.1634		0.0058	
p-value for interaction term[b]	0.0040			
Participants for whom 28-day vital status was not available from any source, *n*/*N* (%)	19/519 (3.7)	12/495 (2.4)	6/277 (2.2)	13/290 (4.5)

a Intervention arm relative to standard care arm, adjusted for centre.
b *p*-value for interaction, adjusted for centre and blunt vs. penetrating injury.

Note
Participants for whom 28-day vital status was not available were not included in this analysis. No participants were excluded for other reasons.

Secondary outcomes

Tables and figures relating to secondary outcomes are presented in *Appendix 2* or below. All results relate to the ITT analysis. Per-protocol analysis of certain secondary outcomes was planned in the protocol, and for these outcomes the results were very consistent with those of the ITT analysis.

Mortality data

There were no statistically significant differences between arms in all-cause mortality and deaths from bleeding at 6 and 24 hours (see *Appendix 2*, *Table 27*). The median (IQR) time to death from bleeding among those who bled was 191 (81–445) and 86 (40–205) minutes in the intervention and standard care arms, respectively.

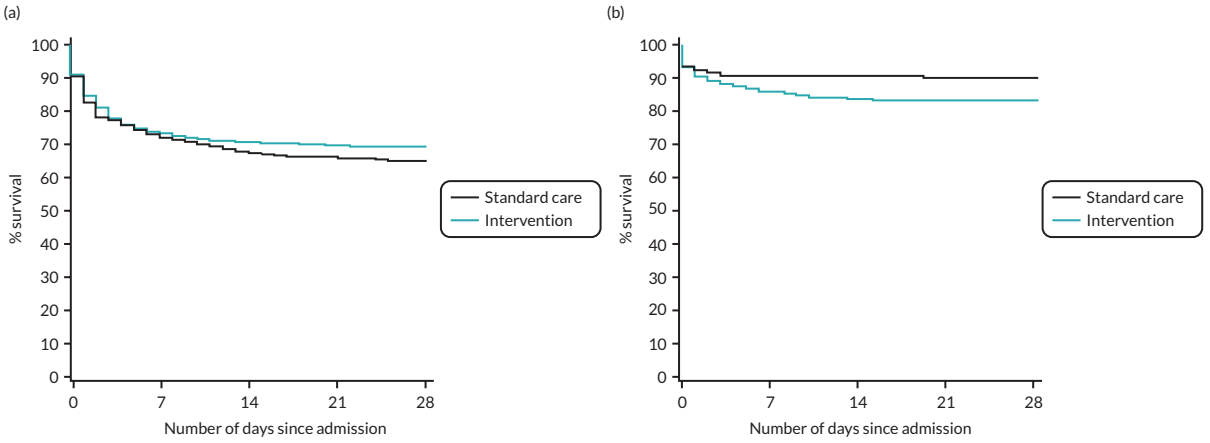

FIGURE 7 Kaplan–Meier survival plots up to 28 days from admission by treatment arm for (a) blunt and (b) penetrating injuries.

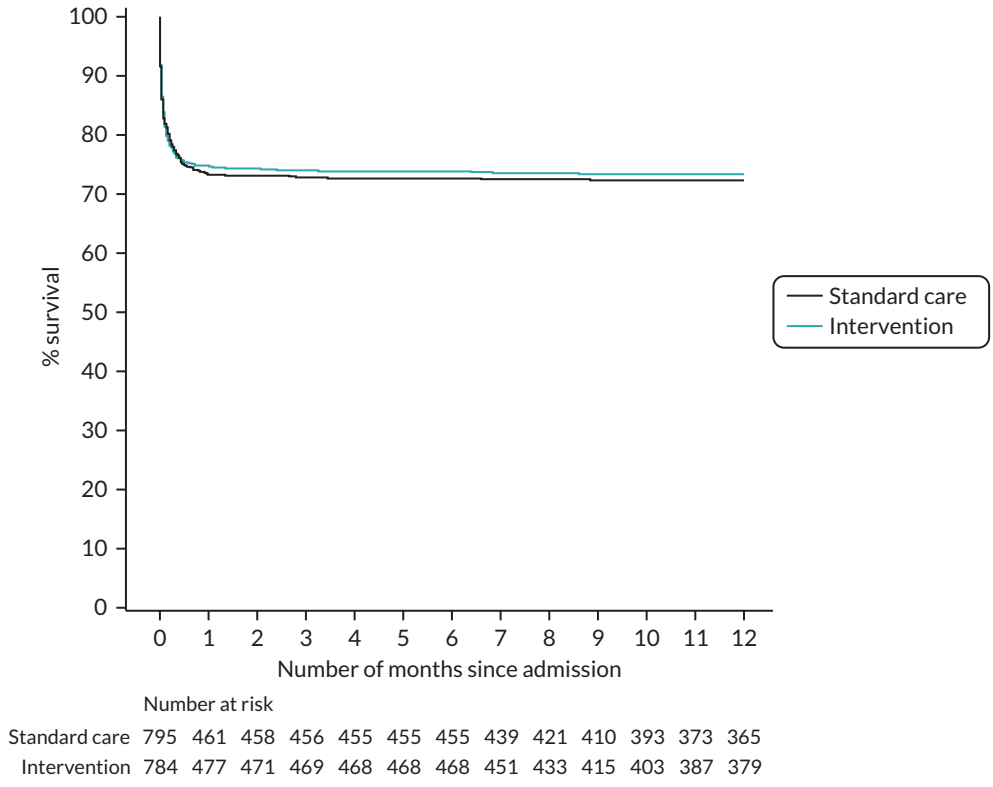

FIGURE 8 Kaplan–Meier survival plot up to 12 months from admission by treatment arm: ITT.

Figure 8 presents an unadjusted Kaplan–Meier plot of survival to 12 months by treatment arm. The estimated mortality rate at 6 months (using the Kaplan–Meier method) was 26.1% for the intervention arm and 27.3% for the standard care arm (see *Appendix 2*, *Table 31*). This gave a hazard ratio of 0.96 (95% CI 0.79 to 1.17) for early cryoprecipitate compared with standard MHP and a *p*-value of 0.6748 for the difference between the arms. After risk adjustment for statistically significant patient factors (Glasgow Coma Scale score, ISS, age, systolic blood pressure and sex), the hazard ratio was 1.08 (95% CI 0.89 to 1.32).

The estimated mortality rate at 12 months was 26.6% for the intervention arm and 27.7% for the standard care arm (see *Appendix 2*, *Table 31*). The primary analysis gave the same hazard ratio as at 6 months, with a *p*-value of 0.7120 for the difference between arms. After risk adjustment for the same statistically significant patient factors, the hazard ratio was 1.09 (95% CI 0.90 to 1.32).

Transfusion requirements

Participants in the intervention arm received more cryoprecipitate per hour from injury to 24 hours ($p < 0.0001$), but the use of other blood components was similar in the two arms (see *Appendix 2*, *Table 28* and *Figures 19 and 20*).

Quality of life

Data completeness for the EQ-5D-5L was poor at discharge (59%) and at 6 months (11%). The median index value at discharge was 0.50 in the standard care arm and 0.51 in the intervention arm, and the median self-evaluated health score at discharge was 60 in the standard care arm and 50 in the intervention arm; the difference in medians was not statistically significant for either measure. There was also no statistically significant difference in GOS at discharge between the two arms. At 6 months, the median index value was 0.66 in the standard care arm and 0.76 in the intervention arm and the median self-evaluated health score was 65 in the standard care arm and 75 in the intervention arm (see *Appendix 2*, *Table 29*).

Hospital resource use and destination of participant at time of discharge from hospital

There was no statistically significant difference between arms in median ventilator-days, critical care stay or hospital stay (see *Appendix 2*, *Table 30*). Forty-nine per cent of participants in each arm were discharged before the end of the study, and the discharge destinations of participants in the two arms were very similar.

Adverse events

The numbers of thromboembolic events and arterial thromboembolic events were similar in the two treatment arms (*Table 8*). There were three serious transfusion-related adverse events, which all occurred in the intervention arm. Two were anaphylaxis (one reported as unlikely to be related to the intervention and the other reported to be possibly related) and one serious adverse event was reported as potential transfusion-associated circulatory overload.

TABLE 8 Safety outcomes

Outcome	Standard care arm (*N* = 805)	Intervention arm (*N* = 799)	Overall (*n* = 1604)	*p*-value
Thrombotic events, *n*	85	85	170	
Venous thromboembolism	59	58	117	
Pulmonary embolus	36	38	74	
Deep-vein thrombosis	23	20	43	
Participants affected, *n*/*N* (%)	57/805 (7.1)	55/799 (6.9)	112/1604 (7.0)	
Arterial thrombotic events	26	27	53	
Myocardial infarction	4	4	8	
Stroke	11	11	22	
Other occlusion of any other artery	11	12	23	
Participants affected, *n*/*N* (%)	26/805 (3.2)	26/799 (3.3)	52/1604 (3.2)	
Cumulative incidence of thrombotic events at day 28, % (95% CI)[a]	12.9 (10.2 to 15.8)	12.7 (10.1 to 15.6)	12.8 (10.9 to 14.8)	0.8852
Serious transfusion-related adverse events, *n*/*N* (%)[b]	0/805 (0)	3/799 (0.4)	3/1604 (0.2)	0.1234

a *p*-value from Fine and Gray model.
b *p*-value for Fisher's exact test.

Chapter 4 Economic evaluation

Aim

The aim of this study was to evaluate the cost-effectiveness of early high-dose cryoprecipitate versus standard-of-care in adult patients with major trauma haemorrhage requiring MHP activation.

Methods

Overview of economic evaluation

We undertook a cost–utility analysis to estimate the within-trial cost-effectiveness of early high-dose cryoprecipitate versus standard-of-care in adult patients with major trauma haemorrhage requiring MHP activation at 28 days following randomisation. The analysis was performed using individual patient-level data from the CRYOSTAT-2 trial. The sample size for the economic analysis was 1581 patients. The outcome measure was the quality-adjusted life-year (QALY), which combines length of life and quality of life, based on the National Institute for Health and Care Excellence (NICE) recommendations.[34] Cost-effectiveness was expressed as the incremental cost per QALY gained based on the differences in costs and QALYs between the intervention and standard care arms. The trial was conducted in the UK (25 sites) and the USA (1 site); data from all participants in the study were included, from the UK and the USA. The perspective for the economic analysis was the UK NHS and Personal Social Services. Costs were calculated in 2022–3 Great British pounds and inflated where necessary using the Consumer Price Index.[35] The time horizon was 28 days. Extrapolation beyond the end of the trial was not undertaken because the within-trial analysis found no evidence of significant differences in costs or benefits between the intervention and standard care arms; 28 days was long enough to reflect all important differences in costs or outcomes between treatments with early high-dose cryoprecipitate and standard of care. Given the time horizon, discounting was not applied to costs or outcomes.

Resource use and costs

For every patient we calculated costs up to 28 days after randomisation. We included the following items of healthcare resource use that a priori were identified as potentially differing between the two treatment arms:

- length of hospital stay
  - number of days in the ICU
  - number of days in the high-dependency unit (HDU)
  - number of days on an inpatient ward

- use of blood products
  - use of RBCs
  - use of FFP
  - use of cryoprecipitate
  - use of platelets
  - use of colloids
  - use of crystalloids.

Resource use data were collected at 28 days post randomisation using trial CRFs, completed by the trial nurses and patients. The CRF used to collect these data, which are included in *Report Supplementary Material 3*.[36–39]

To calculate length of stay in each hospital unit (ICU, HDU, ward), we used the date of admission to that unit and the following date of admission to another unit, or death or discharge. If the patient was

not admitted to another unit, or had died or been discharged by the 28th day after randomisation, we assumed that they remained in the latest reported unit until the 28th day. In cases where the patient was known to have been discharged by the 28th day but the discharge date was missing or the duration of stay in a unit was unknown, we assumed that the length of stay in that unit was the mean length of stay observed across all patients. Length of stay after randomisation for both the initial hospitalisation and any re-admissions were included provided that these occurred in the 28 days after randomisation. All length-of-stay calculations were up to 28 days; therefore, any hospital stays beyond this time were not included, even if the patient had not been discharged by 28 days.

Unit costs were obtained from published sources and inflated where appropriate[35–38] (*Table 9*). For length of hospital stay, we multiplied the daily cost by the number of days spent in each type of unit/ward. For blood products, we multiplied the number of units of each product received by the cost per unit.

Utilities and quality-adjusted life-years

Generic health status was described at 28 days post randomisation using the EQ-5D-5L descriptive system.[40] The EQ-5D-5L contains five dimensions: mobility; self-care; usual activities; pain and discomfort; and anxiety and depression. For each dimension of the EQ-5D-5L, there are five levels (no problems, slight problems, moderate problems, severe problems and unable to/extreme problems).[33] As patients recruited to the trial were initially critically ill following major trauma, completion of the EQ-5D-5L at randomisation was not possible. Therefore, baseline utility was assumed to be zero for all patients. This assumption was made in previous studies in which baseline utility measurement was not possible.[41] EQ-5D-5L health states were converted into utility values using a formula that attaches weights to each level in each dimension based on valuations by UK general population samples;[42] this formula was also used for the small proportion of US trial participants. Utility values of one represent full health, values of zero are equivalent to death and negative values represent states worse than death. Patients who died during the 28-day follow-up period were assigned a utility value of zero at 28 days. A utility profile was constructed for every patient, assuming a straight-line relation between their utility values at randomisation (assumed to be zero) and 28 days (measured). QALYs for every patient from baseline to 28 days were calculated as the area under the utility profile. The implications of our assumptions were therefore as follows. For those patients who survived up to 28 days, QALYs up to 28 days were calculated using the EQ-5D-5L scores measured at 28 days, assuming an EQ-5D-5L score of zero at randomisation, and a linear interpolation between randomisation and 28 days. For decedents between randomisation and 28 days, we assumed zero QALYs. We assigned all the EQ-5D-5D data that were collected to the 28-day measurement point, irrespective of the precise time when this was actually measured.

