Site Initiation Visit

On behalf of the
CRYOSTAT-2 research team
Trial management

• Chief Investigators:
  – Professor Karim Brohi
  – Dr. Simon Stanworth

• Co-Investigators:
  – Dr. Ross Davenport
  – Dr. Nicola Curry

• Sponsor: QMUL

• Funder: NIHR HTA

• Study management: NHSBT CTU
The Ratio of Fibrinogen to Red Cells Transfused Affects Survival in Casualties Receiving Massive Transfusions at an Army Combat Support Hospital

Harry K. Stinger, MD, Philip C. Spinella, MD, Jeremy G. Perkins, MD, Kurt W. Grathwohl, MD, Jose Salinas, PhD, Wenjun Z. Martini, PhD, John R. Hess, MD, Michael A. Dubick, PhD, Clayton D. Simon, MD, Alec C. Beekley, MD, Steven E. Wolf, MD, Charles E. Wade, PhD, and COL John B. Holcomb, MC

patients in each ratio category

Mortality (%)

0 to < 0.2
0.2 to < 0.4
0.4 to < 0.6
≥ 0.6

Ratio of Grams of Fibrinogen/RBC Units (F:R Ratio)

J Trauma 2007; 64(Supp2)
Study background: 
Fibrinogen in trauma

• Fg the first of all proteins to fall
• Hypothermia: increased Fg breakdown
• Acidosis: reduced Fg production
• Haemodilution:
  – Functional deficiency of Fg – worse with colloids (abnormal polymerisation of Fg)
• Fibrinolysis

Hiippala, Anesth Analg. 1995; 81
Martini, Am J Physiol Endocrinol Metab. 2005; 289
Fenger-Eriksen, J Thromb Haemost. 2009; 7
Fibrinogen is a major coagulation protein and deficiency develops earlier than other coagulation factors with use of plasma poor RC
What happens to Fg in trauma?

- ACIT-2 data (n = 517)
- Fg levels are lower on admission
  - Non-coagulopathic: 2.5g/L
  - Coagulopathic: 1.6g/L
- Admission Fg levels
  - independent predictor of 24 hour & 28 day mortality (p<0.001)

Rourke et al, 2012 JTH
UK NIHR Trauma study

- 22 hospitals, between 2009-2011
  - Major trauma centres & trauma units
- N = 12,290
  - 479 major transfusions
  - 146 massive transfusions

- Median times to first Tx:
  - RBC – 43 mins (30 mins)
  - FFP – 93 mins (80 mins)
  - Cryo - 184 mins (156 mins)

- Mortality: 16% at 24h, 25% at 28 d, 32% at 1 year
> 50% of deaths occur in first 3 hrs, with < 10% after 10 h
Intervention group:
Receive cryoprecipitate within 90 minutes of admission

Comparator group:
Receive standard massive haemorrhage protocol
Transfusion Requirements

• No significant difference between groups for Tx of any blood component, excluding cryoprecipitate
Fibrinogen Levels

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>At admission</td>
<td>1.6 (1.43 – 2.14)</td>
<td>1.55 (1.43 – 2.24)</td>
</tr>
<tr>
<td>During active bleeding: nadir Fg</td>
<td>1.80</td>
<td>0.60</td>
</tr>
<tr>
<td>24 hours</td>
<td>2.97 (2.15 – 3.90)</td>
<td>3.03 (2.43 – 3.26)</td>
</tr>
<tr>
<td>7 days</td>
<td>5.66 (5.00 – 7.71)</td>
<td>5.84 (5.45 – 7.00)</td>
</tr>
</tbody>
</table>
28 day mortality and SAEs

<table>
<thead>
<tr>
<th>SUBJECTS</th>
<th>INTENTION TO TREAT</th>
<th>PER TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CRYO</td>
<td>STANDARD</td>
</tr>
<tr>
<td>N</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>28 day mortality</td>
<td>2 (10.0)</td>
<td>6 (28.6)</td>
</tr>
<tr>
<td>ICU Days</td>
<td>11 (5–17)</td>
<td>18 (16–20)</td>
</tr>
<tr>
<td>In patient Days</td>
<td>31 (29–33)</td>
<td>30 (22–38)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SUBJECTS</th>
<th>INTENTION TO TREAT</th>
<th>PER TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>Total number of serious adverse events</td>
<td>7</td>
<td>11</td>
</tr>
</tbody>
</table>
Study Background

• Fibrinogen falls early in trauma haemorrhage
• Low fibrinogen is an independent predictor of death
• Deaths from early bleeding occur within 3 – 6 hours of hospital admission
• UK practice: fibrinogen replacement often occurs late

• CRYOSTAT1 showed:
  – Fg levels maintained
  – No harm
  – Possible mortality benefit
Hypothesis and aims

