

# Freeze-dried plasma administration in trauma

## Review of literature and key findings

APRIL 2023

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The information in this resource should not replace a clinician's professional judgement.

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## Executive summary

The NSW Institute of Trauma and Injury Management (ITIM) Trauma Innovation Committee (TIC) reviewed the evidence on freeze-dried plasma (FDP) for the treatment of trauma-related critical bleeding in NSW. It sought to answer the clinical question: In traumatic critical bleeding, is FDP a reasonable alternative to fresh-frozen plasma (FFP)?

Currently in NSW, standard trauma management for critical bleeding involves replacing clotting factors with donor (allogeneic) blood products including FFP. However, in rural and remote NSW and prehospital areas, often they are not available. Delay in activating blood-product based resuscitation has been associated with an increase in mortality.<sup>1</sup> As injured people in rural and remote NSW face long delays to definitive intervention in a trauma centre, alternative options need to be considered. Alternative options could ensure these severely injured patients can access blood products in a more timely and equitable manner.

The current evidence suggests that FDP is comparable to FFP regarding mortality outcomes, safety profile, and need for additional blood products. FDP has been used as part of blood transfusion strategies in many countries around the world. There are also several logistical benefits of FDP including longer shelf life, reduced wastage and ease of storage and transport. Considering the current evidence outlined in this report, ITIM has formed the following views:

- FDP is a reasonable alternative to FFP in traumatic critical bleeding, particularly in rural and regional areas and medical retrieval transports where access to blood products is currently limited.
- There may be enough evidence and international experience<sup>2</sup> to support the introduction of FDP for clinical use in trauma patients requiring massive transfusion.
- Any implementation of FDP is best conducted under controlled conditions such as research or quality improvement with use, adverse events and outcomes closely monitored by the NSW Trauma Registry.

# Background

In Australia, injury is a leading cause of death, illness, and disability.<sup>3</sup> Haemorrhage is responsible for over 35% of prehospital deaths, and over 40% of deaths within the first 24 hours.<sup>4</sup> Most of these deaths are considered preventable if the right treatment was available at the right time.

Major haemorrhage from trauma can cause acute traumatic coagulopathy (ATC), a profound and complex derangement of the coagulation system. It results in catastrophic bleeding and is associated with a mortality rate of 25-40%.<sup>5,6</sup>

Resuscitation and replacement of blood loss in traumatic critical bleeding can be achieved by replacing red blood cells (RBCs), platelets, and plasma. A ratio of 1:1:1<sup>7,8</sup> is associated with improved outcomes and reduced mortality.<sup>9-12</sup> This ratio is widely implemented in hospitals by military and civilian emergency medical systems.<sup>13</sup>

Cases of traumatic critical bleeding in rural and remote NSW are particularly challenging when compared with metropolitan areas.<sup>14</sup> People injured in rural and remote NSW can face prolonged delays to definitive surgical-trauma care. The distance from a trauma service, protracted transport and scene times and inadequate resuscitation resources, such as blood products, are real challenges to sustaining life.

Blood products from local blood banks can be transported to other locations to address critical bleeding. This is known as the retrieval transfusion procedure (RTP).<sup>15</sup> Although RTP is a successful program challenges remain, especially in providing plasma products.

As a result, treating clinicians rely more heavily on blood products to manage haemorrhage, aiming to sustain life until surgical haemostasis can be achieved. Because blood products are difficult to

obtain in prehospital and rural settings, patients are at higher risk of a poor outcome. The need to seek alternative solutions such as FDP has been the impetus for this and similar reports, including [Fibrinogen administration in prehospital trauma](#).

The NSW ITIM TIC reviewed the evidence for FDP; comparing FDP against FFP in the management of trauma-related critical bleeding. It also examines the potential role FDP could have in the NSW trauma system.

## Who is this document for?

This information is for staff involved in acute trauma care including:

- prehospital clinicians
- transfusion specialists
- rural clinicians
- their governing authorities.

It is designed for those considering FDP as an option in the management of traumatic critical bleeding, especially in austere environments where access to allogeneic blood products is not readily available. It is focused on NSW conditions but could be applied to other jurisdictions and contexts.