TABLE 9 Unit costs

Cost component	Unit	Unit cost (£, 2022–3)	Source of unit cost data
Blood products			
RBC	Per unit of product	153.30	NHS Blood and Transplant[37]
FFP	Per unit of product	42.59	NHS Blood and Transplant[37]
Cryoprecipitate	Per pooled bag	221.85	NHS Blood and Transplant[37]
Platelets	Per unit of product	240.90	NHS Blood and Transplant[37]
Colloids	Per 500 ml of product	3.44	Campbell *et al.*[38]
Crystalloids	Per 500 ml of product	0.92	Campbell *et al.*[38]
Hospital stay			
ICU	Per day	1838	Walsh *et al.*,[33] NICE,[34] ONS,[35] Agus *et al.*,[36] Massou and Morris (personal communication)
HDU	Per day	1189	Walsh *et al.*,[33] NICE,[34] ONS,[35] Agus *et al.*,[36] Massou and Morris (personal communication)
Ward	Per day	557	Walsh *et al.*,[33] NICE,[34] ONS,[35] Agus *et al.*,[36] Massou and Morris (personal communication)

Statistical methods

We addressed missing values of the volume of blood products received and EQ-5D-5L scores at 28 days using multiple imputation for each treatment arm separately.[43,44] Patient age, sex, injury type (blunt/penetrating), early receipt of tranexamic acid, ISS and Glasgow Coma Scale were used in the multiple imputation models as additional explanatory variables. We used an iterative Markov chain Monte Carlo procedure based on multivariate normal regression, generating 20 imputed data sets.

We investigated the incremental costs and incremental effectiveness of the intervention using regression analysis based on the participant-level costs and outcomes data. We regressed costs, separately for the costs of hospital stay and cost of blood products, and all cost components combined, against an indicator variable for the intervention arm using generalised linear model regression (gamma family and log link) to account for the skewness of the cost data.[45] We regressed QALYs (with and without imputation) against an indicator variable for the intervention arm using ordinary least squares regression. In these regression models, we did not adjust for covariates, and we report the coefficient and marginal effect of the intervention arm (for the analysis of QALYs gained the marginal effect is the coefficient).

The incremental cost per QALY gained was calculated as the incremental cost divided by the QALYs gained; this was computed using the results from the regression analyses as the marginal effect of the coefficient on the indicator variable for the intervention arm in the cost regression model divided by the coefficient on the indicator variable for the intervention arm in the QALY regression model.

We used the 'multiple imputation nested within bootstrapping' approach suggested by Brand *et al.*[44] We calculated the mean value for each observation across the 20 imputed data sets and ran the regression analyses described below on this data set. We then reran this analysis 1000 times, using non-parametric bootstrapping, resampling the mean values with replacement.

We repeated the above process investigating cost-effectiveness for subgroups and participants differentiated by sex, age (< 70 years vs. ≥ 70 years) and injury type (blunt vs. penetrating).

We created a scatterplot to display the 1000 bootstrapped replications using the incremental QALYs with imputation. A cost-effectiveness acceptability curve showing the probability that early cryoprecipitate would be cost-effective compared with standard care at a range of values for the maximum willingness to pay for a QALY was generated based on the proportion of these 1000 bootstrap replications with positive incremental net monetary benefits (calculated as the mean incremental QALYs per patient with early cryoprecipitate multiplied by the maximum willingness to pay for a QALY minus the mean incremental cost per patient with early cryoprecipitate).

Results

Resource use and costs

In our sample, the overall mean length of stay in the ICU across all patients was 6.5 days [standard deviation (SD) 8.5 days] and the median was 3 days (IQR 0–10 days) (*Table 10*). The overall mean length of stay in the HDU was 1.8 days (SD 3.5 days) and the median was 0 days (IQR 0–3 days). The mean length of stay on the ward overall was 5.8 days (SD 7.0 days) and the median was 3 days (IQR 0–10 days). The mean and median total lengths of stay overall across all patients were 14.1 days (SD 11.0 days) and 12 days (IQR 3–28 days), respectively. All length of hospital stay values were similar in the intervention and standard care arms.

In terms of the volume of blood products received, the mean and median number of RBC units overall across all patients were 6.5 (SD 7.7) and 4 (IQR 2–8), respectively. The mean and median number of FFP units overall were 5.4 (SD 6.9) and 4 (IQR 2–7), respectively. For cryoprecipitate these values were 2.0 (SD 2.5) and 3 (IQR 0–3), respectively. For platelets they were 0.8 (SD 1.5) and 0 (IQR 0–1), respectively.

TABLE 10 Descriptive statistics for resource use measures

	Obs	Mean	SD	Median	IQR	Minimum	Maximum
Hospital stay							
ICU (days)							
Overall	1581	6.5	8.5	3	0–10	0	28
Intervention arm	785	6.4	8.5	3	0–9	0	28
Standard care arm	796	6.6	8.6	3	0–10	0	28
HDU (days)							
Overall	1581	1.8	3.5	0	0–3	0	28
Intervention arm	785	1.9	3.7	0	0–3	0	28
Standard care arm	796	1.7	3.4	0	0–3	0	24
Ward (days)							
Overall	1581	5.8	7.0	3	0–10	0	28
Intervention arm	785	5.7	7.0	3	0–10	0	28
Standard care arm	796	5.8	7.1	3	0–10	0	28
Total (days)							
Overall	1581	14.1	11.0	12	3–28	0	28
Intervention arm	785	14.1	10.9	12	4–28	0	28
Standard care arm	796	14.2	11.1	13	3–28	0	28
Blood products							
RBC (units)							
Overall	1577	6.5	7.7	4	2–8	0	92
Intervention arm	784	6.6	7.7	4	2–8	0	52
Standard care arm	793	6.4	7.7	4	2–7	0	92
FFP (units)							
All patients	1577	5.4	6.9	4	2–7	0	78
Intervention arm	784	5.5	7.0	3	2–7	0	52
Standard care arm	793	5.3	6.8	4	2–7	0	78
Cryoprecipitate (pooled bags)							
Overall	1577	2.0	2.5	3	0–3	0	22
Intervention arm	784	3.1	2.4	3	3–3	0	22
Standard care arm	793	1.0	2.0	0	0–2	0	22
Platelets (units)							
Overall	1577	0.8	1.5	0	0–1	0	19
Intervention arm	784	0.8	2.0	0	0–1	0	16
Standard care arm	793	0.8	1.6	0	0–1	0	19
Crystalloids (ml)							
Overall	1561	2108	2171	1506	100–3100	0	14,905

TABLE 10 Descriptive statistics for resource use measures (*continued*)

	Obs	Mean	SD	Median	IQR	Minimum	Maximum
Intervention arm	775	2167	2087	1778	500–3142	0	14,905
Standard care arm	786	2021	2235	1473	0–3000	0	14,250
Colloids (ml)							
Overall	1561	99	521	0	0–0	0	11,500
Intervention arm	775	95	541	0	0–0	0	11,500
Standard care arm	786	103	500	0	0–0	0	8000

Obs, observations.

For crystalloids the mean and median volumes in millilitres overall were 2108 (SD 2171) and 1506 (IQR 100–3100), respectively. For colloids they were 99 (SD 521) and 0 (IQR 0–0), respectively. All blood product values were similar for the intervention and standard care arms, with the exception of cryoprecipitate, where the mean and median values were 3.1 (SD 2.4) and 3 (IQR 3–3) in the intervention arm and 1.0 (SD 2.0) and 0 (IQR 0–2) in the standard care arm.

The mean total cost per patient (including the costs of length of hospital stay and blood products) was £19,477 (SD £16,207) in the intervention arm and £19,236 (SD £16,681) in the standard care arm (*Table 11*). In both arms, approximately 90% of the total cost was accounted for by the cost of hospital stay, and 10% by the cost of blood products. ICU costs accounted for most of the cost of hospital stay, accounting for approximately 70% of the cost of hospital stay and 62% of the total cost.

Utilities and quality-adjusted life-years

Mean EQ-5D-5L utility scores at 28 days overall across all patients were 0.294 (SD 0.339) (*Table 12*). Mean QALYs overall were 0.011 (SD 0.013) with no imputation and 0.012 (SD 0.013) with imputation. Both mean EQ-5D-5L utility scores at 28 days and mean QALYs were similar in the intervention and standard care arms.

Incremental cost–utility analysis

The results of the regression analyses for costs across the whole sample indicate that there were significant differences in the cost of blood products between the intervention and standard care arms (costs were £519 higher in the intervention arm; $p < 0.0001$; *Table 13*). The differences between the costs associated with the length of hospital stay and the total costs were not statistically significant in either of the two arms (both $p > 0.7$). The results of the regression analyses for QALYs (without and with imputation) indicate that the between-arm differences in QALYs were small (both QALYs gained < 0.0002) and not statistically significant (both $p > 0.7$).

The incremental cost per QALY gained for intervention versus standard care is £1,121,509 based on the QALYs gained calculated without imputation and £1,348,181 based on the QALYs gained calculated with imputation (numbers may not be directly calculated from the values in *Table 13* due to rounding). The high, unattractive incremental cost-effectiveness ratios associated with early cryoprecipitate compared with standard MHP are due to the higher cost of blood products that is not offset by lower costs elsewhere, and the negligible QALY gains/losses.

In terms of the subgroup analyses (*Tables 14–16*), the regression analyses were largely qualitatively the same as for the whole sample: the cost of blood products was significantly higher for the intervention arm; for all other cost variables and the QALY variables there were no significant differences between early cryoprecipitate and standard MHP, and the QALYs gained were negligible in magnitude, making the interpretation of the incremental cost per QALY gained difficult.

TABLE 11 Descriptive statistics for costs

	Obs	Mean	SD	Minimum	Maximum
Hospital stay					
ICU (£)					
Overall	1581	12,029	15,789	0	51,479
Intervention arm	785	11,799	15,700	0	51,479
Standard care arm	796	12,255	15,883	0	51,479
HDU (£)					
Overall	1581	2192	4256	0	33,318
Intervention arm	785	2276	4417	0	33,318
Standard care arm	796	2109	4091	0	33,318
Ward (£)					
Overall	1581	3241	3959	0	15,622
Intervention arm	785	3230	3937	0	15,622
Standard care arm	796	3251	3983	0	15,622
Total (£)					
Overall	1581	17,462	16,241	0	51,479
Intervention arm	785	17,306	16,062	0	51,479
Standard care arm	796	17,616	16,425	0	51,479
Blood products					
RBC (£)					
Overall	1577	999	1178	0	14,103
Intervention arm	784	1017	1176	0	7971
Standard care arm	793	982	1181	0	14,103
FFP (£)					
Overall	1577	232	293	0	3322
Intervention arm	784	235	298	0	2214
Standard care arm	793	229	287	0	3322
Cryoprecipitate (£)					
Overall	1577	454	543	0	48,807
Intervention arm	784	690	526	0	4880
Standard care arm	793	221	452	0	4880
Platelets (£)					
Overall	1577	198	365	0	4577
Intervention arm	784	200	368	0	3854
Standard care arm	793	196	362	0	4577

TABLE 11 Descriptive statistics for costs (*continued*)

	Obs	Mean	SD	Minimum	Maximum
Crystalloids (£)					
Overall	1561	4	4	0	27
Intervention arm	775	4	4	0	27
Standard care arm	786	4	4	0	26
Colloids (£)					
Overall	1561	1	3	0	79
Intervention arm	775	1	3	0	79
Standard care arm	786	1	3	0	55
Total (£)					
Overall	1578	1888	2127	0	21,937
Intervention arm	784	2148	2140	0	16,259
Standard care arm	794	1632	2083	0	21,937
Total costs (£)					
Hospital stay plus blood products					
Overall	1578	19,356	16,443	0	64,658
Intervention arm	784	19,477	16,207	0	64,658
Standard care arm	794	19,236	16,681	0	61,333

TABLE 12 EuroQol-5 Dimensions, five-level version utility scores and QALYs

	Obs	Mean	SD	Minimum	Maximum
EQ-5D-5L utility scores at 28 days					
Overall	1061	0.294	0.339	−0.285	1.000
Intervention arm	516	0.293	0.337	−0.285	1.000
Standard care arm	545	0.294	0.341	−0.285	1.000
QALYs					
QALYs (no imputation)					
Overall	1061	0.011	0.013	−0.010	0.038
Intervention arm	516	0.011	0.012	−0.010	0.038
Standard care arm	545	0.011	0.013	−0.010	0.038
QALYs (with imputation)					
Overall	1581	0.012	0.013	−0.011	0.038
Intervention arm	785	0.012	0.013	−0.011	0.038
Standard care arm	796	0.013	0.013	−0.010	0.038

TABLE 13 Results of regression analyses for costs and QALYs

	Coefficient	95% CI	*p*-value	Marginal effect
Total cost of hospital stay				
Intervention arm	−0.017	−0.109 to 0.073	0.705	−310
Total cost for blood products				
Intervention arm	0.276	0.163 to 0.389	< 0.0001	519
Total cost				
Intervention arm	0.011	−0.074 to 0.096	0.803	210
QALYs (without imputation)				
Intervention arm	0.00004	−0.0016 to 0.0015	0.848	
QALYs (with imputation)				
Intervention arm	0.0005	−0.002 to 0.008	0.455	

TABLE 14 Results of regression analyses for costs and QALYs: subgroup analysis by sex

Sex		Coefficient	95% CI	*p*-value	Marginal effect
Female (*n* = 330)	**Total cost of hospital stay**				
	Intervention arm	−0.050	−0.237 to 0.137	0.600	−864
	Total cost for blood products				
	Intervention arm	0.201	−0.031 to 0.432	0.089	365
	Total cost				
	Intervention arm	−0.026	−0.204 to 0.152	0.773	−500
	QALYs (without imputation)[a]				
	Intervention arm	0.0003	−0.0026 to 0.0031	0.862	
	QALYs (with imputation)				
	Intervention arm	0.001	−0.001 to 0.004	0.361	
Male (*n* = 1251)	**Total cost of hospital stay**				
	Intervention arm	−0.009	−0.116 to 0.098	0.866	−161
	Total cost for blood products				
	Intervention arm	0.296	0.166 to 0.455	< 0.01	560
	Total cost				
	Intervention arm	0.206	−0.070 to 0.111	0.656	399
	QALYs (without imputation)[b]				
	Intervention arm	−0.0001	−0.0019 to 0.0017	0.912	
	QALYs (with imputation)				
	Intervention arm	−0.001	−0.002 to 0.001	0.238	

a *n* = 248.
b *n* = 813.

