EVIDENCE REPORT

Fibrinogen administration in prehospital trauma

Review of literature and key findings

MARCH 2022

Contents

NSW GOVERNMENT | AGENCY FOR CLINICAL INNOVATION

NSW Institute of Trauma and Injury Management

Agency for Clinical Innovation
1 Reserve Road St Leonards NSW 2065
Locked Bag 2030, St Leonards NSW 1590

T +61 2 9464 4666 | F +61 2 9464 4728
E aci-info@health.nsw.gov.au | www.aci.health.nsw.gov.au

Produced by: NSW Institute of Trauma and Injury Management

Further copies of this publication can be obtained from the Agency for Clinical Innovation website at **www.aci.health.nsw.gov.au**

Disclaimer: Content within this publication was accurate at the time of publication.
This work is copyright. It may be reproduced in whole or part for study or training purposes subject to the inclusion of an acknowledgment of the source. It may not be reproduced for commercial usage or sale. Reproduction for purposes other than those indicated above, requires written permission from the Agency for Clinical Innovation.

Preferred citation: NSW Agency for Clinical Innovation. *Fibrinogen administration in prehospital trauma: Evidence report.* Sydney: ACI; 2022.

SHPN (ACI) 190381
ISBN 978-1-76081-210-2

Version: V2; ACI_3942 [02/22] Date amended: March 2022
Review Date: 2027

Trim: ACI/D19/2182

© State of New South Wales (NSW Agency for Clinical Innovation) 2022.
Creative Commons Attribution No derivatives 4.0 licence.
Exclusions from Creative Commons licence, which may not be reproduced without express permission: the ACI logo, and the icons on p.1, which are used here under commercial licence.

Fibrinogen administration in prehospital trauma

Evidence at a glance

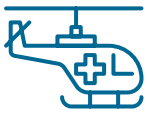
Fibrinogen concentrate (FC) is freeze dried fibrinogen, a vital clotting factor. This report considers if FC is a reasonable alternative to allogeneic products in the prehospital setting by examining the literature regarding patient mortality, intensive care unit (ICU) length of stay, safety, need for additional blood products, storage, administration and costs.

1.

Patients with traumatic critical bleeding usually require replacement of clotting factors with donor (allogeneic) blood products.

2.

Allogeneic blood products may not be available in the prehospital setting, particularly in regional and rural areas where the time to definitive trauma care is usually longer than in metro areas.



3.

This report looks at evidence for whether FC could be provided for treatment in the prehospital setting, e.g. Helicopter Emergency Medical Services (HEMS).

Key points in the report

- Current published evidence is low quality.

- Suggests FC in hospital setting is safe and effective.

- Logistic advantages for FC with storage, preparation and more rapid administration.

Outcomes

In the absence of allogenic products, FC could be considered as a reasonable prehospital alternative. This is best conducted under clinical trial conditions.

Executive summary

In NSW, standard trauma management for critical bleeding involves replacing clotting factors with donor (allogeneic) blood products, including cryoprecipitate, platelets and fresh frozen plasma (FFP). These are readily available in many hospitals. However, they may not be available in the prehospital setting, particularly in rural and remote NSW. People injured in rural and remote areas may face long delays to definitive intervention in a trauma centre. It has been proposed by senior clinicians that NSW Ambulance (NSWA) Helicopter Emergency Medical Service (HEMS) teams be equipped with fibrinogen concentrate (FC) to treat coagulation derangements where allogeneic products are not available.

This document is the NSW Institute of Trauma and Injury Management (ITIM) Trauma Innovation Committee (TIC) review of the evidence on FC for the treatment of trauma-related critical bleeding in the prehospital context, as well as the role fibrinogen replacement plays in critical bleeding generally. It presents a review of the available literature on fibrinogen replacement with regards to:

- patient outcomes of mortality
- intensive care unit (ICU) length of stay
- safety, risks and the need for additional blood products
- the logistical issues of product storage
- administration and costs
- the potential role that FC could play in the prehospital setting.

Critical bleeding from traumatic injury causes derangements in coagulation and has a direct relationship to mortality.[1, 2] Fibrinogen is a pivotal clotting factor. It is the first clotting factor to fall to critical low levels following haemorrhage. Low levels are associated with poorer outcomes, and are an independent predictor of mortality.[3-6]

However, survival is associated with fibrinogen replacement.[7-12] Clotting factor replacement using cryoprecipitate and FFP is integral to managing bleeding in traumatic injury.[7-13] In the major hospital setting, these products are easily obtained and are part of the standard management of traumatic injury. However, in the prehospital setting, these allogeneic products are not generally available, particularly in rural and remote NSW.

The literature and general consensus support that FC in the hospital setting is considered safe and efficacious and is likely to have similar positive benefits in the prehospital setting. However, although there is some evidence supporting the use of FC in critically-bleeding patients, the use of allogeneic products remains the clinical standard of practice.

In the absence of allogeneic products to manage critical bleeding in the prehospital context, there is a likelihood of poorer outcomes and FC may be a reasonable alternative. Further to this, due to the lack of high-level evidence supporting the prehospital use of FC, any intention of regularly administering prehospital FC is best done under clinical trial conditions.

Introduction

In Australia, injury is a leading cause of death, illness and disability.[14] Haemorrhage is responsible for over 35% of prehospital deaths, and over 40% of deaths within the first 24 hours.[15] The majority of these deaths are considered preventable with the right treatment available at the right time.

Managing patients with trauma-related critical bleeding in rural and remote NSW is particularly challenging when compared with metropolitan areas.[16] People who are injured in these areas face prolonged delays to definitive surgical trauma care because of both their physical distance from a trauma service, and the protracted transport and scene times that accompany helicopter and fixed wing transfers.

As a result, treating clinicians rely more heavily on blood products to manage haemorrhage, aiming to sustain life until surgical haemostasis can be achieved. In the prehospital setting, allogeneic blood products are difficult to obtain, and without them, these patients are at higher risk of a poor outcome.

NSW ITIM, an institute within the Agency for Clinical Innovation (ACI), is the body responsible for overseeing, coordinating and supporting the NSW trauma system. ITIM is supported by five committees of senior trauma clinicians, one of them being the TIC. The TIC provides clinical subject matter expertise on project feasibility, desirability, execution, and implementation to the ITIM executive. It also assists with communicating ITIM initiatives to the trauma network.

This document is the NSW ITIM TIC's review of the evidence for fibrinogen replacement for critical bleeding in trauma, in the form of allogeneic products (cryoprecipitate, FFP, and platelets) and the non-allogeneic product, FC. It addresses the potential role that FC could play in the prehospital setting.

Method

Question design

This report looked at published evidence regarding suitability of FC for prehospital use. The question was framed: "Is FC administration a reasonable alternative in the absence of cryoprecipitate when clinically indicated in the prehospital context?"

Document structure

There are two main components in this review:

1. Examination of the current worldwide evidence on FC, with a focus on safety, efficacy, mortality, ICU length of stay, need for additional blood products, serum fibrinogen response and cost.
2. The response to the above question based on evidence reviewed and expert consensus.

Who is this document for?

This document is designed for prehospital clinicians and their governing authorities who are considering FC as an option in the management of traumatic critical bleeding, where allergenic blood products are not available. It is focused on NSW but could be applied to other jurisdictions and contexts.

Search methodology

Literature was attained by searching the PubMed database, using the following search terms; "Fibrinogen concentrate", "trauma" and "prehospital". The term "prehospital" limited the search to six results. To increase the sensitivity, prehospital was removed. Additional limits were set including papers published 2005–2021 as of September 2021 and only written in English resulting in 132 articles.

Other articles are referenced in this document, that were not part of the initial search. These are listed in the references section.