- Early fibrinogen supplementation, in the form of cryoprecipitate, will reduce bleeding and improve 28 day survival

- A randomised controlled trial to evaluate the effects on mortality of early administration of 3 pools of cryoprecipitate to adult patients with major trauma haemorrhage
Cryoprecipitate

“G” number Unique identifier matching donor and patient

Product label “CRYOPRECIPITATE”

What is it?
Cryoprecipitate is a blood product prepared from plasma and contains fibrinogen, von Willebrand factor, factor VIII, factor XIII and fibronectin.
Study design

• Randomised, unblinded, controlled trial

• Comparing:
  – 3 pools of cryoprecipitate (≈6g fibrinogen) plus MHP
  – Standard MHP alone

• 1568 patients
• UK and North America
• Duration of recruitment in the UK: 36 months
• Follow up: 12 months
Study sites

Major Trauma Centres in England

October 2016
Eligibility: Inclusion Criteria

• Consent process in UK: initial waiver

• Adult patients affected by traumatic injury
  – Judged to be 16 years or older

• Participant deemed to have on-going active haemorrhage

And requires

• Activation of the local major haemorrhage protocol for treatment of blood loss

And has started or has received

• At least one unit of any blood component
Eligibility: Exclusion criteria

One or more of the following:
• Transferred from another hospital
• Trauma team leader deems the injury incompatible with life
• More than 3 hours elapsed from the time of injury
Study outcomes

Primary

• All cause mortality at day 28

Secondary

• All cause mortality (including death from bleeding) at 6 hours, 24 hours, 6 months and 12 months from admission
• Death from bleeding at 6 hours and 24 hours
• Transfusion requirements, in numbers of units, for RBC, platelets, FFP & cryoprecipitate at 24 hours from admission, including prehospital transfusion
• Destination of participant at time of discharge from hospital
• Quality of life measures: EQ-5D-5L, GOSE at discharge and 6 months
• Hospital resource use up to discharge or day 28
Sample size

• CRYOSTAT2 aims to detect an absolute mortality difference of 7% from a baseline mortality of 26%
• 90% power, 5% significance
• Including stopping rules
• Overall sample size: 1568 (UK: n=1142)
• 2.5% drop outs included
Study Schedule

- Pragmatic
- No extra bloods
- Recording of transfusions & use of TXA can be retrospectively at 24 hr

<table>
<thead>
<tr>
<th>Timepoint**</th>
<th>Admission</th>
<th>Enrolment</th>
<th>Post randomisation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ENROLMENT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eligibility Screen</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Informed Consent/Assent</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomisation/Allocation</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>INTERVENTION</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cryoprecipitate (3 pools, 15 units) in addition to MHP</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major haemorrhage protocol (MHP) alone</td>
<td>X</td>
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<td></td>
</tr>
<tr>
<td><strong>ASSESSMENTS</strong></td>
<td></td>
<td></td>
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<tr>
<td>Participant characteristics</td>
<td>X</td>
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<td></td>
</tr>
<tr>
<td>Clinical Assessment</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time of first dose of TXA</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RBC, FFP, cryo, platelets (including pre-admission)</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Serious Adverse Events</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Participant destination at discharge</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glasgow Outcome Score</td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>EQ5D-5L</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

*Timepoints are:

- $T_0$ – Enrolment & allocation of early cryoprecipitate, must be within 90 minutes of admission
- $T_1$ – cryoprecipitate administered, must be started within 90 minutes of admission
- $T_2$ – 6 h (± 1 h) from admission
- $T_3$ – 24 h (± 4 h) from admission
- $T_4$ – date of discharge or day 28 (± 4 days) from admission whichever is the sooner
- $T_5$ – 6 months (± 14 days)
- $T_6$ – ≥12 months (mortality data post discharge to be captured by flagging with the ONS)
Data collection

Mortality
- **At discharge or Day 28** (whichever is sooner)
  - Site research team to monitor SAEs (incl Death) during admission
- **Post discharge or Day 28 up to 1 year**
  - Mortality data collected centrally by ONS

EQ5D-5L and GoS
- **At discharge or Day 28** (whichever is sooner)
  - Site research team to collect via PROMS/GOS questionnaire and transcribe onto CRF
- **At 6 months**
  - Collected centrally by TARN
Trial Management
NHS Blood & Transplant

Joanne Lucas
Trial Manager

Amy Evans
Trial Coordinator

Claire Foley
Clinical Operations Manager
Trial Governance

- Trial Steering Committee
- Trial Management Group
- Data Monitoring Committee

Regular progress reports to:
- Sponsor
- Funders (NIHR HTA Programme)
- HRA & REC
Study Algorithm