## What is plasma?

Plasma is the fluid that carries red cells, white cells, platelets, clotting factors, proteins and nutrients through the blood vessels. Approximately 55% of blood is plasma. Once the red cells are removed, fresh plasma is frozen and known as FFP. FFP is the liquid portion of whole blood made either from apheresis plasma, or by depleting whole blood of all blood cells. FFP contains all the coagulation factors.<sup>16</sup>

## Why an interest in plasma?

Plasma is considered the gold standard in the treatment of severe coagulopathy and blood loss in trauma.<sup>17</sup> It is reported to be able to correct endothelial damage after trauma.<sup>18</sup> Plasma is a vital component in a massive transfusion protocol (MTP)<sup>19</sup> when given alongside RBCs at ratios of FFP:RBC 1:2 or 1:1.<sup>20</sup>

Renewed interest in plasma – especially in the form of extended life plasma (ELP), and its reported mortality reduction in early trauma – came into greater focus with the publishing of the PAMPer trial.<sup>21</sup> The PAMPer trial was a multicentre, cluster-randomised trial (n=501) examining ELP in aeromedical transport and its potential benefits to outcomes for 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 with the standard treatment arm. However, three other randomised control trials examining prehospital plasma +/- red cell administration demonstrated no survival advantage and/or haematological improvements compared with standard treatment. They are:

- Control of Major Bleeding After Trauma (COMBAT) trial<sup>22</sup> that compared red cells and FFP to normal saline
- Resuscitation with pre-hospital blood products (RePHILL) trial<sup>23</sup> that compared red cells and FDP to normal saline
- Prehospital Lyophilized Plasma (PREHO-PLYO) trial<sup>24</sup> that compared FDP to normal saline.

The results of these three trials don't necessary suggest that plasma is of no benefit, but may point out that the timing of plasma administration is important.<sup>22</sup> This is because the three trials administered plasma in urban environments and in the early phases of resuscitation. Whereas the PAMPer trial had longer transport times with a significant survival benefit. The current evidence of all four trials suggests that plasma may have the greatest benefit to patients who have long transport times to a trauma centre.

## The challenges for NSW trauma

In NSW, plasma in the form of FFP is limited to an estimated 40 of 220 hospitals<sup>25</sup> (see Appendix 1). As well, these obstacles need to be overcome:

- the distribution of FFP is geographically reduced in rural areas compared with metropolitan areas
- FFP is a limited resource requiring specialist management in storage and thawing processes, such as a blood bank
- delivering FFP to hospitals that urgently require it is logistically challenging and can prolong critical time windows.<sup>20, 26</sup>

Despite the evidence for plasma in trauma resuscitation,<sup>21</sup> equitable access to plasma remains a challenge, especially in rural NSW. Zaza et al report that patients in smaller hospitals or prehospital environments without access to plasma could suffer worse outcomes due to clinicians being forced to resort to crystalloid solutions.<sup>2</sup> This can exacerbate a practice associated with poor patient outcomes<sup>27, 28</sup> because of dilutional coagulopathy.<sup>20</sup>

## Extended-life plasma explained

Extended-life plasma (ELP) is thawed FFP that can be stored between 2-6°C for up to five days.<sup>29</sup> At the time of writing, we understood that Royal Prince Alfred, Westmead, John Hunter, and Liverpool hospitals had an ELP program, with a well-considered inventory program in place that sometimes partnered with a retrieval service.

An advantage of ELP is that it can be rapidly available for emergency use and can be used in prehospital resuscitation due to its transportability. However, ELP is probably not suitable for most hospitals that stock FFP, as it is likely to not be used causing unacceptable wastage.

At the time of this review, head-to-head studies of FDP efficacy have used FFP as the control. ELP is more commonly used in pre-hospital services, compared with in-hospital practice. To date there have been no comparative studies of FDP versus ELP. ELP has similar coagulation activity to FFP. However, some studies report that some coagulation factors drop over time with ELP.<sup>30</sup>

## What is freeze-dried plasma?

FDP is FFP that has undergone the process of lyophilisation to produce a freeze-dried product, allowing it to be reconstituted and administered. FDP is made from either single (i.e. LyoPlas) or multiple donors (i.e. French lyophilized plasma (FLYP)). Several manufacturers have produced FDP over the decades.