TABLE 15 Results of regression analyses for costs and QALYs: subgroup analysis by injury type

Injury type		Coefficient	95% CI	*p*-value	Marginal effect
Blunt (*n* = 1014)	**Total cost of hospital stay**				
	Intervention arm	0.015	0.089 to 0.119	0.779	308
	Total cost for blood products				
	Intervention arm	0.178	0.034 to 0.322	0.015	325
	Total cost				
	Intervention arm	0.028	−0.067 to 0.123	0.560	633
	QALYs (without imputation)[a]				
	Intervention arm	0.006	−0.001 to 0.002	0.498	
	QALYs (with imputation)				
	Intervention arm	0.003	−0.001 to 0.002	0.676	
Penetrating (*n* = 567)	**Total cost of hospital stay**				
	Intervention arm	−0.075	−0.116 to 0.098	0.866	−874
	Total cost for blood products				
	Intervention arm	0.437	0.254 to 0.620	< 0.01	857
	Total cost				
	Intervention arm	−0.001	−0.168 to 0.166	0.988	−17
	QALYs (without imputation)[b]				
	Intervention arm	−0.003	−0.006 to 0.000	0.082	
	QALYs (with imputation)				
	Intervention arm	−0.003	−0.005 to −0.001	0.023	

a *n* = 726.
b *n* = 335.

TABLE 16 Results of regression analyses for costs and QALYs: subgroup analysis by age group

Age group		Coefficient	95% CI	*p*-value	Marginal effect
< 70 years (*n* = 1414)	**Total cost of hospital stay**				
	Intervention arm	−0.037	−0.133 to 0.058	0.441	−668
	Total cost for blood products				
	Intervention arm	0.283	0.160 to 0.406	< 0.01	543
	Total cost				
	Intervention arm	−0.006	−0.092 to 0.079	0.866	−124
	QALYs (without imputation)[a]				
	Intervention arm	0.0003	−0.002 to 0.001	0.752	
	QALYs (with imputation)				
	Intervention arm	−0.001	−0.002 to 0.001	0.247	

continued

TABLE 16 Results of regression analyses for costs and QALYs: subgroup analysis by age group (*continued*)

Age group		Coefficient	95% CI	*p*-value	Marginal effect
≥ 70 years (*n* = 167)	**Total cost of hospital stay**				
	Intervention arm	0.143	−0.188 to 0.473	0.397	2007
	Total cost for blood products				
	Intervention arm	0.156	−0.128 to 0.441	0.281	236
	Total cost				
	Intervention arm	0.144	−0.164 to 0.451	0.359	2242
	QALYs (without imputation)[b]				
	Intervention arm	−0.0003	−0.003 to 0.002	0.848	
	QALYs (with imputation)				
	Intervention arm	0.0004	−0.003 to 0.003	0.819	

a *n* = 932.
b *n* = 129.

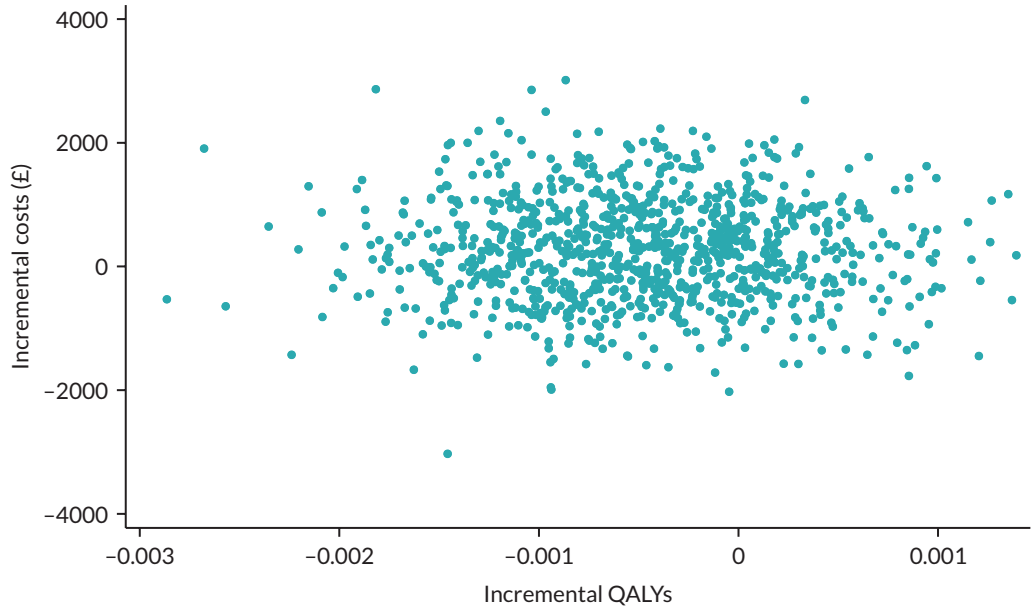

FIGURE 9 Scatterplot showing 1000 bootstrap replications of the incremental costs and QALYs associated with early cryoprecipitate vs. standard MHP.

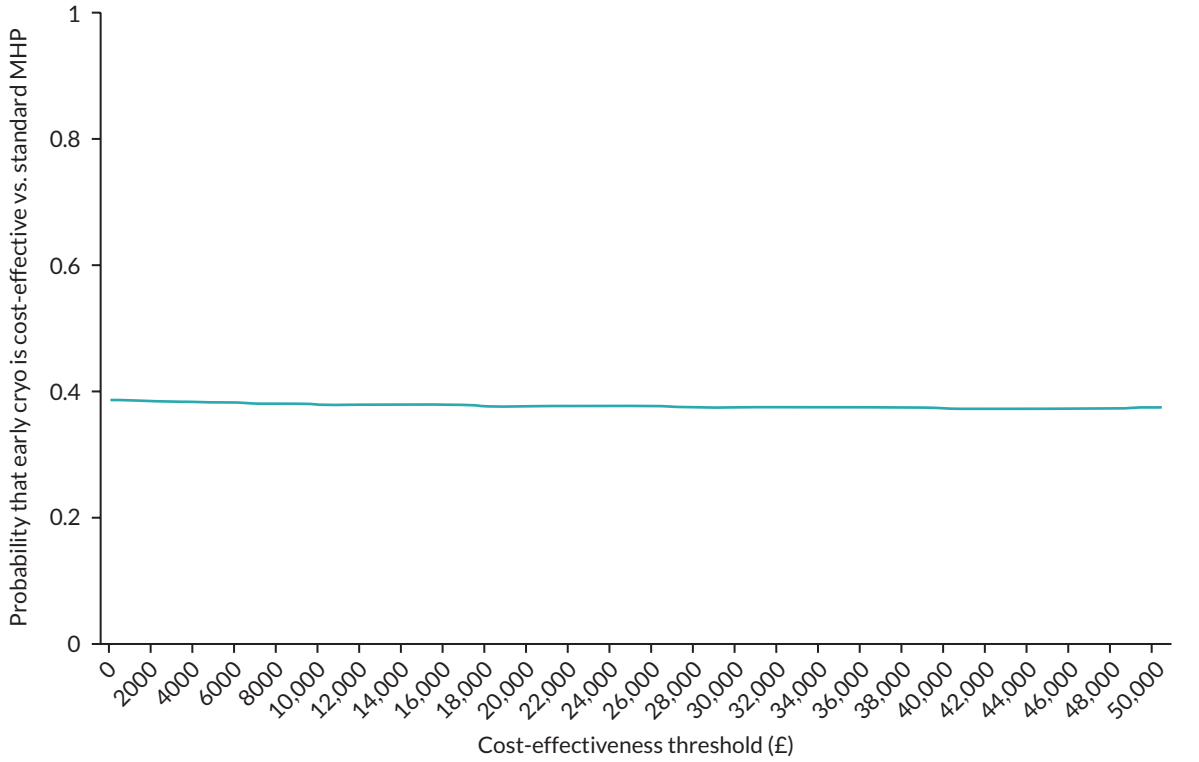

FIGURE 10 Cost-effectiveness acceptability curve showing the probability that early cryoprecipitate is cost-effective vs. standard MHP for a range of cost-effectiveness thresholds.

The scatterplot showing the bootstrap replications is shown in *Figure 9*. The cost-effectiveness acceptability curve is shown in *Figure 10*. This shows that the probability that early cryoprecipitate is cost-effective versus standard MHP is just under 0.4 across a range of plausible values of the cost-effectiveness threshold.

Summary

Our economic analysis to evaluate the cost-effectiveness of using early high-dose cryoprecipitate versus standard of care in adult patients with major trauma haemorrhage requiring MHP activation showed that there are no differences in terms of costs and outcomes. The findings mean that there is no reason to prefer early high-dose cryoprecipitate to standard of care based on cost or value-for-money grounds.

Chapter 5 Discussion

Overall interpretation and generalisability

The main result from this study is that the use of early high-dose cryoprecipitate given to all patients pre-emptively as an additional treatment for severe injury-related bleeding did not confer an improvement in overall survival when compared with standard treatment alone. The population enrolled in the study was representative of a severely injured cohort of patients and was in line with our prior data and trial design estimates. Our findings do not support empiric fibrinogen supplementation for all patients suspected of bleeding. Fibrinogen is known to be critical to the clotting process, and further research is required to understand whether selected critically injured patients with low fibrinogen levels can be identified who might benefit from fibrinogen supplementation. The findings question the approach of transfusion support that is unselected and aimed at all trauma patients irrespective of their baseline characteristics.

To the best of our knowledge, CRYOSTAT-2 is, to date, the largest interventional study, and also the first transatlantic study, of critically bleeding trauma patients. Research in the field of trauma is challenging, and it necessitates the co-ordination of clinicians, and, in this study, blood transfusion staff, in a 24/7, time-critical setting. The trial successfully enrolled at all MTCs in the UK and delivered this high-quality study during a period of disruption due to the COVID-19 pandemic. The UK major trauma networks represent an important and substantial resource of future trauma trials.

Implications for research

Fibrinogen replacement in the presence of low fibrinogen levels is known to be important.[14,17] CRYOSTAT-2 administered cryoprecipitate to an unselected group of patients. It remains possible that fibrinogen therapy will be effective in subgroups of patients. Eligibility for CRYOSTAT-2 was made on the presence of clinical features, for example evidence of significant injury and active bleeding, including haemodynamic parameters and clinical acumen. Blood fibrinogen levels were not required for entry into CRYOSTAT-2. Previous smaller studies (CRYOSTAT-1,[21] E-FIT,[24] FiiRST[22]) reported that fibrinogen levels at admission are typically low (e.g. median fibrinogen of 1.6–1.9 g/l) in this patient group. There might be some support for targeting fibrinogen supplementation from the results of the recent iTACTIC trial, which compared MHP therapy guided by either standard clotting tests or point-of-care viscoelastic haemostasis assays in a similar population of patients as in CRYOSTAT-2.[46] Only around one-quarter of those entered into the iTACTIC study were coagulopathic. In this study, viscoelastic haemostasis assay-treated participants received more fibrinogen therapy than those in the standard clotting test group, and there was a suggestion that the coagulopathic participants had better outcomes with viscoelastic haemostasis assay-guided treatment. Importantly, at admission the groups had median (IQR) fibrinogen levels of 2.0 g/l (1.4–2.4 g/l) (standard clotting test arm) and 1.9 g/l (1.5–2.4 g/l) (viscoelastic haemostasis assay arm), with coagulopathic participants accounting for 32% and 25%, of each cohort, respectively.[46] Further research is required to explore the effectiveness and safety of fibrinogen therapy at different levels of hypofibrinogenaemia.