Background

Coagulopathy in trauma

Major haemorrhage can cause acute coagulation abnormalities. Acute traumatic coagulopathy (ATC) is a profound and complex derangement of the coagulation system that occurs in response to major trauma. It results in catastrophic bleeding, occurs within minutes of injury and is associated with a mortality rate of 25-40%.[1, 2]

Clotting factors are considered integral to managing bleeding in traumatic injury.[13] In critical bleeding they are administered alongside red blood cells to provide a balanced replacement of blood and to manage ATC.[13] The National Blood Authority (NBA) recommends that use of massive transfusion protocol (MTP), including the dose, timing and ratio of blood component therapy, is associated with reduced mortality.[13] Within the hospital environment, MTPs have been widely adopted and proven to have short and long term survival benefits in critical bleeding.[17]

Fibrinogen is a key clotting factor. It is produced in the liver at a rate of 2-5g per day, with normal plasma levels being 2-4.5 grams per litre (g/L). Fibrinogen is converted to fibrin after being activated by tissue and vascular injury or bleeding.[18] It creates a crosslinked mesh to hold platelet plugs together, occluding blood vessels and arresting excessive bleeding.[19]

In critical bleeding, serum fibrinogen falls quickly to dangerous levels, much faster than red blood cells do.[10] Low fibrinogen is associated with poorer outcomes and is an independent predictor of mortality in patients with severe trauma.[3-6] Treating low fibrinogen is considered to be highly important in the management of critical bleeding. Evidence suggests that supplementing fibrinogen early increases survival through improvements in coagulation.[7-10, 12, 20]

A review of the literature in relation to fibrinogen replacement, found that internationally there are variations in the recommendations about the levels at which to replace fibrinogen in critically-bleeding patients.

Recommendations for levels where fibrinogen should be replaced include:

- The NBA and Canadian guidelines recommend replacing at less than 1g/L.[21]
- The European trauma guideline recommends replacing at ≤1.5g/L.[22]
- Hagemo et al. recommend replacing at less than 2.29g/L.[23]
- In obstetric patients with postpartum haemorrhage, replacement is recommended at less than 2g/L.[24]

The likelihood of death within 28 days of trauma-related bleeding was reduced by 0.08% with every unit increase in fibrinogen concentration. This highlights that the negative impact of low fibrinogen concentrations may still be underestimated in daily trauma care when compared to current guidelines.[23]

Clotting factor replacement

In Australia, the allogeneic products used to replace clotting factors are cryoprecipitate, FFP, extended life plasma (ELP) and platelets. Non-allogeneic products available in NSW are FC, prothrombin complex and other single factor preparations. Fibrinogen supplementation, specifically, is provided by transfusion of FFP or ELP, cryoprecipitate or FC (only congenital conditions and approved trials). These products are described below.

Allogeneic clotting factors

Fresh frozen plasma (FFP)

- FFP is the liquid portion of whole blood made either from apheresis plasma, or by depleting whole blood of all blood cells. One unit of FFP contains all of the coagulation factors.[25]
- FFP is used to treat trauma patients requiring replacement clotting factors, patients on blood thinning medications to reverse the effects, and to replace missing plasma proteins or other substances.[25]
- FFP contains anti-A and anti-B antibodies, and therefore must be type-matched to the patient. FFP can be stored for 12 months at or below -25°C.[25]
- FFP is not recommended to correct hypofibrinogenemia due to its high volume and relatively low fibrinogen levels.[26]

Extended life plasma (ELP)

- ELP has similar characteristics and therefore clinical utility to FFP and in most cases can be considered a complementary component.[27]
- ELP is thawed FFP which can be stored up to 5 days at temperatures 2-6°C.[27]
- Advantage of ELP is it is available immediately for emergency use.[27]
- ELP has been implemented in several NSW retrieval services after the PAMPer study.[28]
- ELP is not recommended to correct hypofibrinogenemia due to its high volume and relatively low fibrinogen levels.[29]

Cryoprecipitate

- Cryoprecipitate is a concentrated blood component made from FFP. Cryoprecipitate contains blood clotting proteins, including fibrinogen, factors VIII and XIII, and von Willebrand factor. One unit of cryoprecipitate contains greater than or equal to 140mg of fibrinogen.[25]
- Cryoprecipitate is used to treat patients with low or poorly functioning clotting proteins, particularly fibrinogen, and particularly in the context of bleeding, invasive procedures or trauma.[25]
- Cryoprecipitate can be stored for 12 months at or below -25°C. Once thawed, it must be stored at 20-24°C until transfusion, and then used within 4-6 hours.[25]
- Cryoprecipitate is the accepted treatment for fibrinogen replacement in critical bleeding but similar to FC, is only supported by low level evidence.[3, 4, 13] Jensen et al. stated in their systematic review that there was limited evidence comparing FC to cryoprecipitate and concluded it was not possible to recommend one product over another. [30]

Platelets

- Platelets are fragments of megakaryocyte cells and are obtained by separating them from whole blood or through apheresis. Platelets are activated by chemicals that are released from damaged tissue. Following activation, they change shape, clump together and stick to damaged tissue. This ‘platelet plug’ begins the process of clot formation and bleeding control.[18]
- Platelet transfusions are used to treat patients with low or non-functioning platelets, who are bleeding or at high risk of bleeding, and who are unlikely to make their own platelets in a timely manner.[25]

- Platelets are stored at room temperature, between 20-24°C. As a result, they are at a higher risk of bacterial contamination and have a shelf life of only seven days. A unit of platelets needs to be constantly rocked during storage to prevent the platelets clumping together.[25]

Access to allogeneic clotting factors

- In the hospital setting in NSW, allogeneic clotting factors are obtained through local blood banks and are administered as part of a standard management strategy for trauma-related critical bleeding.
- Only a relatively small number of NSW public hospitals hold allogeneic clotting factors (i.e. approximately 40 of 220 hospitals hold FFP).
- In the prehospital setting, allogeneic clotting factors are obtained, when available, from local network blood inventories via an agreement between NSW Health Pathology and the NSWA HEMS, known as the Retrieval Transfusion Procedure (RTP).[31]
- Some NSW HEMS teams have begun carrying limited quantities of ELP. This appears to be dependent on local arrangements and capacity of the supplying blood bank. Regional HEMS teams are not likely to have access to ELP.
- Despite having the RTP and ELP, NSWA HEMS teams continue to report difficulties in obtaining enough products for trauma patients, particularly in rural and remote NSW. In rural and remote NSW, FFP, cryoprecipitate and platelets are not held in every blood inventory. Where they are held, the specifications about product storage, preparation and transfer distances limit the number of units available for prehospital patients. Furthermore, as these products are shared between the NSWA HEMS and the local hospitals, there can be negative flow-on effects if in-hospital patient demands are not met when blood products are allocated to a NSWA HEMS.