FDP was first used by the US Army during World War 2. Millions of British and American soldiers received FDP until hepatitis transmission became a problem.<sup>31</sup> FDP was eventually phased out in the US.<sup>32</sup> Meanwhile, other countries started FDP production. This included the French producing FLYP from 1949 to 1984, providing nearly 40,000 units to French military forces during the Indochina War.<sup>33</sup>

Production was suspended in 1985 due to the human immunodeficiency virus (HIV). It began again in 1991 and continues to this day.<sup>33</sup>

For decades, FDP has been routinely used to treat major trauma in civilian hospitals, prehospital and military environments in many countries, such as Germany, France, Norway and South Africa.<sup>26</sup>

## Why consider freeze-dried plasma?

There are several challenges associated with using FFP. It can be difficult ensuring timely delivery in emergency situations, due to storage and thawing requirements. An example of this is in hospital MTP activations that aim to achieve a plasma to red cell ratio of 1:1 or 1:2 within the first hour of admission. Evidence suggests that these ratios are difficult to achieve with only 15% of patients receiving 1:2 in the first hour.<sup>34</sup>

By contrast, FDP is readily available, easy to store, transportable, and can be administered quickly and safely.<sup>2</sup> FDP could prove to be a solution to locations such as small rural hospitals unable to store FFP due to logistical challenges. This report examines the current evidence for FDP and if it could be applied to the NSW trauma system without compromising safety and efficacy.

# Method

## Question design

This report examined published evidence regarding whether FDP is suitable for rural, regional and prehospital use. The following question was framed: In traumatic critical bleeding, is FDP a reasonable alternative to FFP? This question became the basis of the literature search and body of this review.

## Document structure

There are two main components:

1. Examination of the current international evidence on FDP, with a focus on safety, efficacy, mortality, intensive care unit (ICU) length of stay, need for additional blood products, logistics, storage and cost.
2. The response to the above question is based on the evidence reviewed and expert consensus. Consensus was formed in consultation with the TIC and broad external consultation with various specialist groups, such as trauma and haematology clinicians.

## Search methodology

Literature was obtained by searching the PubMed database, using these search strategies.

1. Search terms “fdp” [Title/Abstract] and freeze-dried plasma [Title/Abstract] OR “lyophilized plasma”[Title/Abstract]) AND ((humans [Filter]) AND (English [Filter]) AND (2010:2021[pdat])).

This search yielded 81 articles.

Other articles that were not part of the initial search are referenced in this document and listed in the reference section.

Further to literature searched, the TIC investigated FDP availability in Australia and overseas by making direct enquiries to relevant organisations.

## Expert consensus

Consensus was achieved in consultation with haematologists, trauma clinicians, blood governance committees and retrieval specialists. This was especially important in addressing the question: What are the potential implications for NSW?

This question shaped the recommendation sections. Consensus was achieved by sending the draft evidence review document to members with instructions to comment on these sections.

## Literature review

A review of the literature available on plasma replacement (FDP and allogenic products) focused on the patient outcomes of:

- mortality
- ICU length of stay
- safety
- the need for additional blood products.

The literature review also considered logistical issues of product storage, administration, and cost to the health system.

The availability of plasma in rural and remote NSW as demonstrated in [Appendix 1: Hospitals in NSW that store FFP](#), highlights the difficulties accessing plasma for trauma patients with critical bleeding in remote NSW and the prehospital setting. Therefore, the need to consider providing an option, such as FDP, should be front of mind when translating the current evidence.

## Mortality

Using two recent systematic reviews, table 1 shows that nine articles that included mortality as an endpoint were identified. Two directly compare FDP to FFP.

The two studies as shown in table 2 comparing FDP to FFP showed no mortality difference between the two study arms.<sup>34,39</sup> Mok et al's meta-analysis of these two studies found no difference between FDP or FFP in mortality.<sup>20</sup>

**Conclusion:** There is limited, low-quality evidence to demonstrate a benefit in survivability for trauma patients in haemorrhagic shock when treated with FDP. Limited evidence suggests that FDP and FFP have comparable effects on mortality.