FEISTY-2 (Fibrinogen Early In Severe Trauma StudY-2), which is recruiting in Australia (NCT05449834),[47] will evaluate the differential effect using a primary end point of 'days alive out of hospital at day 90 after injury' of cryoprecipitate or fibrinogen concentrate. Eligible trauma patients will be selected for study entry according to similar clinical criteria to CRYOSTAT-2 but also on the basis of having a low fibrinogen level. A point-of-care fibrinogen testing device that could be used at scene would also be an avenue to explore for rapid, guided treatment of severely injured, bleeding patients.[48]

There may also be a differential effect of fibrinogen replacement according to mechanism of injury. In one of the prespecified subgroup analyses of our trial, there was a signal of potential harm seen in patients with penetrating injury who were allocated to receive early high-dose cryoprecipitate. Participants with penetrating injury alone had higher mortality with early cryoprecipitate (cryoprecipitate vs. standard care 16.2% vs. 10.0%; OR 1.74, 95% CI 1.20 to 2.51), whereas for those affected by blunt injury alone, there was a suggestion that 28-day mortality was lower (cryoprecipitate vs. standard care 30.4 % vs. 34.8%; OR 0.82, 95% CI 0.62 to 1.09). This finding persisted after risk adjustment and is an area for future research. It is possible also that these groups may represent different severities of TIC and therefore different degrees of hypofibrinogenaemia.

The selection of primary outcome, whether all-cause mortality or death due to bleeding, has been extensively discussed in the literature of trials of tranexamic acid.[49] We noted that deaths due to bleeding varied between arms, perhaps suggesting that the clots that formed after administration of cryoprecipitate may be more resistant to clot breakdown. Further adequately powered trials would be needed to address the outcome of deaths due to bleeding, alongside mechanistic work, at the level of the developing clot, to learn more about the differential importance of clot formation balanced against clot breakdown.[20,50]

Other considerations for further research

The optimal dose and efficacy of cryoprecipitate and fibrinogen administration in trauma patients remain unclear given our results. It is also recognised that many patients receive plasma transfusions that contain less concentrated amounts of fibrinogen. In addition to exploring the correction of coagulopathy, future research should explore the prevention of development of coagulopathy, including new therapeutic approaches to the inflammatory and metabolic derangements that result in TIC and increased bleeding.[51] A more exploratory route for future research includes the potential for transfusing manipulated blood components, for example sources of fibrinogen that are less resistant to breakdown in vivo.

This study found a 59% and then 11% capture rate of patient-reported outcomes at discharge and 6 months, respectively. Future research could be directed towards further PPIE work exploring how to optimise patient-reported outcome data.

Research in the context of other clinical settings of hypofibrinogenaemia

The role of fibrinogen replacement or supplementation has been tested in other settings of major bleeding. In major obstetric haemorrhage, low fibrinogen blood levels at the start of major bleeding are a predictor of large volume blood loss and poor outcomes.[52–54] However, and similar to our finding in this study, administration of fibrinogen replacement in a non-guided manner (e.g. without a blood test result) does not improve outcomes.[55] Importantly, there are only a few distinct causes of postpartum haemorrhage (in particular placental abruption or intrauterine death) that are strongly associated with low fibrinogen levels early in the course of postpartum haemorrhage.[56] Randomised controlled trial data on postpartum haemorrhage have also shown that if a woman experiencing postpartum haemorrhage has a blood fibrinogen level of > 2 g/l, there is no benefit (defined as a reduction in transfusion need) in giving fibrinogen replacement.[57]

Implications for decision-makers

This study supports the ongoing use of current MHP practices, whereby concentrated fibrinogen therapies such as cryoprecipitate are given often in the second ‘MHP pack’, or reactively in response to repeated monitoring of fibrinogen levels.

There are two main ways to administer concentrated doses of fibrinogen: cryoprecipitate and fibrinogen concentrate. Clinical evaluation of these two products, aiming to determine whether one product is superior to the other, has led – so far at least – to the conclusion that there is no difference in terms of efficacy, transfusion outcome or safety concerns.[19,58] It therefore seems reasonable to surmise that the results of CRYOSTAT-2 would have been similar had fibrinogen concentrate been used as the replacement source.

Limitations

CRYOSTAT-2 was designed to be pragmatic, to facilitate participant recruitment in a challenging and time-critical clinical environment and to ensure that, in rapidly changing clinical situations, the clinicians responsible for each participant were able to treat their patient as safely as possible. The pragmatic design allowed site teams to enrol patients successfully and consistently into the trial despite the demands of the environment. However, the lack of additional interventions such as blood sampling, and particularly not knowing the baseline fibrinogen level prior to study intervention, means that we are limited in our ability to explore the reasons for a lack of difference between treatment arms, and effects of cryoprecipitate in patients with and without TIC, and the impact on restoration of fibrinogen levels. Additionally, there was no possible placebo for this trial, and this has limited our ability to compare efficacy when patient populations varied – most notably across the different time periods of intervention.

Only 434 (54%) of the 799 participants in the intervention arm started the cryoprecipitate within 90 minutes and received all three pools. This reflects the difficulty of administering an intervention that takes time to be defrosted and transported to the patient, as well as the changing clinical situation such that many patients did not have all three pools due to their bleeding stopping.

Blood fibrinogen levels were not collected as part of this study, following analysis of the CRYOSTAT-1 trial as well as data from a large European observational study (ACIT2: Activation of Coagulation and Inflammation in Trauma-2; ISRCTN12962642). Owing to the size of CRYOSTAT-2, and the aim for every major trauma centre to be able to actively recruit eligible patients without the need for research nurse support 24/7, a balance between pragmatism and study procedures was sought. A choice therefore was made not to take and store coagulation blood samples before patient recruitment. However, central trial data collection of baseline fibrinogen blood sample results, where they were taken for clinical reasons, would have added to the ability to interrogate the admission fibrinogen level and associations with outcomes.

Each recruiting site followed its local MHP, and this may have included the use of viscoelastic testing to guide transfusion therapy. No data were collected about which sites used, or did not use, viscoelastic testing for MHP guidance in patients. We cannot exclude the possibility that the MHP in some recruited patients was additionally guided by viscoelastic testing results and therefore those patients might have received cryoprecipitate earlier than patients in centres where viscoelastic testing was not available.

These caveats do not detract from CRYOSTAT-2's primary intention, to evaluate the real-world potential for early empiric cryoprecipitate supplementation in the context of MHP activation, which was not impacted by these limitations. Despite our wide geographic coverage of the UK, we were able to open only one site in the USA due to the lengthy regulatory approvals process required. While the results from the US site are in line with those from the UK, a broader representation would have been more desirable to demonstrate wider applicability.

A not uncommon challenge in trauma-related research is the high percentage of 'loss-to follow-up' data for the longer-term outcomes. Our low rate of questionnaire returns reflected this and we were not able to fully analyse the QALY using a 6- or 12-month time frame. Moving forward, future studies will need to think about more innovative ways to collect long-term data on participants.

Conclusions

The results from the CRYOSTAT-2 study demonstrate that in a very complex and heterogenous population of patients, unselected early administration of high-dose cryoprecipitate will not have a survival benefit in addition to MHP. Cryoprecipitate and other forms of fibrinogen supplementation should probably be reserved for those patients with a known or suspected deficiency, although further research is needed to explore this.

Equality, diversity and inclusion

Participant representation

CRYOSTAT-2 was a trial that was conducted at every MTC in England, as well as additional sites in Northern Ireland and the USA. By including every possible site across England, the study team hoped to be as inclusive and as representative of the study population as possible.

Severe injury is more frequently encountered by men, and our trial numbers reflect this, with approximately 80% of the participants being male. There were no exclusion criteria that meant that men were more readily recruited than women (e.g. no exclusions were stipulated for pregnant women or for women of childbearing age).

Data on ethnicity were not collected as part of the study participant characteristics, except in the single US site, and therefore it is not possible to be certain that the study was fully representative of the local populations at each site.

Reflections on the research team and wider involvement

The core research team was made up of near-equal numbers of women and men and spanned several clinical and ethnic backgrounds. More widely, at the major trauma centre sites the study team facilitated the inclusion of both clinical and laboratory teams, which brought professionals together at each hospital who had previously not been commonly in contact. At the TMG meetings, there was support for more junior members of the team, with career development opportunities provided. Investigator meetings were held that focused on the research experiences of the sites involved and gave the clinical and laboratory teams a platform to enable the sharing of good trial practices. Members of our PPI group sat on the TSC.

Patient and public involvement

The CRYOSTAT-2 trial design was significantly shaped by PPIE. There were two questions that were of particular importance to the trial design and were directly influenced by the views of our PPI group and a survey of the wider public. These were the primary end point (e.g. survival, functional status, or other) and the most acceptable process for obtaining consent into an emergency study in which the majority of eligible patients lacked capacity. In 2014, the PPI group (which included mostly previous patients who had been affected by significant injury requiring blood transfusion) met initially in Oxford to discuss these two important trial design questions. Following this meeting, a survey was conducted to evaluate the views of a larger number of trauma patients and members of the public. The consensus from these two PPIE events was that survival was the most important outcome, and this view was shared across previously injured patients and lay members of the public (n = 50). However, there was a lack of agreement about the most acceptable consenting process, for example whether a legal representative or a waiver of consent should be used. In the light of these results, in April 2016 a follow-on face-to-face PPI meeting was conducted in London, which focused on consent. The CRYOSTAT-2 team gave a presentation (‘Consenting: how best to do it in emergency studies’) and a morning of interactive

discussion was held. The outcome of this meeting was twofold: (1) the consent process for the study was defined and subsequently used in CRYOSTAT-2 and (2) the specific PPI group for CRYOSTAT-2 was formed: PAIR.

The face-to-face meetings, during which free and open discussion was possible, were the most informative for the clinical research team. The clinical team worked hard to include previously injured patients in the PPI meetings – a group of patients who can be hard to engage – and it is possible that an earlier observational trauma study that the clinical research team had been involved with helped to encourage this engagement. The views of both previously injured patients and members of the public – who provided interesting insights into how gaining consent for patients lacking capacity might be best approached – complemented each other and enabled a balanced view to be sought for our specific trial questions. These engagements worked well. Furthermore, a snapshot of a larger number of members of the public using a simple survey also worked well for less in-depth questions.

Two PPI members sat on our TSC. One was an experienced PPI advocate, and the other was a less experienced member. Our TSC chairperson was always mindful of the need to discuss trial matters in an accessible manner for all members of the committee. Training in trial methodology/oversight for our PPI TSC members was not easily accessible, and this is an area where more support could be offered to individuals.

Further reflecting on the PPIE involvement in CRYOSTAT-2, another area where we may be able to improve is the engagement of a PPIE specialist who perhaps could be employed within the trial and act as an advisor to the clinical research team to direct ongoing PPIE involvement, including training the PPI group members, hosting PPIE events and disseminating trial results.

Dissemination

CRYOSTAT-2 results will be disseminated in several ways. The primary publication has been published in *JAMA*, and dissemination has included webinars to publicise results to coincide with the publication of the primary results paper. The results will be discussed with all the trial teams from the major trauma centres in UK (12 March 2024). The results will also be presented and discussed at scientific trauma/haematology/transfusion conferences, which will inform clinicians and scientists further about this study.

The trial website was a well-used resource during the trial itself and is a platform from which the published papers available by request to corresponding author. Additional websites led by the chief investigators for CRYOSTAT-2 as well as the NIHR social media platforms and alternative forms of social media, including Twitter/X, and/or the Science Media Centre, were used as routes for the dissemination of medical data to the wider public. The results will also be discussed at the PAIR and Oxford Blood Group PPI meetings to explore ways to disseminate and contextualise our findings for the wider public and policy-makers.

Additional information

Contributions of authors

Nicola Curry (https://orcid.org/0000-0002-3849-0688) (Consultant Haematologist, Co-Investigator) was involved in the design, conduct, analysis and reporting phases of the study.

Ross Davenport (https://orcid.org/0000-0002-8593-6582) (Consultant Trauma and Vascular Surgeon, Co-Investigator) was involved in the design, conduct, analysis and reporting phases of the study.

Helen Thomas (https://orcid.org/0000-0002-7017-7739) (Head of Clinical Trial Statistics) was involved in the design, conduct, analysis and reporting phases of the study.

Erin Fox (https://orcid.org/0000-0002-8843-5054) (Study Management in US) was involved in the conduct phase of the study .

Joanne Lucas (https://orcid.org/0000-0002-3390-9654) (Clinical Trial Manager) was involved in the conduct and reporting phases of the study.

Amy Evans (https://orcid.org/0000-0002-6664-9342) (Clinical Trial Manager) was involved in the conduct and reporting phases of the study.

Efthalia Massou (https://orcid.org/0000-0003-0488-482X) (Research Associate in Statistics) was involved in the analysis and reporting phases of the study.

Rupa Sharma (https://orcid.org/0009-0000-5414-0859) (Clinical Data Manager) was involved in the conduct phase of the study.

Shaminie Shanmugaranjan (https://orcid.org/0009-0009-2091-4014) (Statistician) was involved in the analysis and reporting phases of the study.

Claire Rourke (https://orcid.org/0000-0002-7631-9275) (Clinical Operations Manager) was involved in the design, conduct and reporting phase of the study.