1. Trauma participant admitted to ED
2. Patient fulfils all inclusion and none of exclusion criteria
3. Randomise

**Intervention group**
- 3 pools early cryoprecipitate plus standard MHP
  - Follow-up to 1 year or death (whichever is sooner)

**Comparator group**
- Standard MHP alone
  - Follow-up to 1 year or death (whichever is sooner)

If the patient does not fulfils all inclusion and none of exclusion criteria, then:
- Patient not randomised
- Standard management given
- Follow-up to 1 year or death (whichever is sooner)
Screening & Eligibility

• Only consider those who have already triggered the Major Haemorrhage Protocol - this avoids screening errors
• Complete screening logs
• Only choose one reason for non-randomisation
<table>
<thead>
<tr>
<th>No.</th>
<th>Patient Initials</th>
<th>Age</th>
<th>Sex (M/F)</th>
<th>Date considered for eligibility (dd/mm/yy)</th>
<th>Meets eligibility? Y/N</th>
<th>*If not eligible, enter reason code</th>
<th>Randomised? Y/N</th>
<th>*If not randomised, enter reason code</th>
<th>If randomised, enter randomisation number</th>
<th>Date randomised (dd/mm/yy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>R</td>
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<td>R</td>
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<tr>
<td>2.</td>
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<td>3.</td>
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<td></td>
<td>R</td>
</tr>
</tbody>
</table>

1. Emergency waiver of consent not obtained
2. The patient is judged to be aged <16 years
3. Patient is not affected by traumatic injury
4. The patient is deemed by the attending clinician not to be actively bleeding
5. The patient has not received at least one unit of any blood component
6. The patient has been transferred from another hospital
7. The trauma leader deems the injury incompatible with life
8. More than 3 hours have elapsed from the time of injury
9. Unavailability of the research team
10. Patient entered into another clinical trial that does not allow co-enrolment (please state acronym of trial)
11. The patient died
12. Other: please specify
Data management

• Screening Logs
  – To be completed monthly

• Patient Identifiable Information
  – To be completed monthly

• Paper CRFs
  – Enrolment, Eligibility, Randomisation, Study visits, SAEs, GOSE at discharge
  – TARN data at discharge (EQ-5D-5L)
Rapid identification

- Think about the possibility of the patient being eligible for the trial before they arrive
- Please **DO NOT** randomise patients before they arrive, even if the MHP has been activated in advance as the clinical picture can change
- Ask HEMS at handover if the patient is in the RePHILL trial – we can’t co-enrol patients with this study
- Doctor or nurse who are study trained to assess eligibility of patients on arrival in ED
- **Trauma Team Leader must confirm** eligibility
Consent

• Initial waiver- automatic

• If patient is incapacitated, a personal consultee is approached

• If no personal consultee, a professional consultee is approached (within 1 week)

• Capacity of patient should be checked periodically. Informed patient consent sought when patient is able
Randomisation

- Randomisation in ED or Blood bank
- Details in CRF & in red box
- Open lowest sequentially numbered envelope
- Check tamper proof seal is in tact, sign
- Reveal allocation and check card and envelope numbers match
- Record date on list of randomisation numbers in box
Randomisation
Randomisation

Randomisation Number: R00001

This participant has been randomised to receive:

Early Cryoprecipitate AND Standard Major Haemorrhage Protocol

Early cryoprecipitate (3 pools) to be administered within 90 minutes of admission

Randomisation Number: R00002

This participant has been randomised to receive:

Standard Major Haemorrhage Protocol ONLY
Randomisation in ED

Think about potential patients before they arrive in ED

On arrival in ED
Ask HEMS – is the patient in the RePHILL study?
Doctor or nurse who are trial trained assesses eligibility

Trauma Team Leader must confirm eligibility

Randomisation
Take out the next sequentially numbered envelope in the box
Write date and time of randomisation on the back of the envelope and sign it
Open the envelope and read the group allocation
Return the envelope to the back of the box – never destroy any envelopes!

Intervention patients:
Call blood bank
Activate MHP and tell blood bank patient is CRYOSTAT-2 intervention group and request 3 pools of cryoprecipitate
OR
If MHP already activated, tell blood bank patient is CRYOSTAT-2 intervention group and request 3 pools of cryoprecipitate

Cryoprecipitate arrives in ED*
Administer cryoprecipitate

*ED, or other patient location (e.g. theatres, radiology)
Randomisation in blood bank

Call from ED
Call received from ED to activate MHP OR if MHP already activated, ED call blood bank and say the patient is eligible for the CRYOSTAT-2 study
Ask/double check the patient is to be randomised to CRYOSTAT-2
Ask if Trauma Team Leader has confirmed eligibility
Note name of caller
Randomisation
Take out the next sequentially numbered envelope in the box
Write date and time of randomisation on the back of the envelope and sign it
Open the envelope and read the group allocation
Give the caller the randomisation number (RXXXXX) and group allocation
Return the envelope to the back of the box – never destroy any envelopes!