**Table 1: Studies that include mortality outcomes**

Authors	Design	Sample size	Blinding	Comparison/control
Martinaud et al. <sup>35</sup>	Prospective review	87	Nil	Nil
Sunde et al. <sup>36</sup>	Retrospective	16	Nil	Nil
Cuenca et al. <sup>37</sup>	Retrospective	11	Nil	Packed red blood cells/whole blood
Vitalis et al. <sup>38</sup>	Prospective observational	28	Nil	Nil
Garrigue et al. <sup>34</sup>	Randomised open-label trial	FLyP 23, FP 24	Nil	FP (4U)
Nguyen et al. <sup>39</sup>	Retrospective before/after	FDP 43, FFP 29	Nil	FP
Shlaifer et al. <sup>40</sup>	Retrospective	FDP 48, control 48	Nil	Tranexamic acid (TXA) 1g
Benov et al. <sup>41</sup>	Retrospective	FDP 75	Nil	TXA
Glassberg et al. <sup>42</sup>	Observational	10	Nil	Nil



Table 2: Studies comparing FDP to FFP on mortality

Author group	Mortality control (FFP)	Mortality intervention (FDP)	p-value
<b>Nguyen et al.<sup>39</sup></b>	<b>N = 29</b>	<b>N = 43</b>	
24 hour	9 (31%)	9 (21%)	0.591
Haemorrhage-related	5 (17%)	3 (7%)	0.293
28 day	10 (34%)	11 (26%)	0.703
<b>Garrigue et al.<sup>34</sup></b>	<b>N = 24</b>	<b>N = 23</b>	
All cause in-hospital within 30 days	7 (29%)	5 (22%)	0.56

## Intensive care unit and hospital length of stay

We were unable to find literature that used ICU and/or hospital length-of-stay outcome measures related to FDP. Until large prospective randomised trials are conducted that seek these endpoints, no conclusions are available.

**Conclusion:** No studies were found that reported on ICU or hospital length of stay for FDP.

## Need for additional blood products

Although vital, blood transfusion carries inherent risks. These risks incrementally increase with further blood administration and is associated with an increased risk in mortality and various morbidities.<sup>43</sup> This is important when reviewing an alternative product such as FDP, with a desire to find an alternative that is equal or superior to its comparator FFP. This is because it is best to avoid the need for additional blood products if possible.

Garrigue et al's randomised control trial reports that FDP (FLyP) required less fibrinogen replacement (median 2 grams) when compared with FFP (median

3 grams) in trauma.<sup>34</sup> However, this finding was not statistically significant.<sup>20</sup> Red cell and crystalloid/colloid requirements remained the same between the FDP and FFP groups.<sup>34</sup>

Two observational animal studies demonstrated that FDP subjects (n = 72, n = 216) received significantly less RBC when compared with FFP alone.<sup>44, 45</sup> Another study (n=96) reported no difference in RBC transfusions between FDP versus Hartmann solution.<sup>46</sup>

Nguyen et al's retrospective study (level IV evidence), examining the comparison between FDP and FFP in severe trauma patients, reported significantly fewer cases of massive transfusion in the FLYP group (n=43) than in the FFP group (n=29) with 7% and 45% respectively (p < 0.0001).<sup>39</sup>

**Conclusion:** There is low to moderate evidence suggesting no difference in the need for additional blood products for patients receiving FDP compared with FFP. This suggests that FDP and FFP are comparable products. However, there are signals that FDP has a time advantage in initial and subsequent transfusion intervals over FFP. This may reduce downstream demands for further blood products. However, it needs to be confirmed by prospective and randomised trials.

## Safety profile

The safety profile of FDP was studied by examining reports of adverse reactions and infection risk documented in the literature. Using FFP as a baseline, comparison was made between FFP and FDP.