Alice Newton (https://orcid.org/0009-0009-1437-7953) (Statistician) was involved in the conduct and analysis phases of the study.

Alison Deary (https://orcid.org/0000-0001-8351-4186) (Head of Clinical Operations) was involved in the design and conduct phases of the study.

Nikki Dallas (https://orcid.org/0009-0009-9604-027X) (Data Management Support Officer) was involved in the conduct phase of the study.

Chloe Fitzpatrick-Creamer (https://orcid.org/0009-0000-8064-6108) (Clinical Trial Administrator) was involved in the conduct phase of the study.

Jeanette M Podbielski (https://orcid.org/0000-0003-4053-8553) (Study Management in US) was involved in the conduct phase of the study.

Charles E Wade (https://orcid.org/0000-0003-0055-5885) (Trauma Surgeon) was involved in the conduct phase of the study.

Antoinette Edwards (https://orcid.org/0000-0003-1427-0725) (Executive Director, TARN) was involved in the design and conduct of the study.

Jonathan Benger (https://orcid.org/0000-0001-6131-0916) (Professor of Emergency Care, Co-investigator) was involved in the design, conduct and reporting phases of the study.

Stephen Morris (https://orcid.org/0000-0002-5828-3563) (Professor of Health Services Research) was involved in the design, conduct, analysis and reporting phases of the study.

Bryan A Cotton (https://orcid.org/0000-0003-4184-6742) (Trauma Surgeon) was involved in the conduct phase of the study.

James Piercy (https://orcid.org/0000-0003-4891-7259) (expert lay representative) was involved in the design, conduct and reporting phases of the study.

Laura Green (https://orcid.org/0000-0003-4063-9768) (Consultant Haematologist) Co-Investigator, was involved in the design, conduct and reporting phases of the study.

Karim Brohi (https://orcid.org/0000-0003-0643-8866) (Professor of Trauma Sciences, Chief Investigator) was involved in the design, conduct, analysis and reporting phases of the study.

Simon Stanworth (https://orcid.org/0000-0002-7414-4950) (Consultant Haematologist, Co-Chief Investigator) was involved in the design, conduct, analysis and reporting phases of the study.

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Trial Steering Committee

Professor Beverley Hunt OBE (Chairperson), Professor Jason L Sperry (Clinical Specialist), Dr Alastair Nimmo (Clinical Specialist), James Piercy (Patient Representative) and Kathryn Orchard (Patient Representative).

Data Monitoring Committee

Professor Timothy Coats (Chairperson), Professor Gavin Murphy (Clinical Specialist) and Professor Paul White (Independent Statistician).

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Participating sites

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St George's Hospital: Dr Phil Moss, Professor Heather Jarman and Steve Wilshire.

Royal London Hospital: Dr Ross Davenport and Dr Laura Green.

King's College London: Dr Fleur Cantle, Dr Jeff Keep and Kenneth Amenyah.

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Aintree University Hospital: Dr Abdo Sattout, Rebecca Wright and Jan Gorry.

Royal Preston Hospital: Dr Kirsty Challen and Alan Noyon.

Salford Royal Hospital: Dr Dan Horner and Lydia Baxter.

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Patient data statement

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that they are stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Ethics statement

The South Central – Oxford C Research Ethics Committee reviewed the protocol and supporting documents for the CRYOSTAT-2 trial and provided a favourable ethics opinion on 26 May 2017 (Research Ethics Committee reference 17/SC/0164).

Information governance statement

Queen Mary University of London and NHS Blood and Transplant are committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679.

Under the Data Protection legislation, Queen Mary University of London and NHS Blood and Transplant are joint Data Controllers; NHS Blood and Transplant is the Data Processor and process personal data in accordance with the Data Controllers' instructions. You can find out more about how they handle personal data, including how to exercise your individual rights and the contact details for the Data Protection Officer, here: www.nhsbt.nhs.uk/privacy/; www.qmul.ac.uk/privacy/.

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/JYTR6938.

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Publications

Marsden M, Benger J, Brohi K, Curry N, Foley C, Green L, *et al.*; CRYOSTAT-2 investigators. Coagulopathy, cryoprecipitate and CRYOSTAT-2: realising the potential of a nationwide trauma system for a national clinical trial. *Br J Anaesth* 2019;**122**:164–9. https://doi.org/10.1016/j.bja.2018.10.055

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Appendix 1 Consent procedure overview

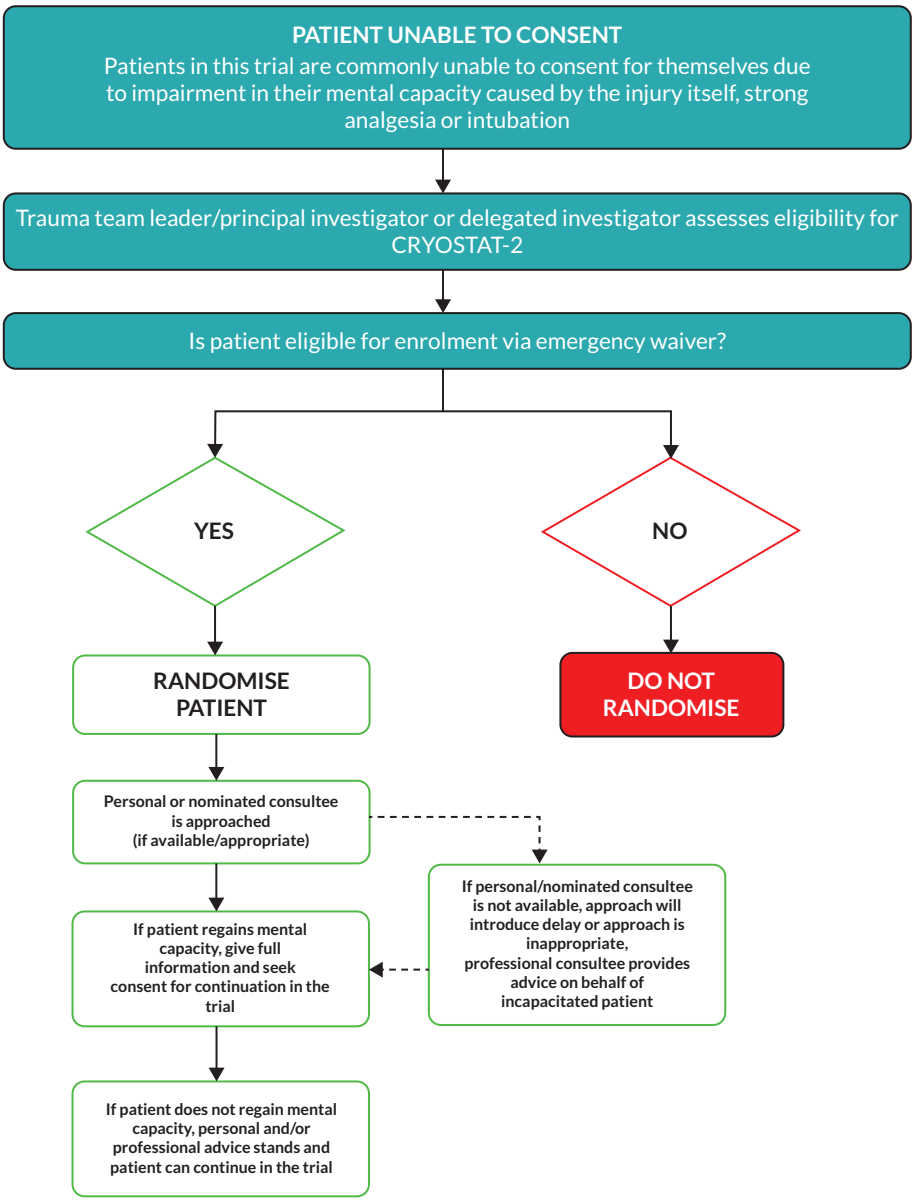

FIGURE 11 Consent procedure overview.

Appendix 2 Additional tables and figures

TABLE 17 Recruitment by study site

Sites	Total number randomised
Royal London Hospital	213
John Radcliffe Hospital	29
University Hospital Southampton	92
St George's Hospital	141
St Mary's Hospital, London	202
King's College Hospital, London	49
Derriford Hospital, Plymouth	28
Addenbrooke's Hospital, Cambridge	39
Southmead Hospital, Bristol	49
James Cook University Hospital, Middlesbrough	57
Leeds General Infirmary, Leeds	71
Queen's Medical Centre, Nottingham	62
Royal Victoria Infirmary, Newcastle upon Tyne	39
Hull Royal Infirmary, Hull	16
Northern General Hospital, Sheffield	46
Queen Elizabeth Hospital, Birmingham	126
Royal Preston Hospital, Preston	19
Royal Sussex County Hospital, Brighton	5
University Hospital, Coventry	56
Royal Stoke University Hospital	18
Manchester Royal Infirmary	52
Salford Royal Hospital	42
Aintree University Hospital, Liverpool	100
University Hospital of Wales, Cardiff	2
Royal Victoria Hospital, Belfast	2
Houston, TX	49
Overall	1604

Baseline characteristics for different subgroups

TABLE 18 Baseline characteristics, by cryoprecipitate timing: data are number/total number (%) for categorical variables, and median (IQR) for continuous variables

	Standard care arm (*n* = 805)	Intervention arm					Overall (*n* = 1604)
		EC < 45 (*n* = 101)	EC 46–60 (*n* = 147)	EC 61–90 (*n* = 273)	EC ≥ 90 (*n* = 128)	EC unknown (*n* = 150)	
Subjects							
Male	633/796 (80)	81/101 (80)	115/147 (78)	218/273 (80)	97/128 (76)	107/136 (79)	1251/1581 (79)
Age (years)	40 (26–55)	41 (28–52)	34 (24–53)	39 (26–55)	37 (25–55)	41 (27–58)	39 (26–55)
Time from injury to admission to emergency department (minutes)	77 (55–100)	89 (69–107)	76 (56–100)	72 (52–96)	70 (53–91)	83 (60–104)	76 (55–100)
Injuries and physiology at admission to emergency department							
Blunt injury	519/796 (65)	60/101 (59)	87/147 (59)	174/273 (64)	82/128 (64)	92/136 (68)	1014/1581 (64)
ISS	29 (18–43)	33 (17–43)	29 (17–45)	29 (17–43)	29 (18–43)	27 (16–42)	29 (18–43)
Head AIS ≥ 4	191/664 (29)	20/82 (24)	32/132 (24)	47/235 (20)	24/111 (22)	34/105 (32)	348/1329 (26)
Systolic blood pressure (mmHg)	103 (83–126)	98 (78–121)	104 (80–126)	99 (84–122)	104 (84–126)	107 (92–130)	103 (83–125)
Heart rate (per minute)	108 (88–127)	110 (91–130)	110 (92–128)	109 (86–128)	108 (85–125)	103 (85–121)	108 (88–127)
In cardiac arrest	17/735 (2)	3/88 (3)	2/132 (2)	3/252 (1)	2/122 (2)	2/123 (2)	29/1452 (2)
Glasgow Coma Scale score	13 (3–15)	3 (3–14)	12 (3–14)	14 (3–15)	15 (7–15)	12 (3–15)	14 (3–15)
Pre hospital							
RBC (units)	0 (0–2)	1 (0–2)	0 (0–2)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–2)
FFP (units)	0 (0–1)	0 (0–2)	0 (0–1)	0 (0–1)	0 (0–0)	0 (0–1)	0 (0–1)
Crystalloids (ml)	0 (0–250)	0 (0–300)	0 (0–350)	0 (0–250)	0 (0–250)	0 (0–300)	0 (0–250)
Colloids (ml)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
TXA administered	639/796 (80)	86/100 (86)	118/147 (80)	209/272 (77)	92/128 (72)	110/136 (81)	1254/1579 (79)

EC, early cryoprecipitate; TXA, tranexamic acid.

Note
Summary of missing data: data on all characteristics were missing for 23 participants. In addition, ISS, cardiac arrest and blood pressure were missing for 246, 129 and 119 participants, respectively. There were a small number of missing data for other items.

TABLE 19 Baseline characteristics, by injury type: data are number/total number (%) for categorical variables, and median (IQR) for continuous variables

	Blunt		Penetrating		
	Standard care arm (*n* = 519)	Intervention arm (*n* = 495)	Standard care arm (*n* = 277)	Intervention arm (*n* = 290)	Overall (*n* = 1604)
Subjects					
Male	384/519 (74)	355/495 (72)	249/277 (90)	263/290 (91)	1251/1581 (79)
Age (years)	46 (30–60)	46 (30–60)	30 (22–43)	30 (22–42)	39 (26–55)
Time from injury to admission to emergency department (minutes)	88 (67–108)	84 (66–106)	57 (44–78)	59 (41–83)	76 (55–100)
Injuries and physiology at admission to emergency department					
Blunt injury	519/519 (100)	495/495 (100)	0/277 (0)	0/290 (0)	1014/1581 (64)
ISS	38 (27–50)	36 (26–48)	18 (11–26)	17 (10–26)	29 (18–43)
Head AIS ≥ 4	176/453 (39)	143/437 (33)	15/211 (7)	14/228 (6)	348/1329 (26)
Systolic blood pressure (mmHg)	104 (82–128)	100 (84–125)	102 (84–126)	104 (84–124)	103 (83–125)
Heart rate (per minute)	107 (88–126)	108 (89–126)	109 (87–129)	107 (87–128)	108 (88–127)
In cardiac arrest	9/479 (2)	7/453 (2)	8/256 (3)	5/264 (2)	29/1452 (2)
Glasgow Coma Scale score	6 (3–15)	12 (3–15)	15 (11–15)	14 (8–15)	14 (3–15)
Pre hospital					
RBC (units)	0 (0–2)	0 (0–2)	0 (0–1)	0 (0–1)	0 (0–2)
FFP (units)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)
Crystalloids (ml)	0 (0–250)	0 (0–300)	0 (0–100)	0 (0–100)	0 (0–250)
Colloids (ml)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
TXA administered	439/519 (85)	406/495 (82)	200/277 (72)	209/288 (73)	1254/1579 (79)

TXA, tranexamic acid.