Non-allogeneic clotting factors

Prothrombin complex

- Prothrombin complex is a non-allogeneic clotting factor derived from plasma.[32]
- It is used in the prevention and treatment of bleeding in patients with acquired prothrombin complex factor deficiency, requiring partial or complete reversal (e.g. reversal of warfarin anti-coagulant therapy). It is also recommended for the prevention and treatment of bleeding in patients with single or multiple congenital deficiency of factor II, IX and X. It is not routinely administered as a substitute for FFP.[32]

Fibrinogen concentrate

- FC is a non-allogeneic clotting factor. It is a freeze dried lyophilised preparation of fibrinogen. One glass vial contains 900mg of fibrinogen and is administered in doses of 4-8g.[33] A dose of 4g increases serum fibrinogen levels by approximately 1g/L.[34]
- FC is used to replace fibrinogen.
- FC is stored at 2-8°C and has a five-year shelf life from the date of manufacture.[35]
- If the product has been taken from cold storage, and then not required, the product should be returned to cold storage as soon as possible. Reuse of the unconstituted material is acceptable if the material is not out of cold storage for more than six days or exceed 40°C at any time.[34]

Access to non-allogeneic clotting factors

- In Australia, FC is registered under the product name "RiaSTAP: human fibrinogen 1g powder for injection vial". It is approved under the Therapeutic Goods Act (TGA) for the treatment of acute bleeding episodes in patients with the congenital fibrinogen deficiencies of afibrinogenaemia and hypofibrinogenaemia.[35, 36] It is used under a clinical trials framework (i.e. Fibrinogen Early In Severe Trauma Study (FEISTY) trial), and currently used off label in MTPs such as in the Queensland Health Service.[37, 38]
- Internationally, several European countries began using FC in the 1990s after a rise in infections from allogeneic blood products led to a desire for risk-free alternatives. Post-marketing surveillance at the time demonstrated overall product safety, and in certain countries, such as Germany, FC has remained the only fibrinogen product available to treat low fibrinogen of any form. In these countries, FC is also considered standard therapy for major trauma patients requiring a MTP.[39] FC was used in the reversal of trauma-induced coagulopathy (RETIC),[40] randomised trial evaluating the use of prothrombin complex concentrate to improve survival in patients with traumatic coagulopathy (REPLaCE)[41] and zero-plasma trial (ZEPLAST)[42] trials internationally.

Literature review

A review of the literature available on fibrinogen replacement (FC and allogenic products) was undertaken, particularly looking at patient outcomes of mortality, ICU length of stay, safety, risks and the need for additional blood products. The literature review also considered logistical issues of product storage, administration and cost to the health system. These outcomes are presented below. In NSW, most trauma patients with critical bleeding in the prehospital setting do not receive clotting factors. The outcomes should therefore be considered in this context.

In a 2014 systematic review by Lunde et al., there was beneficial evidence of the use of FC in the hospital setting, with a significant reduction in bleeding and transfusion requirements.[43] However, mortality data was lacking and the standard use of fibrinogen across all settings was only supported by non-randomised studies with methodological shortcomings. The authors concluded that the general use of FC appears premature in the management of bleeding and coagulopathic patients and suggests more studies in this field are required.

The FEISTY and RETIC trials are particularly relevant to this review as they are the first randomised controlled trials to compare FC to an allogeneic product in severe traumatic haemorrhage. FEISTY compared cryoprecipitate to fibrinogen concentrate, and RETIC compared FC to FFP. The results of the RETIC and FEISTY trials are highlighted below for this reason. Please note the FEISTY trial was not powered for secondary outcomes (i.e. results related to mortality, ICU and hospital length of stay were only hypothesised by the author).

Of particular interest is the Ziegler et al. randomised controlled trial (RCT) (n=53), which studied FC administration in prehospital trauma patients, examining clot stability in patients bleeding or presumed to bleed.[44] The FC arm (n=28) was compared against the placebo arm (n=25) by measuring clot stability using fibrin-based thromboelastometry (FIBTEM) assay, before and after intervention. The fibrinogen arm results suggest greater protection against early fibrinogen depletion, promoting rapid blood clot initiation and clot stability when administered compared to the placebo arm. This study also suggests that prehospital administration of FC to severely injured patients is feasible. Mortality, ICU length of stay and need for additional blood products were not study end points for this trial.

Mortality

Only a few studies report on mortality, with either a placebo or an allogeneic product as the comparator to FC.

A feasibility study compared FC to placebo in the treatment of ATC. It showed no significant difference in 28-day mortality rate between the two groups.[45]

Of the three systematic reviews found, two were powered to study mortality outcomes (Mengoli et al.[46] and Stabler et al.[47]) and one was not (Jenson et al.[30]). Mengoli et al. examined the role of FC in ATC, and its impact on mortality. It found no statistical difference between FC and allogeneic blood products on mortality. However, the author commented that the quality of the data was poor, and that further randomised controlled trials would assist with determining the exact role of FC in trauma-related critical bleeding.[46] Stabler et al. examined the efficacy and safety of pre-emptive and goal-directed FC in the management of trauma-related haemorrhage and concluded there was no statistically significant difference in mortality between the fibrinogen and comparator arms.[47]

The RETIC trial compared FC with FFP and reported no significant difference on mortality.[40] However, the trial was terminated early for futility and safety reasons because of the high proportion of patients

in the FFP group who required rescue therapy compared with those in the FC group.

Itagak et al. conducted a single-centre retrospective study and concluded that severe trauma patients (ISS≥16) who received FC within the first hour of emergency department (ED) admission had a significant higher in-hospital survival rate than the control who didn't receive FC.[48]

Hamada et al. noted in their propensity score analysis that FC given within six hours of traumatic haemorrhagic shock did not decrease the 24-hour all-cause mortality.[49]

The FEISTY study looked at the early replacement of fibrinogen in patients with traumatic haemorrhage, comparing the use of FC to cryoprecipitate. Higher mortality was shown in the FC arm. However, the author did note that there were limitations with this outcome due to the baseline group not being entirely balanced. It was noted that 50% of deaths in the FC arm related to unsurvivable head injury, all of which had a pre-hospital Glasgow Coma Scale (GCS) scores of 3 and very likely to have a poor outcome.[50]

Conclusion: There is only a small evidence base regarding survival outcomes for FC in trauma patients, and no strong evidence to suggest FC has additional mortality benefits when compared with allogeneic products.

Intensive care unit and hospital length of stay

Four retrospective studies demonstrated that patients who were given FC spent less time in an ICU than those who received allogeneic products.[41, 51-53]

A study by Schochl found no difference in ICU length of stay but did find a difference in hospital length of stay. Patients who received FC stayed a median 23 days, compared with 32 days for those receiving allogeneic products.[53]

The RETIC trial did not demonstrate statistical differences in ICU or hospital length of stay for patients who received FC, when compared with allogeneic products.

The FEISTY trail had a shorter ICU length of stay: 3.7 (FC) versus 7.7 (cryo) versus 2.9 (neither) days and a shorter hospital length of stay in the FC group: 12 (FC) versus 22 (cryo) versus 14 (neither) days.

Conclusion: There is low level evidence that FC reduces either ICU or overall in-hospital length of stay when compared to allogeneic products.

Need for additional blood products

The National Safety and Quality Health Standards (NSQHS) – Standard 7: Blood and blood products notes the importance of avoiding unnecessary transfusions and the recommended strategies for reducing the need for transfusion, due to the risk that allogeneic blood transfusions pose to patients.[54] The standard highlights that incremental increases of blood products correspond to an increased risk in mortality and various morbidities.[54]

Studies by Rahe-Meyer and Nienaber found there was a reduction in allogeneic transfusions of red blood cells (RBCs), platelets and FFP for patients who received FC.[52, 55]

Schochl's retrospective analysis compared FC and prothrombin complex concentrate (PCC) to a standard FFP-based therapy.[53] In examining the need for red blood cells (RBCs) post administration, Schochl found that significantly more patients in the FFP group required a RBC and/or platelet transfusion than the FC and PCC group.[53]

The RETIC trial found that patients treated with FC received fewer RBC transfusions than those treated with FFP.[40] Furthermore, it found that patients who did not receive FC were more likely to receive a massive transfusion and platelets.[40]

Itagak et al. observed that the FC group had significantly higher amounts of transfusions during the first six hours after ED arrival, although the FC and control groups had similar total amounts of transfusions (RBC, FFP and PC) between 6 hours and 24 hours after ED arrival.[48]

The FEISTY trial revealed that blood product transfusion and fluid resuscitation were similar in both FC and cryoprecipitate arms.[50]

Stabler et al. revealed there was no statistical difference between FC and control in packed RBC, fresh frozen plasma, or platelet transfusion requirements and thromboembolic events.[47]

Conclusion: There is evidence to suggest that FC may reduce the overall need for blood products, and that there is a reduction in both patient risk and health system costs associated with this.