## Adverse reactions

For context and as a baseline, it is important to understand the adverse reactions of FFP. The incidence of FFP adverse reaction is between 1:1300 and 1:1700 events per transfusion with minor allergic reactions being most common. Severe reactions are less common with 1:66000 to 1:285000 for transfusion-related lung injury (TRALI) and allergic reactions between 1:18000 and 1:172000 per transfusion.<sup>42</sup>

For FDP, the French haemovigilance system has recorded more than 1000 administrations of FLYP with no significant side effects documented. The German Red Cross has recorded more than 200,000 units of their single donor FDP with no reported evidence of higher incidence of major adverse reactions compared with FFP.<sup>42</sup>

Mok et al's recent systematic review and meta-analysis reports on one patient with chills/rigors; and four cases of transient erythema. The strength of available evidence for adverse effects from FDP is of low-to-moderate quality, thus preventing definitive conclusion. However, there is also no evidence of increased transfusion reaction.<sup>20</sup>

The National Bioproducts Institute in South Africa has used FDP since 1996 with a strong safety record.<sup>47</sup> Reports state that Bioplasma FDP has a 80% reduction in transfusion-related adverse effects when compared with FFP.<sup>48</sup>

The German national authority for blood products reported on the adverse reaction for LyoPlas and FFP between 2007-2011, as shown in table 3. This data suggests that adverse reactions are overall similar to each other. The German Red Cross also reports that there was no evidence of FDP (LyoPlas) having a higher incidence of adverse reactions when compared with FFP.<sup>26</sup> It is important to note that more than 90% of data comes from passive haemovigilance from civilian healthcare facilities.

**Table 3: Reported adverse reactions 2007-2011 in Germany<sup>26</sup>**

Adverse reactions	LyoPlas (n=237,850 units)	FFP (n= 343,821 units)
Urticaria	54	63
Fever	24	14
Severe hypotonia including anaphylactic shock	3	5
Bronchospasm	1	3
Transfusion-related acute lung injury (TRALI)	None reported*	None reported*

\*Safety procedures using plasma only from male donors and female donors without children or female donors with children having additional antibodies screening have been in place from 2006. This likely accounts for the absence of TRALI cases in both groups.

Several smaller studies and case series involving military and civilian cohorts reporting on FDP usage list no adverse reactions.<sup>36, 49-51</sup>

Although the level of evidence is low, the current evidence suggests that FDP is comparable to FFP in relation to adverse reactions.<sup>26</sup>

## Infection risk

Although FDP has previously had issues relating to disease transmission, this has improved with better screening and employed pathogen reduction strategies.<sup>33</sup>

It is important to note, and establish a baseline, regarding the overall infectious risk when comparing FFP and FDP. The incidence of blood-borne infections for plasma is less than 1:1000000 for hepatitis C and HIV and 1:280000 for hepatitis B.<sup>42</sup> The German Red Cross LyoPlas is made from a single donor whereas FLYP is made from pooling multiple donors (approximately 10). FLYP theoretically has a probability of having a higher infection risk than a single donor unit. However, with modern pathogen inactivation methods<sup>2</sup> and current haemovigilance practices in place, this doesn't seem to have occurred.

Infection control procedures are different between FDP manufacturers. The German Red Cross LyoPlas mandates a second serologic screening four months after collection of its donors. This reduces the overall shelf life of the product. The French blood bank manufacturers of FLYP use a chemical and ultraviolet radiation process to minimise the risk of infection.<sup>42</sup> It could be argued that FDP has a technically reduced infection-risk profile due to the additional processes used to mitigate infection. However, large studies comparing FFP to FDP are currently not available.

Since LyoPlas was approved in Germany for transfusion in 2007, in the reporting period between

2007 and 2011, more than 230,000 units have been transfused without any virus transmission reported.<sup>52</sup>

**Conclusion:** Currently there is low-to-moderate evidence available regarding the safety profile of FDP. No specific study was found comparing the safety profile of FDP and FFP. The evidence regarding the safety of FFP and FDP is weak, coming mainly from retrospective case series and passive haemovigilance data (Level IV and V). However, there is no evidence that FDP is superior or inferior to FFP regarding adverse reactions and infection risk. FDP has been extensively used in many European countries. Current evidence suggests that it is likely to have a comparable safety profile to FFP with the majority of reported adverse effects being minor and self-resolving.