Note
Summary of missing data: data on all characteristics were missing for 23 participants. In addition, ISS, cardiac arrest and blood pressure were missing for 246, 129 and 119 participants, respectively. There were a small number of missing data for other items.

Sensitivity analyses

TABLE 20 Risk-adjusted multivariable marginal model for all-cause mortality at 28 days

Risk factor	OR[a] (95% CI)	*p*-value
Glasgow Coma Scale score (per one-unit increase)	0.80 (0.77 to 0.84)	< 0.0001
ISS score (per one-unit increase)	1.03 (1.02 to 1.04)	< 0.0001
Participant age (spline term)	See *Figure 9*	< 0.0001
Systolic blood pressure (spline term)	See *Figure 10*	< 0.0001
Intervention arm[b]	1.15 (0.93 to 1.42)	0.1984

a Adjusted OR from logistic regression model, also adjusted for centre.
b Treatment arm was not statistically significant in the model, but the treatment effect adjusted for the factors above is presented.

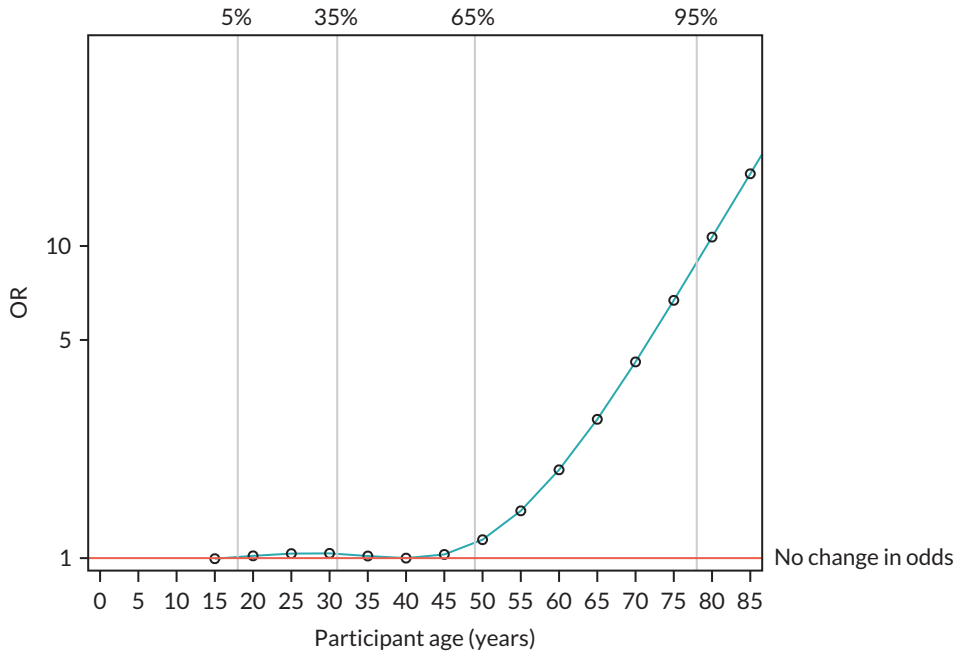

FIGURE 12 Risk-adjusted OR by participant age, relative to a baseline participant at age 40 years.

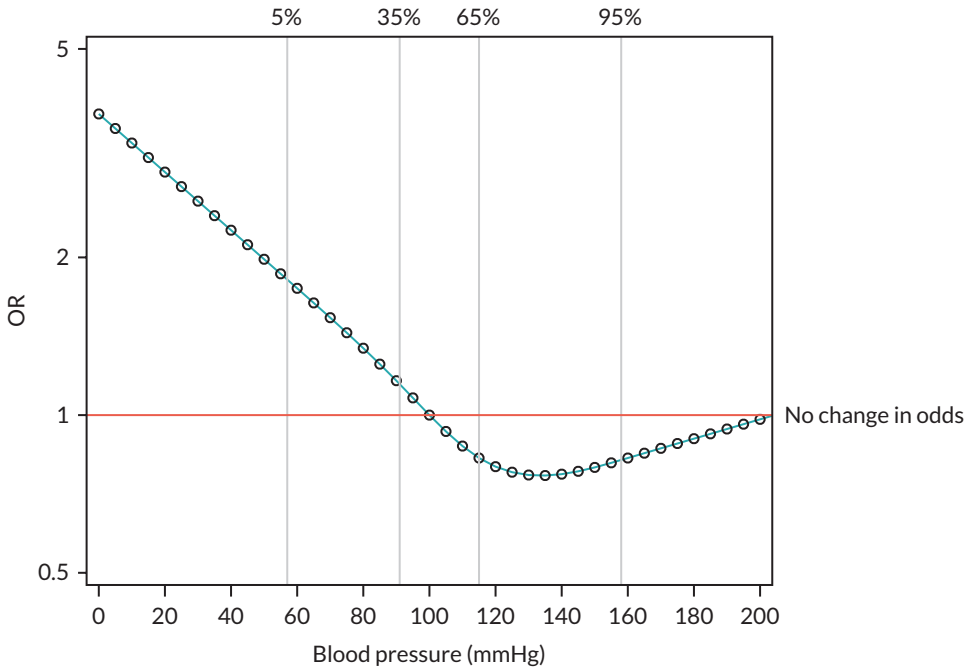

FIGURE 13 Risk-adjusted OR by systolic blood pressure, relative to a baseline participant with systolic blood pressure of 100 mmHg.

TABLE 21 Exclusions from per-protocol cohort, by treatment arm: *n*/*N* (%)

Reason for exclusion	Standard care arm (*n* = 805)	Intervention arm (*n* = 799)	Overall (*n* = 1604)
Randomised in error	40/805 (5.0)	29/799 (3.6)	69/1604 (4.3)
Clinically significant protocol deviation	3/805 (0.4)	1/799 (0.1)	4/1604 (0.2)
Died within 90 minutes of arrival	46/805 (5.7)	37/799 (4.6)	83/1604 (5.2)
No blood products after arrival	32/805 (4.0)	33/799 (4.1)	65/1604 (4.1)
Included in per-protocol analysis	707/805 (87.8)	727/799 (91.0)	1434/1604 (89.4)

	Standard care arm, *n*/*N* (%)		Intervention arm, *n*/*N* (%)		OR (95% CI)	*p*-value
Main ITT	201/771	(26.1)	192/760	(25.3)	0.96 (0.75 to 1.23)	0.7406
Per-protocol	154/683	(22.5)	163/706	(23.1)	1.03 (0.77 to 1.37)	0.8272
Early cryo timing						
Early cryo ≤ 45 minutes from admission	201/771	(26.1)	33/96	(34.4)	1.45 (0.91 to 2.31)	0.1195
Early cryo 46–60 minutes from admission			42/144	(29.2)	1.16 (0.78 to 1.73)	0.4550
Early cryo 61–90 minutes from admission			44/267	(16.5)	0.57 (0.38 to 0.87)	0.0093
Early cryo > 90 minutes from admission			31/123	(25.2)	1.00 (0.62 to 1.60)	0.9870
Cryo administered						
Early cryo – no cryo administrated	201/771	(26.1)	39/123	(31.7)	1.28 (0.70 to 2.34)	0.4084
Early cryo – some cryo administrated			153/637	(24.0)	0.90 (0.72 to 1.13)	0.3600
Subgroup analyses						
Participant location						
UK	198/748	(26.5)	187/737	(25.4)	0.95 (0.75 to 1.20)	0.6385
Non-UK	3/23	(13.0%)	5/23	(21.7)	1.85 (0.36 to 9.47)	0.4434
Head AIS score						
< 4	79/472	(16.7)	92/506	(18.2)	1.11 (0.79 to 1.55)	0.5450
≥ 4	94/191	(49.2)	77/157	(49.0)	1.00 (0.61 to 1.63)	0.9910
Participant sex						
Female	53/155	(34.2)	56/164	(34.1)	1.00 (0.65 to 1.53)	0.9960
Male	148/616	(24.0)	136/596	(22.8)	0.94 (0.67 to 1.31)	0.6901
Participant age						
< 70 years	146/681	(21.4)	149/687	(21.7)	1.01 (0.75 to 1.37)	0.9318
≥ 70 years	49/84	(58.3)	40/69	(58.0)	1.01 (0.55 to 1.88)	0.9661
Injury type						
Blunt	174/500	(34.8)	147/483	(30.4)	0.82 (0.62 to 1.09)	0.1634
Penetrating	27/271	(10.0)	45/277	(16.2)	1.74 (1.20 to 2.51)	0.0058
Sensitivity analyses						
Switching 2% of outcomes inferred based on discharge	203/771	(26.3)	193/760	(25.4)	0.95 (0.75 to 1.21)	0.6944
Unadjusted for centre	201/771	(26.1)	192/760	(25.3)	0.96 (0.76 to 1.21)	0.7179

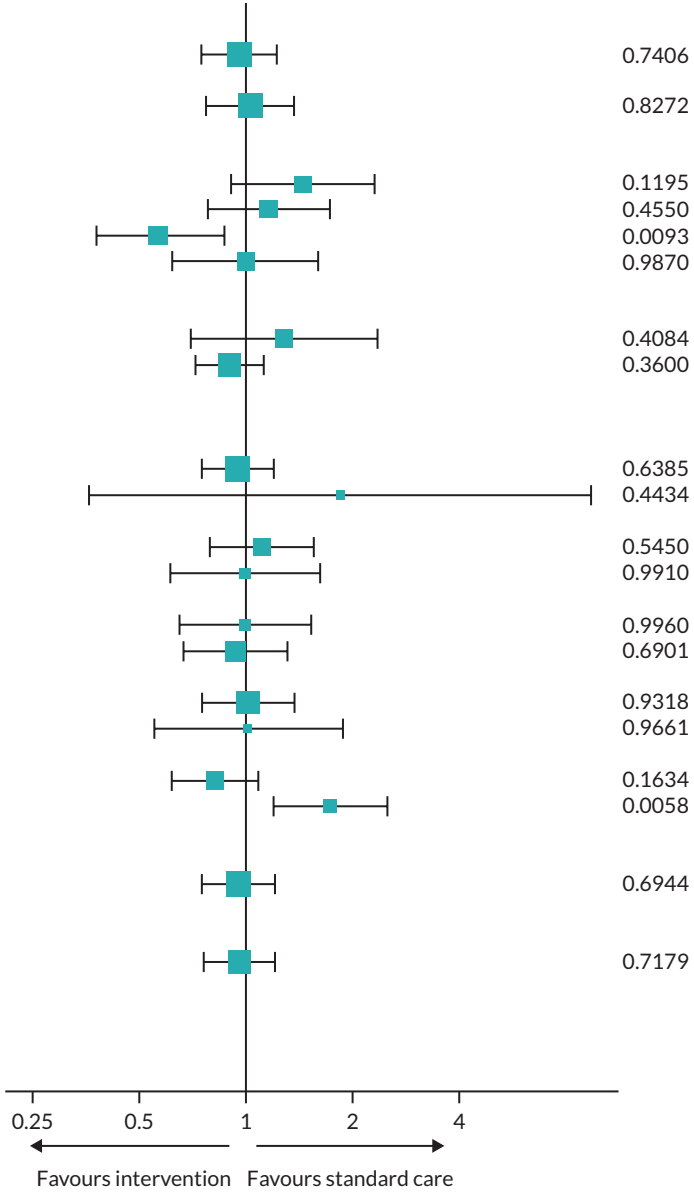

FIGURE 14 Forest plot of ORs and CIs for main ITT and per-protocol analyses of the primary outcome, subgroup analyses and sensitivity analyses.

TABLE 22 All-cause mortality at 28 days in the standard care arm and the intervention arm for those who did or did not receive any cryoprecipitate

Cryoprecipitate group	Mortality rate, *n*/*N* (%)	Relative risk (95% CI)[a]	OR (95% CI)[a]	*p*-value[b]
Standard care arm	201/771 (26.1)	1.00	1.00	
Intervention arm: no cryoprecipitate received	39/123 (31.7)	1.19 (0.79 to 1.81)	1.28 (0.70 to 2.34)	0.4084
Intervention arm: some cryoprecipitate received	153/637 (24.0)	0.93 (0.79 to 1.09)	0.90 (0.72 to 1.13)	0.3600

a Relative to standard arm overall, adjusted for centre.
b Wald test *p*-value from logistic regression model, adjusted for centre.

Note
Participants for whom 28-day vital status was not available were not included in this analysis. No participants were excluded for other reasons.