Serum fibrinogen response

One study by Jensen et al. demonstrated that there were increases in fibrinogen levels and reduced bleeding after equivalent doses of FC and cryoprecipitate; however, FC was not superior to cryoprecipitate with these markers.[30]

A systematic review by Kozek-Langenecker et al. compared four studies looking at the clinical effectiveness of FC and FFP. The review found that following administration, plasma fibrinogen levels were significantly higher in the FC group than in the FFP group (control). However, at the subsequent assessment point, there was no significant difference between the groups.[56]

The FEISTY trial revealed that FC was more rapidly delivered compared to cryoprecipitate, with fibrinogen levels increased appropriately in either product.[50] Seebold et al. also echoes FEISTY regarding FC's rapid delivery to replace fibrinogen in severe traumatic haemorrhage compared to allogeneic products.[57]

Conclusion: There is evidence to suggest FC can achieve faster results in critical bleeding compared to FFP and cryoprecipitate, and it behaves similarly to allogeneic products in terms of uptake and return to baseline levels.

Safety

A comparison between FC and allogeneic clotting factors for several clinical safety markers is described below and presented in Table 1. The clinical safety markers compared include:

- cross-infection
- haemolytic and transfusion-related acute lung injury (TRALI)
- transfusion-associated circulatory overload (TACO)
- ABO/Rh incompatibility
- adverse drug reactions and the requirement for rescue therapy.

Allogeneic clotting factors used to replace fibrinogen (FFP and cryoprecipitate) carry a risk, though this is relatively low, of causing life-threatening reactions. According the Australian Red Cross Blood Service, the incidence of ABO/Rh incompatibility is 1:40,000 transfusions.[58] Types of reactions include, haemolytic transfusion reactions, transfusion-transmitted bacterial or viral infection, anaphylaxis, TRALI and TACO.[58]

FC is a pasteurised, pathogen-inactivated product, with antigens and antibodies removed. Compared to allogeneic products, this process theoretically reduces the chance of cross-infection and TRALI.[58] Furthermore, FC is administered in smaller volumes than allogeneic clotting factors, and is therefore associated with a lower risk of TACO.[59]

The literature and pharmacovigilance studies reported an overall low rate of adverse events with FC.[60]

A study by Solomon et al. reviewed post-marketing safety reports and clinical studies published between 1986 and 2013, looking at the incidence of adverse drug reactions. The study found 383 adverse drug reactions out of 652,824 occasions where patients had been treated with a standard dose (4g) of FC, with variations in clinical indications and settings. Solomon noted that 106 of these may have been attributed to a hypersensitivity reaction, thromboembolic event or virus transmission.[60] He concluded that FC has a promising safety profile, with few adverse drug reactions and low thromboembolic events following administration for a range of indications.[60]

The RETIC trial compared the difference between FC and FFP in reversing ATC. The trial terminated early after a disproportionately high number of patients in the FFP group required rescue therapy,[40] suggesting that FFP carries additional clinical risks compared to FC when used in reversing ATC.

The FEISTY trial had similar thromboembolic complications in both FC and cryoprecipitate arms.[50]

Overall, FC is found to have a consistent safety profile with few adverse drug reactions (ADRs) documented in most studies.

Conclusion: There is evidence to suggest that FC has safety benefits over the allogeneic products FFP and cryoprecipitate.

Table 1: Theoretical risks and clinical differences of cryoprecipitate and fibrinogen concentrate

Product risks	Cryoprecipitate	Fibrinogen concentrate
ABO mismatch	Potential	No
Plasma-associated adverse events (e.g. TRALI)	Potential	No
Thromboembolic risk (high dose) Excess factor VIII, von Willebrand factor Excess fibrinogen	Potential Not if target concurrent dosing	No Not if target concurrent dosing
Recorded thromboembolic (AE)	Potential risk	Very rare (3.5 / 10 dose episodes)[5]
Clinical differences		
Inventory management	Frozen stocks of ABO-specific	Single product at 2-8°C
ABO cross-matching	Yes, unless AB cryo available	No
Time to correct hypofibrinogenaemia	Order/thaw/documentation/ infusion time (60 min)	On-site stocks, rapid reconstitution (5-10 min) and infusion (20 sec/1g)
Group AB patients with high fibrinogen requirements	Supply issue with risk of non-AB product use	Non-issue
Donor source	Single donor units, Australia	Pooled donor product, USA, and Germany
Pathogen inactivation	No	Yes
Product purity	Crude factors in residual plasma	Purified in buffers and albumin
Factor VIII	Yes	No
vWF	Yes	No
ABO matching required	Yes	No
Storage	Frozen (<-25°C)	Lyophilised, 2-8°C
Shelf life	12 months	60 months
Preparation	Product request, thaw or warm	Reconstitute at room temp

Product storage

See Appendix 1.

Product administration

Fibrinogen is currently replaced using FFP, cryoprecipitate or FC. Collins' modelling tool of fibrinogen supplementation (summarised in Table 2) is a theoretical comparison of the number of units or vials, and the volume required of FFP, cryoprecipitate or FC, to increase plasma fibrinogen levels by approximately 1g/L.[29]

Table 2: Collins' modelling tool of fibrinogen supplementation[29]

	Fresh frozen plasma	Cryoprecipitate	Fibrinogen concentrate
Amount (unit or vial)	28 units	33 units	5 vials
Volume (ml)	7,000	412.5	250
Resultant fibrinogen level (g/L)	1.70	1.71	1.78

The Collins modelling tool highlights some advantages of FC over FFP and cryoprecipitate for patients requiring fibrinogen supplementation, including:

- smaller fluid volumes required for comparable effect, thus reducing the risk of volume overload
- easier and faster preparation – reconstitution 5 vials of FC at point of care verses defrosting 28 to 33 units of FFP or cryoprecipitate respectively at a blood bank
- potential faster preparation to delivery time.

Cost to the health system

FC is comparatively more expensive than cryoprecipitate. However, evidence above suggests that FC may reduce the overall need for blood products. There is a reduction in health system costs associated with this.

Table 3: Costs of providing a 3g dose of either fibrinogen concentrate or cryoprecipite

Product	Dose	Units	Cost
Whole blood cryoprecipitate	3g *	10	$1,650
Fibrinogen concentrate	3g	3	$2,355

*Fibrinogen levels in cryoprecipitate are approximate values only due to natural variation of individual donors. Costing information is from NBA's National product price.[33]

Note: A standard dose of FC, according to the Australian Red Cross Lifeblood, in patients with critical bleeding requiring massive transfusion, is 3-4g.[25]

PAMPer study and extended life plasma (ELP)

The PAMPer study was a multicentre, cluster-randomised trial (n=501), examining ELP in aeromedical transport and its potential benefits to outcomes of trauma patients at risk of haemorrhagic shock. The results demonstrated a 10% reduction in mortality at 30 days associated with the ELP group, when compared to the standard treatment arm.[28] The study included both interhospital transfers and primary retrieval transports with transport times ranging from 39 to 52 minutes. A smaller study by Moore et al. (n=144) was stopped for futility with no survival benefit associated with ELP administration in prehospital ground transport.[61] In this study, transport times were significantly shorter at around 16 to 19 minutes. There are important implications regarding the PAMPer results for NSW, and consequently, several HEMS services now carry ELP.