Intervention patients:
Thaw 3 pools of cryoprecipitate for transfer following usual local procedures (e.g. porters)
Use study specific labels/boxes or yellow study bags to clearly identify that this is study cryoprecipitate

*Cryoprecipitate arrives in ED*
Administer cryoprecipitate

*ED, or other patient location
(e.g. theatres, radiology)*
Administration of the intervention

- Follow **usual** local procedures to deliver cryoprecipitate to ED (e.g. porter), deviation from these can cause confusion and missed checks.
- Always carry out your patient and blood product ID checks.
- Do not use a blood warmer.
- If the patient goes to interventional radiology or theatre, study cryoprecipitate can be given there as long as the staff administering it are:
  
  1. Aware of the study and it’s aims
  2. Know what the intervention is

* Make sure Anaesthetists know not to normalise ratios *

* Remember that the aim is to administer cryoprecipitate within 90 minutes of arrival in ED – think about location of administration *

Tell your Intensivists, Anaesthetists and Theatre colleagues about the study!
Randomisations in error

• Once the randomisation envelope is opened, the patient is in the study
• Randomised patients are included in the intention to treat analysis
• File note to CTU with reason randomised in error
• Follow up and data collection as usual

Common examples
• MHP activated on pre-alert – patient arrives with no major haemorrhage
• Confusion about if the patient has received or started one unit of a blood product (HEMS or land ambulance) on arrival – check in handover
• Patient already enrolled in RePHILL study – make part of your routine HEMS handover questions
CRF

• Four main sections
• Guidelines on facing pages
• Any member of research team can sign
• Send confirmation of randomisation to CTU
• Form 4 – includes areas outside ED
• Form 5 - cumulative Cryo
• Form 7- n/a if patient died relates to Q9
• Hospital resource use
• Can send partially completed forms
Transmittal forms

CRF or SAE reporting

Email CRFs to cryostat2@nhsbt.nhs.uk

Email SAEs to serious_adverse_events@nhsbt.nhs.uk
Data management

• Screening Logs
  – To be completed monthly

• Patient Identifiable Information
  – To be completed monthly

• Paper CRFs
  – Enrolment, Eligibility, Randomisation, Study visits, SAEs, GOSE at discharge
  – TARN data at discharge (EQ-5D-5L)
Training

• Core Research Team attend SIV and sign SIV attendance log
• Cascade training by PI or delegate
• Research Nurses to have mandatory training in Blood Transfusion Awareness/Safe Transfusion Practice
• Follow SOP on roles, responsibilities and training required
• Annual training updates for staff revised each year and sent to sites
Safety Reporting

Serious Adverse Events

Definition of a Serious Adverse Event (SAE) or Serious Transfusion related Adverse Reaction

Respectively, any adverse event, adverse transfusion reaction or unexpected adverse transfusion reaction that:

1. Results in death
2. Is life-threatening*
3. Requires hospitalisation or prolongation of existing hospitalisation**
4. Results in persistent or significant disability or incapacity

*The term ‘life-threatening’ in the definition of ‘serious’ refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition (including elective procedures that have not worsened) do not constitute an SAE.
Serious Adverse Events

• Only SAEs and Transfusion related SAEs, not AEs
• Should be reported up to hospital discharge or day 28, whichever is sooner
• Form to be completed and reported within 24 hours of becoming aware
• Also complete narrative form for additional information - send with SAE form ideally but max. 5 days after first report
• Send via email to NHSBT CTU
Serious transfusion related adverse events

• Any untoward and unintended response to a transfused blood component
• Should be reported up to hospital discharge or day 28, whichever is sooner
• Report locally as usual (SHOT etc.)
• Completed forms and report within 24 hours of becoming aware, narrative in max. 5 days
• Send via email to NHSBT CTU
Serious breaches

- A 'serious breach' is a breach that is likely to affect to a significant degree: the safety or physical or mental integrity of the participants; or the scientific value of the trial.
- Report immediately of becoming aware to CTU by phone AND email
- Do not wait for local investigations to be complete
- Examples include drug or blood product errors, failures of local Trust policies
- CTU will work with sites to resolve issues
Top Tips

• Provide local checklists or guides to help clinical teams identify appropriate patients
• If no approximate time of injury is known, use time of 999 call
• Use the annual training updates for refresher training and for new staff – must be evidenced
• Teams may wish to “run-in” the study to iron out any local issues
• Work closely with blood bank staff and TARN Coordinators
• Contact us with any queries
Any Questions?

Twitter @CRYOSTAT_2
Email CRYOSTAT2@nhsbt.nhs.uk
Website www.cryostat2.co.uk