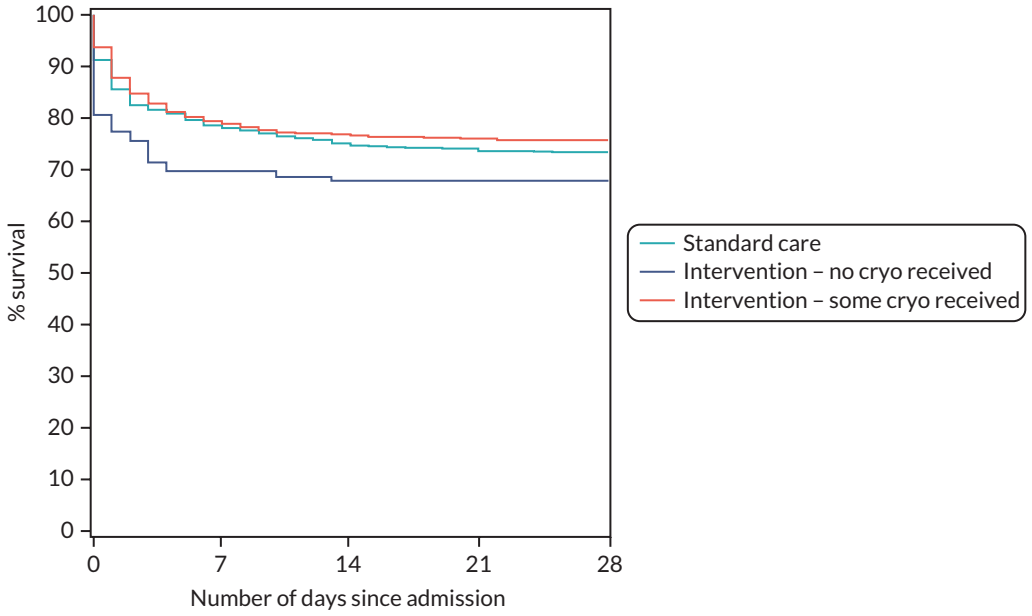

FIGURE 15 Kaplan–Meier survival plot up to 28 days from admission by treatment arm and whether or not any cryoprecipitate given.

Subgroup analyses

TABLE 23 All-cause mortality at 28 days by treatment arm: UK participants vs. US participants

Outcome	UK participants		USA participants	
	Standard care arm (*n* = 780)	Intervention arm (*n* = 775)	Standard care arm (*n* = 25)	Intervention arm (*n* = 24)
Participants who died on or before day 28 from admission, *n*/*N* (%)	198/748 (26.5)	187/737 (25.4)	3/23 (13.0)	5/23 (21.7)
Relative risk[a] (95% CI)	0.96 (0.81 to 1.14)		1.67 (0.42 to 6.55)	
OR[a] (95% CI)	0.95 (0.75 to 1.20)		1.85 (0.36 to 9.47)	
p-value for subgroup	0.6385		0.4434	
p-value for interaction term[b]	0.4092			
Participants for whom 28-day vital status was not available from any source, *n*/*N* (%)	32/780 (4.1)	38/775 (4.9)	2/25 (8.0)	1/24 (4.2)

a Intervention relative to standard care arm, adjusted for centre.
b *p*-value for interaction, adjusted for centre and UK vs. USA.

Note
Participants for whom 28-day vital status was not available were not included in this analysis. No participants were excluded for other reasons.

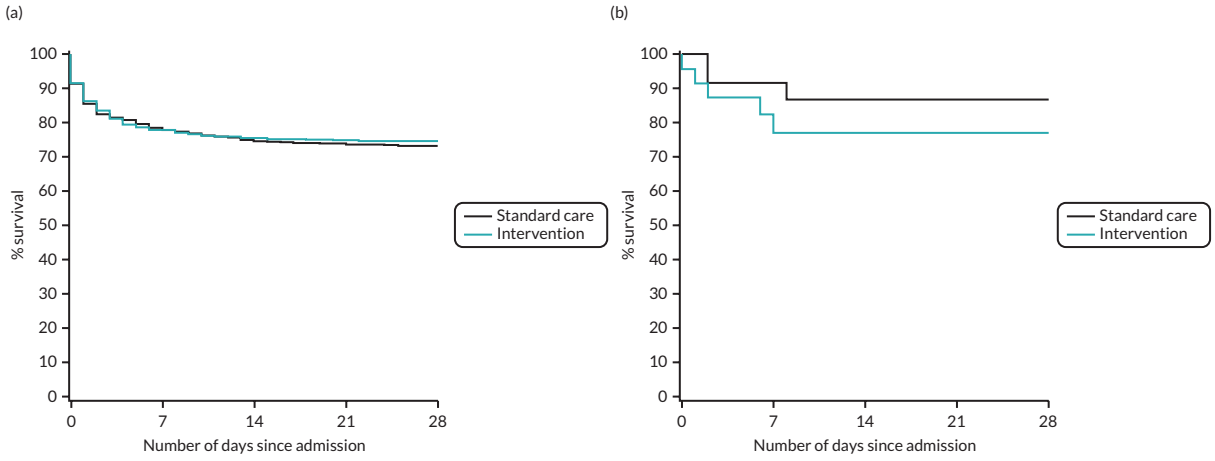

FIGURE 16 Kaplan–Meier survival plots up to 28 days from admission by treatment arm for (a) UK and (b) USA.

TABLE 24 All-cause mortality at 28 days by treatment arm: head AIS < 4 vs. head AIS ≥ 4

Outcome	Head AIS < 4		Head AIS ≥ 4	
	Standard care arm (*n* = 473)	Intervention arm (*n* = 508)	Standard care arm (*n* = 191)	Intervention arm (*n* = 157)
Participants who died on or before day 28 from admission, *n*/*N* (%)	79/472 (16.7)	92/506 (18.2)	94/191 (49.2)	77/157 (49.0)
Relative risk[a] (95% CI)	1.09 (0.82 to 1.44)		1.00 (0.78 to 1.28)	
OR[a] (95% CI)	1.11 (0.79 to 1.55)		1.00 (0.61 to 1.63)	
p-value for subgroup	0.5450		0.9910	
p-value for interaction term[b]	0.7408			
Participants for whom 28-day vital status was not available from any source, *n*/*N* (%)	1/473 (0.2)	2/508 (0.4)	0/191 (0.0)	0/157 (0.0)

a Intervention arm relative to standard care arm, adjusted for centre.
b *p*-value for interaction, adjusted for centre and AIS < 4 vs AIS ≥ 4.

Note
Participants for whom 28-day vital status was not available were not included in this analysis in addition to 205 participants excluded owing to missing head AIS.

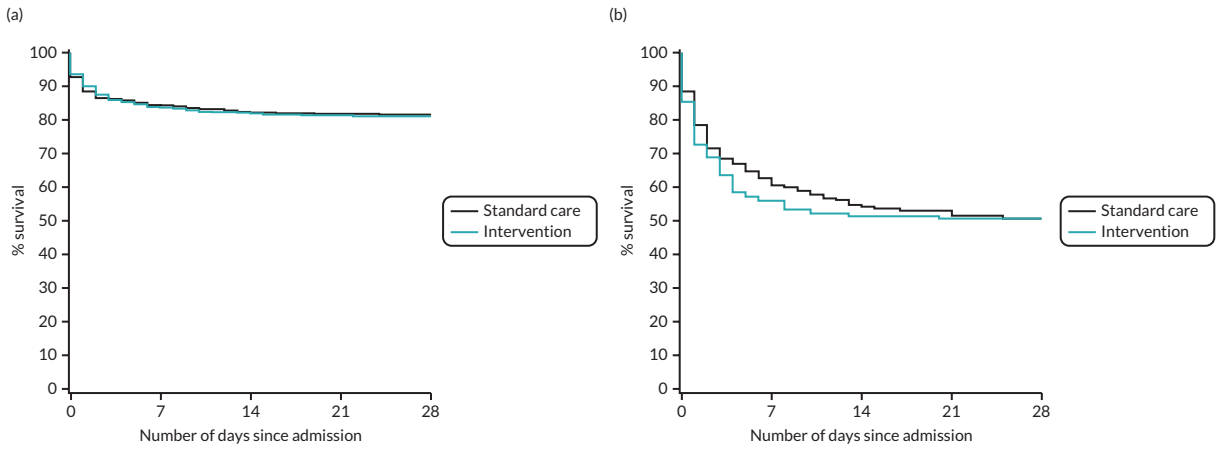

FIGURE 17 Kaplan–Meier survival plots up to 28 days from admission by treatment arm for (a) head AIS < 4 and (b) head AIS ≥ 4.

TABLE 25 All-cause mortality at 28 days by treatment arm: participant sex

Outcome	Male		Female	
	Standard care arm (*n* = 633)	Intervention arm (*n* = 618)	Standard care arm (*n* = 163)	Intervention arm (*n* = 167)
Participants who died on or before day 28 from admission, *n*/*N* (%)	148/616 (24.0)	136/596 (22.8)	53/155 (34.2)	56/164 (34.1)
Relative risk[a] (95% CI)	0.95 (0.74 to 1.23)		1.00 (0.76 to 1.32)	
OR[a] (95% CI)	0.94 (0.67 to 1.31)		1.00 (0.65 to 1.53)	
p-value for subgroup	0.6901		0.9960	
p-value for interaction term[b]	0.8204			
Participants for whom 28-day vital status was not available from any source, *n*/*N* (%)	17/633 (2.7)	22/618 (3.6)	8/163 (4.9)	3/167 (1.8)

a Intervention arm relative to standard care arm, adjusted for centre.
b *p*-value for interaction, adjusted for centre and sex.

Note
Participants for whom 28-day vital status was not available were not included in this analysis. No participants were excluded for other reasons.

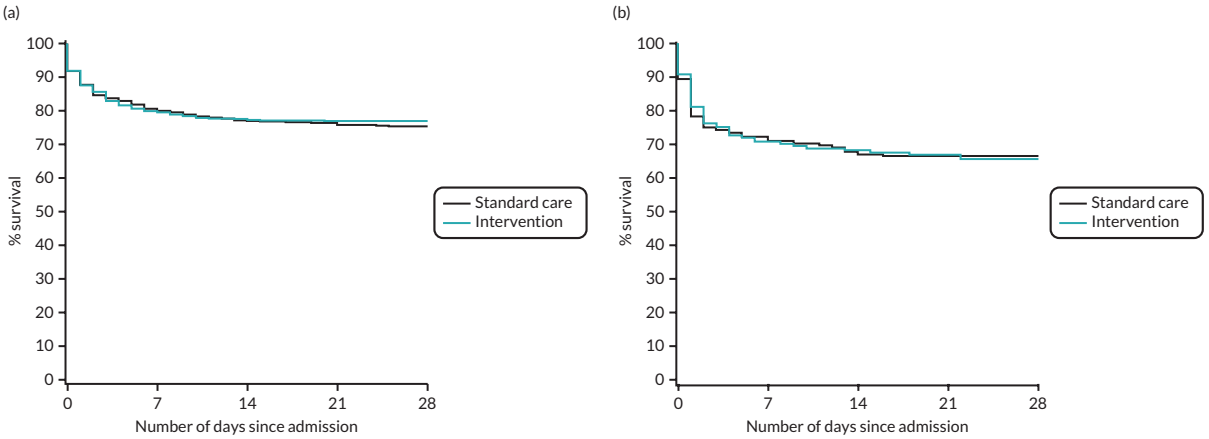

FIGURE 18 Kaplan–Meier survival plots up to 28 days from admission by treatment arm for (a) male and (b) female patients.

TABLE 26 All-cause mortality at 28 days by treatment arm: participant age < 70 vs. ≥ 70 years

Outcome	< 70 years		≥ 70 years	
	Standard care arm (*n* = 704)	Intervention arm (*n* = 710)	Standard care arm (*n* = 86)	Intervention arm (*n* = 71)
Participants who died on or before day 28 from admission, *n*/*N* (%)	146/681 (21.4)	149/687 (21.7)	49/84 (58.3)	40/69 (58.0)
Relative risk[a] (95% CI)	1.01 (0.80 to 1.28)		1.01 (0.78 to 1.30)	
OR[a] (95% CI)	1.01 (0.75 to 1.37)		1.01 (0.55 to 1.88)	
p-value for subgroup	0.9318		0.9661	
p-value for interaction term[b]	0.9999			
Participants for whom 28-day vital status was not available from any source, *n*/*N* (%)	23/704 (3.3)	23/710 (3.2)	2/86 (2.3)	2/71 (2.8)

a Intervention arm relative to standard care arm, adjusted for centre.
b *p*-value for interaction, adjusted for centre and < 70 vs. ≥ 70 years.

Note
Participants for whom 28-day vital status was not available were not included in this analysis in addition to 10 participants excluded owing to missing age.