Summary of key findings

HEMS teams manage patients with trauma-related critical bleeding for prolonged periods, in changing conditions, and often without enough blood products to sustain life whilst transferring patients to a hospital able to provide definitive surgical or radiological intervention. For this reason, HEMS teams may not be able to manage traumatic bleeding in accordance with treatment recommendations by the NBA or routine hospital protocols.

Although cryoprecipitate is considered the standard treatment for fibrinogen replacement in Australia and NSW, it is only evidenced by low level or comparable evidence.[3, 4] Little evidence was found reviewing the use of FC in the prehospital setting, but there was evidence available in the in-hospital setting. This report considered the question of whether FC is a reasonable alternative in the absence of allogenic products such as cryoprecipitate in the prehospital trauma setting, and the evidence for this use is summarised below.

The following evidence on fibrinogen replacement in the trauma setting is available:

- Bleeding is a leading cause of preventable mortality in trauma, and serum fibrinogen drops rapidly in traumatic bleeding.[3, 10]
- Low serum fibrinogen is associated with increased mortality.[6, 57, 62]
- Early replacement of fibrinogen in critical bleeding is well supported[13] and associated with improved outcome.[7-12]
- FFP and ELP are limited sources for fibrinogen replacement.[29]
- Evidence was found on FC comparing its use to allogeneic products.[37, 40] However, no high-level studies were available comparing FC to placebos.
- Although research into the use of FC for the management of critical bleeding is ongoing, to date only low level randomised controlled trials were found to have reviewed its efficacy.[43]

Evidence availability on FC use in the trauma setting is as follows:

- FC has been used for three decades in Europe, with post-market research reporting it to be safe.[60]
- Both FC or cryoprecipitate is recommended in the European guideline on management of major bleeding and coagulopathy following trauma.[26]
- The efficacy of FC is comparable to cryoprecipitate with current evidence deliberating on recommending one product over another.[30]
- Cryoprecipitate is the standard treatment for fibrinogen replacement in Australia in critical bleeding.[41, 42]
- Whilst FC is required to be stored between 2 and 8°C,[34] it doesn't require the same cold chain storage conditions and preparation when compared to other blood products, making it more suited to the prehospital environment than allogeneic clotting factors.[18, 25]
- Administration of FC is associated with a reduced need for red blood cell transfusions, when compared to allogeneic products.[40, 52, 53, 63]

- Where a patient receives clotting factors, there is currently no evidence to suggest that FC has a survival benefit over allogeneic clotting factors.[30, 46, 51]
- There is only modest evidence that FC reduces ICU length of stay, when compared to allogeneic clotting factors.[53]

Expert consensus regarding the answer to the question: Is FC administration a reasonable alternative in the absence of cryoprecipitate when clinically indicated in the prehospital context?

- The beneficial effects of FC are still debated, mainly because of low quality published clinical evidence, especially in the paediatric population, and currently there is an insufficient basis for therapeutic or prophylactic guidelines.
- Current evidence suggests FC in the hospital setting is considered safe and efficacious when compared to similar allogenic products. FC has a relatively long safety record, and therefore, is likely to have similar positive benefits in the prehospital setting.
- FC has logistic advantages in storage conditions, space occupancy and preparation, and can be administered more rapidly than cryoprecipitate, making it amendable to field use over comparable allogenic products.[50]
- The standard treatment of administering allogeneic products (i.e. cryoprecipitate) for critical bleeding is supported as the first choice. However, in the absence of allogeneic products, the consensus is that FC could be considered as a reasonable alternative in the prehospital setting.

In the absence of high-level evidence, prehospital administration of FC is best conducted under clinical trial conditions.

Acknowledgements

NSW Institute of Trauma and Injury Management (ITIM)

Mr Jonathan Newman, Project Officer (Secretariat TIC)

Ms Kelly Dee, Clinical Review Officer

Mr Glenn Sisson, Manager

Mr Pooria Sarrami, Research Fellow

Dr Michael Dinh, Clinical Director

Trauma Innovation Committee (TIC)

Mr Dwight Robinson, Disaster Manager, South Western Sydney LHD (LHD) (Co-Chair TIC)

Dr Yashvi Wimalasena, Consultant, NSW Ambulance (Co-Chair TIC)

Mr Jonathan Newman, Project Officer (Secretariat TIC)

Professor Herwig Drobetz, Trauma Director, Northern NSW LHD

Mr Adam Parker, Intensive Care Paramedic, NSW Ambulance

Dr Alan Garner, Staff Specialist, Trauma Director, Nepean Blue Mountains LHD

Mr Alex Peters, Special Operations Paramedic, NSW Ambulance

Mr Christopher Ennis, Critical Care Paramedic, NSW Ambulance

Ms Gayle Van Zyl, Flight Nurse, NSW Air Ambulance

Mr Giles Buchanan, Extended Care Paramedic, NSW Ambulance

Ms Jessica Keady, Nurse Manager, Patient Flow and Transport Unit, Western NSW LHD

Ms Julie Friendship, Paediatric Clinical Nurse Consultant, Prince of Wales Hospital

Matthew Oliver, Emergency Department Co-Director, Sydney LHD

Mr Nick Cockrell, Flight Nurse, NSW Air Ambulance and Emergency Nurse, Northern Sydney LHD

Dr Torgrim (Tom) Soeyland, Staff Specialist, Mid North Coast LHD

Ms Nicole Altmann, Trauma Case Manager, South East Sydney LHD, St George Hospital

External Consultation

We would like to thank the following external peer reviewers who provided feedback and advice:

- Dr Gary Tall, Medical Retrieval Manager, NSW Ambulance
- Dr Brian Burns, Director of Research, Greater Sydney Area HEMS
- Rural and Remote Blood Products Working Group, NSW Ministry of Health
- Dr SV Soundappan, Head of Trauma, Sydney Children's Hospital
- Blood and Blood Governance Committee:
  - Dr Phillip Mondy, Haematologist, Australian Red Cross Lifeblood.
  - Dr Mark Dean, Haematologist, Clinical Lead Transfusion, NSW Health Pathology
  - Dr Jan Fizzell, Senior Medical Advisor, Office of the Chief Health Officer
- Australian Red Cross Lifeblood
  - Dr Wayne Dyer, Senior Research Fellow, Australian Red Cross Lifeblood

Conflict of interest and declarations

TIC members and ITIM staff have declared they have no affiliations, conflicting or financial interests associated with the commercial aspects of fibrinogen concentrate.

Glossary

ADR	Adverse drug reaction. A response to a drug which is noxious and unintended, and which occurs at doses normally used.
ATC	Acute traumatic coagulopathy. An endogenous coagulation abnormality directly induced by trauma and or shock. It differs from indirect mechanisms of shock, such as hypothermia, metabolic acidosis and dilutional coagulopathy, and is associated with increased mortality.
Critical bleeding	A major haemorrhage that is life threatening and likely to result in the need for massive transfusion.
Cryo	Cryoprecipitate made from fresh frozen plasma. It contains proteins, including fibrinogen, that are involved in blood clotting. It is used when a person has reduced levels of fibrinogen or where their fibrinogen is not working properly.
ELP	Extended life plasma. Thawed fresh frozen plasma that can be stored between 2-6°C for up to five days.
ED	Emergency department
FC	Fibrinogen concentrate. A pasteurised drug stored as a lyophilised powder at room temperature, used to supplement plasma fibrinogen.
FEISTY trial	Fibrinogen Early In Severe Trauma Study. A pilot multi-centre randomised controlled trial comparing FC to cryoprecipitate for fibrinogen replacement in severely injured trauma patients. Performed at four major trauma centres in Queensland, Australia.
FFP	Fresh frozen plasma. A unit of blood product that contains all of the coagulation factors.
HEMS	Helicopter Emergency Medical Service
ICU	Intensive care unit
ITIM	Institute of Trauma and Injury Management
Massive transfusion	Defined, in adults, as replacement of >1 blood volume in 24 hours or >50% of blood volume in 4 hours (adult blood volume is approximately 70mL/kg).
MTP	Massive transfusion protocol. A protocol for replacing blood components that should be used in critically bleeding patients anticipated to require massive transfusion.
MTS	Major trauma service. A designated service that can provide the full spectrum of care to all injured patients, from initial resuscitation through to rehabilitation and discharge. There are currently seven adult and three paediatric designated MTSs in NSW.
NBA	National Blood Authority. A statutory authority representing the interests of the Australian, state and territory governments and sits within the Australian Government's health portfolio.

NSQHS Standards	National Safety and Quality Health Service Standards. The standards provide a nationally-consistent and uniform set of measures of safety and quality for application across a wide variety of healthcare services.[64]
NSWA	New South Wales Ambulance
PAMPer trial	Prehospital Air Medical Plasma. An American trial determining the effect of prehospital infusions during air transport of 2 units of AB plasma on 30-day mortality in patients with haemorrhagic shock, as compared to conventional care.
PCC	Prothrombin complex concentrate
PBM	Patient blood management. Individualised and evidence-based care that aims to limit a patient's exposure to blood products and thereby improve patient outcomes.
PRBC	Packed red blood cells. A unit of blood product obtained by removing most of the plasma.
RBC	Red blood cells
RCT	Randomised controlled trial
RETIC trial	Reversal of Trauma-Induced Coagulopathy. A trial assessing the difference in incidence of multi-organ failure after treatment of trauma-induced coagulopathy with fresh frozen plasma or coagulation factor concentrates.
RTP	Retrieval transfusion procedure. A NSW Health Pathology Procedure (NSWHP_PR_025) describing how NSW Retrieval Services interact with NSW Health Pathology blood bank staff to provide blood products to critically-bleeding patients.[65] This procedure applies to patients in the care of NSW Ambulance specialist medical teams who are in the inter-hospital or prehospital phase.
RTS	Regional trauma service. A designated service that can provide the full spectrum of care to patients with minor and moderate injuries, and definitive care to some patients with major injuries, in collaboration with an MTS. The RTS can provide initial assessment, stabilisation, and definitive care, and initiate transfer to an MTS when patients require services that are not available at the RTS.
TACO	Transfusion-associated circulatory overload. Heart failure and pulmonary oedema resulting from rapid infusion or large volumes of blood products.
TIC	Trauma Innovation Committee
TEG/ ROTEM/ ROTEG	Thromboelastography/rotational thromboelastometry/rotational thromboelastography. Different techniques for evaluating the ability of whole blood to coagulate by measuring the time it takes for blood to clot, and the firmness or shear strength of the clot.
TRALI	Transfusion-related acute lung injury. Pulmonary oedema and respiratory distress resulting from an immunological transfusion reaction.

References

1. Brohi K, Cohen MJ, Davenport RA. Acute coagulopathy of trauma: mechanism, identification and effect. Curr Opin Crit Care. 2007;13(6):680-5. DOI: 10.1097/MCC.0b013e3282f1e78f

2. MacLeod JB, Lynn M, McKenney MG, et al. Early coagulopathy predicts mortality in trauma. J Trauma Acute Care Surg. 2003;55(1):39-44. DOI: 10.1097/01.TA.0000075338.21177.EF

3. Levy JH, Welsby I, Goodnough LT. Fibrinogen as a therapeutic target for bleeding: a review of critical levels and replacement therapy. Transfusion. 2014 May;54(5):1389-405; quiz 8. DOI: 10.1111/trf.12431

4. Nascimento B, Levy JH, Tien H, et al. Cryoprecipitate transfusion in bleeding patients. CJEM. 2020 Sep;22(S2):S4-s11. DOI: 10.1017/cem.2019.409

5. McQuilten ZK, Wood EM, Bailey M, et al. Fibrinogen is an independent predictor of mortality in major trauma patients: a five-year statewide cohort study. Injury. 2017;48(5):1074-81. DOI: 10.1016/j.injury.2016.11.021

6. Rourke C, Curry N, Khan S, et al. Fibrinogen levels during trauma hemorrhage, response to replacement therapy, and association with patient outcomes. J Thromb Haemost. 2012;10(7):1342-51. DOI: 10.1111/j.1538-7836.2012.04752.x

7. Ponschab M, Schöchl H, Gabriel C, et al. Haemostatic profile of reconstituted blood in a proposed 1: 1: 1 ratio of packed red blood cells, platelet concentrate and four different plasma preparations. Anaesthesia. 2015;70(5):528-36. DOI: 10.1111/anae.13067

8. Stinger HK, Spinella PC, Perkins JG, et al. The ratio of fibrinogen to red cells transfused affects survival in casualties receiving massive transfusions at an army combat support hospital. J Trauma Acute Care Surg. 2008;64(2):S79-S85. DOI: 10.1097/TA.0b013e318160a57b

9. Schöchl H, Nienaber U, Hofer G, et al. Goal-directed coagulation management of major trauma patients using thromboelastometry (ROTEM)-guided administration of fibrinogen concentrate and prothrombin complex concentrate. Crit Care. 2010;14(2):R55. DOI: 10.1186/cc8948

10. Hiippala ST, Myllyla GJ, Vahtera EM. Hemostatic factors and replacement of major blood loss with plasma-poor red cell concentrates. Anesthesia and Analgesia. 1995;81(2):360-5.

11. Davenport R, Brohi K. Fibrinogen depletion in trauma: early, easy to estimate and central to trauma-induced coagulopathy. Crit Care. 2013 Sep 24;17(5):190. DOI: 10.1186/1364-8535-17-190

12. Fenger-Eriksen C, Lindberg-Larsen M, Christensen AQ, et al. Fibrinogen concentrate substitution therapy in patients with massive haemorrhage and low plasma fibrinogen concentrations. Br J Anaesth. 2008;101(6):769-73. DOI: 10.1093/bja/aen270

13. National Blood Authority Australia. Patient Blood Management Guidelines: Module 1, Critical Bleeding Massive Transfusion, Technical Report, Volume 1 - Review of the evidence and evidence-based recommendations for clinical practice [Internet]. Canberra, ACT: NBA; 2011 [cited 16 September 2021]. Available from: https://www.blood.gov.au/system/files/documents/pbm-module1-tech-vol1_0.pdf

14. NSW Department of Health. The health of the people of New South Wales - Report of the Chief Health Officer, Data Book - Injury and Poisoning. North Sydney, NSW, Population Health Division; 2008.