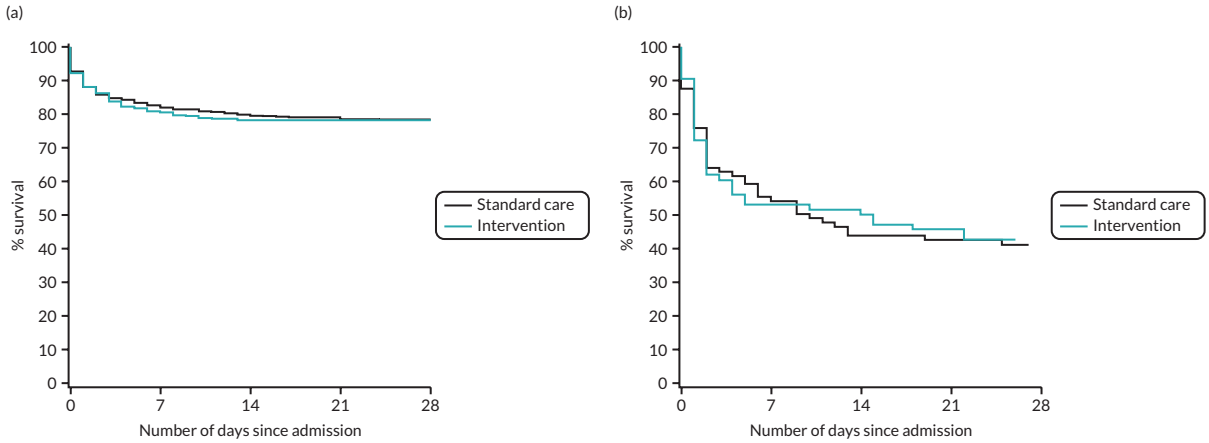

FIGURE 19 Kaplan–Meier survival plots up to 28 days from admission by treatment arm for (a) age < 70 and (b) age ≥ 70 years.

Secondary outcomes

TABLE 27 Mortality data

Outcome	Standard care arm (*n* = 805)	Intervention arm (*n* = 799)	Overall (*n* = 1604)	*p*-value
Mortality at 6 hours from admission, *n*/*N* (%)	68/795 (8.6)	56/784 (7.1)	124/1579 (7.9)	
OR (95% CI) for mortality at 6 hours from admission[a]	0.82 (0.58 to 1.17)			0.2595
Mortality at 24 hours from admission, *n*/*N* (%)	97/794 (12.2)	88/783 (11.2)	185/1577 (11.7)	
OR (95% CI) for mortality at 24 hours from admission[a]	0.91 (0.63 to 1.31)			0.6064
Death from bleeding at 6 hours from admission, *n*/*N* (%)	35/795 (4.4)	32/784 (4.1)	67/1579 (4.2)	
OR (95% CI) for death from bleeding at 6 hours from admission[a]	0.93 (0.54 to 1.58)			0.7675
Death from bleeding at 24 hours from admission, *n*/*N* (%)	39/794 (4.9)	43/783 (5.5)	82/1577 (5.2)	
OR (95% CI) for death from bleeding at 24 hours from admission[a]	1.13 (0.62 to 2.05)			0.6776
Median (IQR) time to death from bleeding among those who bled, in minutes[b]	86 (40–205)	191 (81–445)	132 (59–353)	0.0212

a Intervention arm relative to standard care arm adjusted for centre, from mixed logistic regression model.
b Post hoc *p*-value from Mann–Whitney test.

TABLE 28 Transfusion requirements

Outcome	Standard care arm (*n* = 805)	Intervention arm (*n* = 799)	Overall (*n* = 1604)	*p*-value
Median (IQR) products transfused per participant from injury to 24 hours				
RBC (units)	5 (3–8)	5 (3–9)	5 (3–9)	
Platelets (units)	0 (0–1)	0 (0–1)	0 (0–1)	
FFP (units)	4 (2–8)	4 (2–8)	4 (2–8)	
Cryoprecipitate (units)	0 (0–2)	3 (3–3)	2 (0–3)	
Total blood products (units)	10 (5–18)	12 (7–21)	11 (6–20)	
Crystalloids (ml)	1600 (250–3200)	2000 (700–3500)	1958 (500–3384)	
Colloids (ml)	0 (0–0)	0 (0–0)	0 (0–0)	
Mean products transfused per participant per hour over the first 24 hours				
RBC (units)	0.65	0.63	0.64	0.7588
Platelets (units)	0.05	0.05	0.05	0.8475
FFP (units)	0.47	0.48	0.48	0.9963
Cryoprecipitate (units)	0.06	0.17	0.11	< 0.0001
Total blood products (units)	1.23	1.33	1.28	0.4364
Crystalloids (ml)[2]	101.94	123.71	112.73	0.0802
Colloids (ml)[2]	4.39	7.60	5.98	0.8326

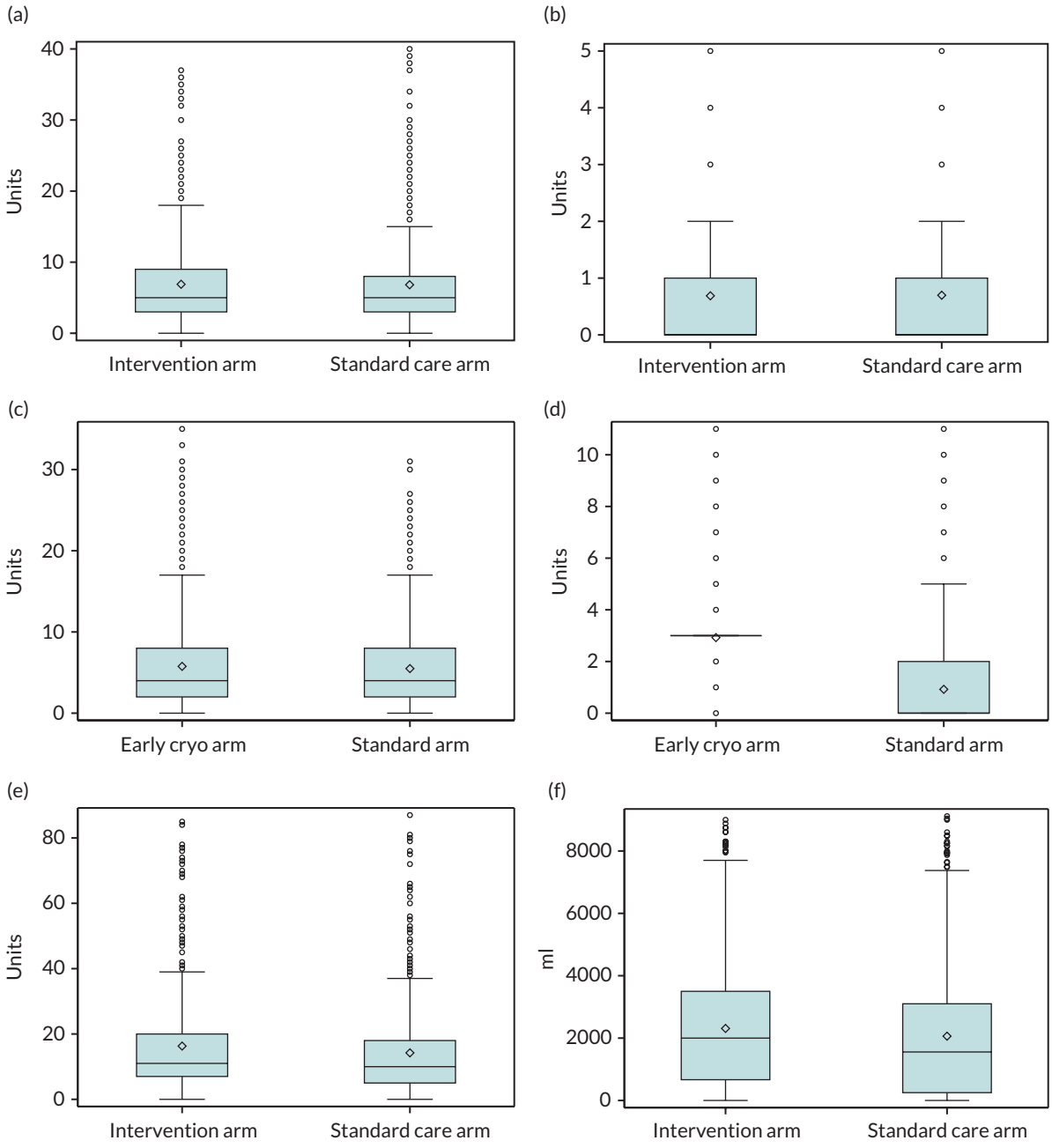

FIGURE 20 Box-and-whisker plots to summarise transfusions administered from injury up to 24 hours from admission, by treatment arm. (a) RBC; (b) platelets; (c) FFP; (d) cryoprecipitate; (e) total blood products; and (f) crystalloids. These box-and-whisker plots show the median (line inside box), IQR (boundary of box), mean (diamond), minimum and maximum (whiskers) and outliers (values 1.5 × IQR above Q3 or below Q1). Extreme outliers for all products, defined as the top 1% of data, were excluded from these plots. Note the differing *y*-axes for each product.

TABLE 29 Quality of life at discharge and 6 months after admission

Outcome	At discharge or day 28 where alive				At 6-month follow-up			
	Standard care arm (*n* = 805)	Intervention arm (*n* = 799)	Overall (*n* = 1604)	*p*-value	Standard care arm (*n* = 805)	Intervention arm (*n* = 799)	Overall (*n* = 1604)	*p*-value
Participants who completed EQ-5D-5L index value questions, *n*/*N* (%)	347/571 (61)	324/569 (57)	671/1140 (59)		47/455 (10)	52/468 (11)	99/923 (11)	
Participants who completed EQ-5D-5L 'health today' question, *n*/*N* (%)	322/571 (56)	306/569 (54)	628/1140 (55)		46/455 (10)	51/468 (11)	97/923 (11)	
Median (IQR) index value[a]	0.50 (0.20–0.73)	0.51 (0.26–0.72)	0.50 (0.22–0.73)	0.8024	0.66 (0.36–0.78)	0.76 (0.63–0.93)	0.70 (0.41–0.86)	N/A
Cohen's *d* for index value (95% CI)	0.01 (−0.14 to 0.17)				0.47 (0.07 to 0.87)			
Median (IQR) self-evaluated health score[a]	60 (40–70)	50 (30–70)	53 (35–70)	0.1015	65 (50–75)	75 (51–85)	70 (50–80)	N/A
Cohen's *d* for self-evaluated health score (95% CI)	−0.13 (−0.29 to 0.03)				0.31 (−0.09 to 0.70)			
Participants who completed GOS questionnaire at discharge *n*/*N* (%)	712/805 (88)	705/799 (88)	1417/1604 (88)					
GOS at discharge, n/N (%)[b]								
Low disability	221/712 (31)	226/705 (32)	447/1417 (32)	0.5540				
Moderate disability	129/712 (18)	129/705 (18)	258/1417 (18)					
Severe disability	153/712 (21)	155/705 (22)	308/1417 (22)					
Persistent vegetative state	27/712 (4)	21/705 (3)	48/1417 (3)					
Death	182/712 (26)	174/705 (25)	356/1417 (25)					

a *p*-value for Mann–Whitney test.
b *p*-value for ordinal regression, adjusted for centre.

Note
Mann–Whitney tests were not conducted on the 6-month follow-up data due to the very low data completeness for these outcomes.

TABLE 30 Hospital stay

Outcome	Standard care arm (*n* = 805)	Intervention arm (*n* = 799)	Overall (*n* = 1604)	*p*-value
Median (IQR) ventilator-days[a,b]	1 (0–7)	1 (0–6)	1 (0–6)	0.8996
Median (IQR) hospital stay[a,b] (days)	11 (3–27)	11 (3–27)	11 (3–27)	0.8810
Median (IQR) first critical care stay[a,b] (days)	4 (1–13)	4 (1–12)	4 (1–12)	0.8538
Participants discharged from hospital, *n*/*N* (%)	374/771 (49)	375/761 (49)	749/1532 (49)	
Destination, *n*/*N* (% of those discharged)				
Home	278/374 (74)	280/375 (75)	558/749 (74)	
Nursing home/rehabilitation facility	8/374 (2)	9/375 (2)	17/749 (2)	
Another hospital	72/374 (19)	63/375 (17)	135/749 (18)	
Other	16/374 (4)	23/375 (6)	39/749 (5)	

a Crude median and IQR that make no allowance for differential follow-up owing to death.
b *p*-value from Fine and Gray model to compare cumulative incidence curves, which allows for differential follow-up owing to death.

TABLE 31 All-cause mortality at 6 and 12 months by treatment arm

Outcome	Standard care arm (*n* = 805)	Intervention arm (*n* = 799)	Overall (*n* = 1604)	*p*-value
Estimated mortality rate at 6 months from admission,[a] % (95% CI)	27.3 (24.3 to 30.7)	26.1 (23.2 to 29.4)	26.7 (24.6 to 29.1)	
Hazard ratio[b] (95% CI)	0.96 (0.79 to 1.17)			0.6748
Hazard ratio also adjusted for participant factors[c] (95% CI)	1.08 (0.89 to 1.32)			
Estimated mortality rate at 12 months from admission,[a] % (95% CI)	27.7 (24.6 to 31.1)	26.6 (23.6 to 30.0)	27.2 (25.0 to 29.5)	
Hazard ratio[b] (95% CI)	0.96 (0.79 to 1.17)			0.7120
Hazard ratio also adjusted for participant factors[c] (95% CI)	1.09 (0.90 to 1.32)			
Participants with missing survival data at all time points, *n*/*N* (%)	10/805 (1)	15/799 (2)	25/1604 (2)	

a Unadjusted Kaplan–Meier estimate.
b Intervention arm relative to standard care arm, adjusted for centre; *p*-value for treatment term in Cox regression model.
c Intervention arm relative to standard care arm adjusted for centre and significant participant factors.

Note
Participants for whom vital status was not available were not included in this analysis. No participants were excluded for other reasons.

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