15. Kauvar DS, Lefering R, Wade CE. Impact of hemorrhage on trauma outcome: an overview of epidemiology, clinical presentations, and therapeutic considerations. J Trauma. 2006;60(S3-11). DOI: 10.1097/01.ta.0000199961.02677.19

16. NSW Agency for Clinical Innovation. Major Trauma in NSW: Jan-June 2016, A Report from the NSW Trauma Registry; NSW Institute of Trauma and Injury Management [Internet]. St Leonards, NSW: NSW Health; 2017 [cited 16 September 2021]. Available from: https://www.aci.health.nsw.gov.au/__data/assets/pdf_file/0013/401332/Major-Trauma-in-NSW-Jan-Jun-2016-A-Report-from-the-NSW-Trauma-Registry.pdf

17. Cotton BA, Gunter OL, Isbell JM, et al. Damage Control Hematology: The Impact of a Trauma Exsanguination Protocol on Survival and Blood Product Utilization. J Trauma. 2008;64(5):1177-83. DOI: 10.1097/TA.0b013e31816c5c80

18. Palta S, Saroa R, Palta A. Overview of the coagulation system. Indian J Anaesth. 2014 Sep-Oct;58(5):515-23. DOI: 10.4103/0019-5049.144643

19. Mosesson MW. Fibrinogen and fibrin structure and functions. J Thromb Haemost. 2005;3(8):1894-904. DOI: 10.1111/j.1538-7836.2005.01365.x

20. Davenport R, Brohi K. Fibrinogen depletion in trauma: early, easy to estimate and central to trauma-induced coagulopathy. Crit Care. 2013 Sep 24;17(5):190. DOI: 10.1186/1364-8535-17-190

21. Droubatchevskaia N, Wong MP, Chipperfield KM, et al. Guidelines for cryoprecipitate transfusion. B C Med J. 2007;49(8):441.

22. Rossaint R, Bouillon B, Cerny V, et al. The European guideline on management of major bleeding and coagulopathy following trauma. Crit Care. 2016;20(1):1-55. DOI: doi.org/10.1186/s13054-016-1265-x

23. Hagemo JS, Stanworth S, Juffermans NP, et al. Prevalence, predictors and outcome of hypofibrinogenaemia in trauma: a multicentre observational study. Crit Care. 2014;18(2):R52. DOI: 10.1186/cc13798

24. Collins P, Cannings-John R, Bruynseels D, et al. Viscoelastometric-guided early fibrinogen concentrate replacement during postpartum haemorrhage: OBS2, a double-blind randomized controlled trial. Br J Anaesth. 2017;119(3):411-21. DOI: 10.1093/bja/aex181

25. Australian Red Cross Lifeblood. Types of Transfusion - Red Cell, Platelet, Plasma, Cryodepleted Plasma, Cryoprecipitate [Internet]. Australia: ARCL; 2021 [cited 16 September 2021]. Available from: https://mytransfusion.com.au/types-of-transfusion

26. Spahn DR, Bouillon B, Cerny V, et al. The European guideline on management of major bleeding and coagulopathy following trauma. Crit Care. 2019;23(1):1-74. DOI: 10.1186/s13054-016-1265-x

27. Australian and New Zealand Society of Blood Transfusion Ltd. Extended life plasma: A framework for preparation, storage and use; 2nd Edition [Internet]. Sydney, NSW: ANZSBT; 2013 [cited 16 September 2021]. Available from: https://anzsbt.org.au/wp-content/uploads/2018/06/ELP_Printer_Friendly_Corrected_Sept2013.pdf

28. Sperry JL, Guyette FX, Brown JB, et al. Prehospital plasma during air medical transport in trauma patients at risk for hemorrhagic shock. N Engl J Med. 2018;379(4):315-26. DOI: 10.1056/NEJMoa1802345

29. Collins P, Solomon C, Sutor K, et al. Theoretical modelling of fibrinogen supplementation with therapeutic plasma, cryoprecipitate, or fibrinogen concentrate. Br J Anaesth. 2014;113(4):585-95. DOI: 10.1093/bja/aeu086

30. Jensen N, Stensballe J, Afshari A. Comparing efficacy and safety of fibrinogen concentrate to cryoprecipitate in bleeding patients: a systematic review. Acta Anaesthesiol Scand. 2016;60(8):1033-42. DOI: 10.1111/aas.12734

31. Shand S, Curtis K, Dinh M, et al. Retrieval transfusion protocol in New South Wales, Australia: A retrospective review of the first 5 years. Transfusion. 2021;61(3):730-7. DOI: 10.1111/aas.12734

32. National Blood Authority Australia. Plasma and Recombinant Products [Internet]. Canberra, ACT: NBA [cited 15 March 2022]. Available from: https://www.blood.gov.au/plasma-and-recombinant-products

33. National Blood Authority Australia. What Blood Products are Supplied - National Product List [Internet]. Canberra, ACT: NBA; 2021 [cited 16 September 2021]. Available from: https://www.blood.gov.au/national-product-list

34. CSL Behring. RiaSTAP Prescribing Information [Internet]. Marburg: CSL Behring; June 2021 [cited 16 September 2021]. Available from: http://labeling.cslbehring.com/PI/US/Riastap/EN/RiaSTAP-Prescribing-Information.pdf

35. National Blood Authority Australia. Management Model for Fibrinogen Concentrate supplied under the national blood arrangements for congenital fibrinogen deficiency [Internet]. Canberra, ACT: NBA [cited 9 April 2019]. Available from: https://www.blood.gov.au/system/files/documents/management-model-fibrinogen-concentrate.pdf

36. Department of Health and Ageing, Therapeutics Good Administration. Australian Public Assessment Report for Human Fibrinogen: Proprietary Prouct Name: RiaSTAP, Submission No: PM-2009-01838-3-4 [Internet]. Canberra: TGA; 2010 [cited 26 September 2021]. Available from: https://www.tga.gov.au/sites/default/files/auspar-riastap.pdf

37. Winearls J, Wullschleger M, Wake E, et al. Fibrinogen Early In Severe Trauma studY (FEISTY): study protocol for a randomised controlled trial. Trials. 2017 May 26;18(1):241. DOI: 10.1186/s13063-017-1980-x

38. Central Queensland Hospital and Health Service. Massive transfusion protocol [Internet]. QLD: Central Queensland Hospital and Health Service; 2017 [cited 16 September 2021]. Available from: https://rockyed.com.au/upload/data/protocols/trauma/massive_transfusion_policy.pdf

39. Kozek-Langenecker SA, Ahmed AB, Afshari A, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology, First update 2016. European Journal of Anaesthesiology (EJA). 2017;34(6):332-95. DOI: 10.1097/EJA.0000000000000630

40. Innerhofer P, Fries D, Mittermayr M, et al. Reversal of trauma-induced coagulopathy using first-line coagulation factor concentrates or fresh frozen plasma (RETIC): a single-centre, parallel-group, open-label, randomised trial. Lancet Haematol. 2017;4(6):e258-e71. DOI: 10.1016/S2352-3026(17)30077-7

41. Rahe-Meyer N, Ranganath R, Gill R, et al. Randomized evaluation of fibrinogen vs placebo in complex cardiovascular surgery (REPLACE): a double-blind phase III study of haemostatic therapy. Br J Anaesth. 2016;117(1):41-51. DOI: 10.1093/bja/aew169

42. Ranucci M, Baryshnikova E. Fibrinogen supplementation after cardiac surgery: insights from the Zero-Plasma trial (ZEPLAST). Br J Anaesth. 2016;116(5):618-23.

43. Lunde J, Stensballe J, Wikkelsø A, et al. Fibrinogen concentrate for bleeding – a systematic review. Acta Anaesthesiol Scand. 2014;58(9):1061-74. DOI: 10.1111/aas.12370

44. Ziegler B, Bachler M, Haberfellner H, et al. Efficacy of prehospital administration of fibrinogen concentrate in trauma patients bleeding or presumed to bleed (FlinTIC): A multicentre, double-blind, placebo-controlled, randomised pilot study. Eur J Anaesthesiol. 2021 Apr 1;38(4):348-57. DOI: 10.1097/eja.0000000000001366

45. Nascimento B, Callum J, Tien H, et al. Fibrinogen in the initial resuscitation of severe trauma (FiiRST): a randomized feasibility trial. Br J Anaesth. 2016;117(6):775-82. DOI: 10.1093/bja/aew343

46. Mengoli C, Franchini M, Marano G, et al. The use of fibrinogen concentrate for the management of trauma-related bleeding: a systematic review and meta-analysis. Blood Transfus. 2017;15(4):318. DOI: 10.2450/2017.0094-17

47. Stabler SN, Li SS, Karpov A, et al. Use of fibrinogen concentrate for trauma-related bleeding: A systematic-review and meta-analysis. J Trauma Acute Care Surg. 2020 Dec;89(6):1212-24. DOI: 10.1097/ta.0000000000002920

48. Itagaki Y, Hayakawa M, Maekawa K, et al. Early administration of fibrinogen concentrate is associated with improved survival among severe trauma patients: a single-centre propensity score-matched analysis. World J Emerg Surg. 2020;15:7. DOI: 10.1186/s13017-020-0291-9

49. Hamada SR, Pirracchio R, Beauchesne J, et al. Effect of fibrinogen concentrate administration on early mortality in traumatic hemorrhagic shock: A propensity score analysis. J Trauma Acute Care Surg. 2020 May;88(5):661-70. DOI: 10.1097/ta.0000000000002624

50. Winearls J, Wullschleger M, Wake E, et al. Fibrinogen early in severe trauma study (FIESTY): Results from an Australian multicentre randomised controlled pilot trial. Crit Care Resusc. 2021;23(1):32-46.

51. Innerhofer P, Westermann I, Tauber H, et al. The exclusive use of coagulation factor concentrates enables reversal of coagulopathy and decreases transfusion rates in patients with major blunt trauma. Injury. 2013;44(2):209-16. DOI: 10.1016/j.injury.2012.08.047

52. Rahe-Meyer N, Pichlmaier M, Haverich A, et al. Bleeding management with fibrinogen concentrate targeting a high-normal plasma fibrinogen level: a pilot study. Br J Anaesth. 2009;102(6):785-92. DOI: 10.1093/bja/aep089

53. Schöchl H, Nienaber U, Maegele M, et al. Transfusion in trauma: thromboelastometry-guided coagulation factor concentrate-based therapy versus standard fresh frozen plasma-based therapy. Crit Care. 2011;15(2):R83. DOI: 10.1186/cc10078

54. Australian Commission on Safety and Quality in Health Care. Australian Safety and Quality Goals for Health Care [Internet]. Sydney, NSW: ACSQHC; 2012 [cited 5 April 2017]. Available from: https://www.safetyandquality.gov.au/publications-and-resources/resource-library/australian-safety-and-quality-goals-health-care

55. Nienaber U, Innerhofer P, Westermann I, et al. The impact of fresh frozen plasma vs coagulation factor concentrates on morbidity and mortality in trauma-associated haemorrhage and massive transfusion. Injury. 2011;42(7):697-701. DOI: 10.1016/j.injury.2010.12.015

56. Kozek-Langenecker S, Sørensen B, Hess JR, et al. Clinical effectiveness of fresh frozen plasma compared with fibrinogen concentrate: a systematic review. Crit Care. 2011;15(5):R239. DOI: 10.1186/cc10488

57. Seebold JA, Campbell D, Wake E, et al. Targeted fibrinogen concentrate use in severe traumatic haemorrhage. Crit Care Resusc. 2019 Sep;21(3):171-8.

58. Australian Red Cross Lifeblood. Adverse events overview [Internet]. Australia: ARCL; 2021 [updated 10 May 2021; cited 16 September 2021]. Available from: https://transfusion.com.au/adverse_events_overview/

59. Marano G, Mengoli C, Franchini M, et al. Fibrinogen concentrate in surgery. Blood Transfus. 2017;15(3):215-7. DOI: 10.2450/2017.0362-16

60. Solomon C, Groner A, Ye J, et al. Safety of fibrinogen concentrate: analysis of more than 27 years of pharmacovigilance data. Thromb Haemost. 2015 Apr;113(4):759-71. DOI: 10.1160/th14-06-0514

61. Moore HB, Moore EE, Chapman MP, et al. Plasma-first resuscitation to treat haemorrhagic shock during emergency ground transportation in an urban area: a randomised trial. The Lancet. 2018;392(10144):283-91. DOI: 10.1016/S0140-6736(18)31553-8

62. Ho D, Chan E, Campbell D, et al. Targeted cryoprecipitate transfusion in severe traumatic haemorrhage. Injury. 2020 Sep;51(9):1949-55. DOI: 10.1016/j.injury.2020.05.044

63. Australian Commission on Safety and Quality in Health Care. Blood Management, Prescribing and clinical use of blood and blood products. Criterion: Prescribing and clinical use of blood and blood products [Internet]. Sydney, NSW: ACSQHC; 2019 [cited 16 September 2021]. Available from: https://www.safetyandquality.gov.au/standards/nsqhs-standards/blood-management-standard/prescribing-and-clinical-use-blood-and-blood-products

64. Australian Commission on Safety and Quality in Health Care. National Safety and Quality Health Service Standards, 2nd ed. - Version 2 [Internet]. Sydney: ACSQHC; 2021 [cited 15 February 2021]. Available from: https://www.safetyandquality.gov.au/publications-and-resources/resource-library/national-safety-and-quality-health-service-standards-second-edition

65. NSW Health Pathology. Retrieval transfusion procedure NSWHP_PR_025. Sydney: NSW Health Pathology; 2020.

Appendix 1: Clotting factors – uses and storage conditions

Product	Description	Use	Storage and special considerations
Fresh frozen plasma	• Liquid portion of whole blood • 1 unit contains all coagulation factors	• Replace clotting factors • Reverse anticoagulants • Replace plasma proteins / other substances	• Lasts 12 months ≤-25˚C • Must be ABO compatible
Cryoprecipitate	• Concentrated blood component made from FFP • Contains fibrinogen (>140mg), factor VIII, factor XIII, von Willebrand factor	• Low or poorly functioning clotting proteins, particularly fibrinogen in the context of bleeding, invasive procedures or trauma	• Lasts 12 months ≤-25˚C • Once thawed must be stored at 20-24˚C until transfusion, then used within 4-6 hours • Must be ABO compatible
Platelets	• Fragments of megakaryocyte cells separated from whole blood or through apheresis	• Low or non-functioning platelets • Bleeding or at high risk of bleeding • Unlikely to make own platelets soon	• Lasts five days at 20-24°C • Requires constant rocking during storage • ABO identical platelets are usually preferred
Prothrombin complex	• Non-allogeneic clotting factor derived from plasma	• Bleeding in patients with acquired prothrombin complex factor deficiency, requiring partial or complete reversal • Bleeding in patients with single/multiple congenital deficiency of factor IX, II, X	
Fibrinogen concentrate	• Freeze-dried, lyophilised fibrinogen • 1 glass vial contains 900mg of fibrinogen	• Replace fibrinogen	• Five-year shelf life, stored at 2-8°C

The Agency for Clinical Innovation (ACI) is the lead agency for innovation in clinical care.

We bring consumers, clinicians and healthcare managers together to support the design, assessment and implementation of clinical innovations across the NSW public health system to change the way that care is delivered.

The ACI's clinical networks, institutes and taskforces are chaired by senior clinicians and consumers who have a keen interest and track record in innovative clinical care.

We also work closely with the Ministry of Health and the four other pillars of NSW Health to pilot, scale and spread solutions to healthcare system-wide challenges. We seek to improve the care and outcomes for patients by re-designing and transforming the NSW public health system.

Our innovations are:

- person-centred
- clinically-led
- evidence-based
- value-driven.

www.aci.health.nsw.gov.au

NSW GOVERNMENT

AGENCY FOR CLINICAL INNOVATION

Our vision is to create the future of healthcare, and healthier futures for the people of NSW.