## Efficacy

FDP may have greater clotting factor properties when compared with ELP. It has been argued that the freezing and defrosting process impacts coagulation proteins and thrombin generation potential, especially as ELP ages.<sup>53</sup> Reports suggest up to 40% reduction in thrombin generation can occur and other significant impacts on coagulation parameters demonstrated on thromboelastography.<sup>54</sup>

FDP has been reported to have similar, or improved, biological efficacy relative to FFP.<sup>26, 34</sup>

The Transfusion for Trauma-induced Coagulopathy and Fibrinogen Concentration (TRAUCC) trial – open label phase 3 randomised trial n=48 – compared FLYP (n=24) and FFP (n=24) where the primary endpoint was fibrinogen levels at 45-minutes post randomisation. The FLYP group had a more rapid, pronounced and longer lasting effect on fibrinogen levels. There were also improvements in coagulopathy and a reduced demand for fibrinogen

concentrate in trauma patients when compared with the FFP group.<sup>34</sup>

Nguyen et al's retrospective single centre study reports no difference in fibrinogen levels between FDP and FFP at three and 24 hours.<sup>39</sup>

Mok et al's systematic review reports that FDP effects on coagulation parameters (i.e. international normalised ratio [INR], prothrombin time [PT] and thromboelastography [TEG]) is comparable to FFP when tested on animal and human subjects. This suggests that FDP retains its coagulation properties through lyophilisation and reconstitution processes. There is currently low-quality evidence that FDP improves coagulation parameters more rapidly when compared with FFP.<sup>20</sup>

It is important to note that single donor FDP may have a greater chance of coagulation factor variability compared with pooled FDP. This may impact coagulation response, up to 100% when administered.<sup>42</sup>

**Conclusion:** The current evidence suggests that FDP is comparable with FFP regarding effects on coagulation parameters, with low-quality evidence that FDP achieves more rapid improvements than FFP. This is likely to be attributed to FDP's logistic ability to be administered sooner than FFP.

## Where is FDP currently used?

FDP is approved in France, the US and Israel for use in austere and military environments (US Army Special Operations Forces<sup>42</sup>). It is approved for civilian care in Germany, Norway, Sweden and Denmark.<sup>55</sup> South Africa and neighbouring countries use Bioplasma for domestic use.<sup>56</sup> It is used in other countries, including the UK, under trial conditions (RePHILL trial<sup>23</sup>) and in prehospital helicopter emergency medical service use.<sup>57</sup>

## Availability

Evidence indicates that there are two main producers of FDP; France and Germany. South Africa produces more modest amounts<sup>2</sup> as shown in table 4. Other countries such as the US are working on producing a FDP product for licence.<sup>2</sup>

Investigations with Red Cross Lifeblood and Commonwealth Serum Laboratory (CSL) reveal that FDP is not available in Australia. There is no knowledge of an application to licence FDP by the Therapeutic Goods Authority at the time of writing.

There also appears to be supply chain issues in certain European countries, such as Norway and UK, that use LyoPlas from Germany. This is attributed to the high demand. The majority of FLYP is used for France's domestic and military needs, with a portion going to the US military.

**Conclusion:** FDP is not available in Australia. With increasing demand and limited producers of FDP, establishing and maintaining a constant supply may be challenging.

## Product storage

Required FDP storage conditions are between 2°C and 25°C.<sup>42</sup> Laboratory testing of LyoPlas demonstrated a decline in fibrinogen activity up to 64% after storage for 34 days at 38°C to 42°C.<sup>26</sup>

Generally, FDP remains stable for two years at either room temp or 4°C.<sup>58</sup> However, shelf life varies between products. Once received from the donor, LyoPlas requires a further three months before being commercially available. The extra three months allows donors to return a negative retest for HIV, hepatitis B virus (HBV) and hepatitis C virus (HCV). This reduces the shelf life of LyoPlas compared with FLYP.<sup>26</sup>

Table 4: Producers of freeze-dried plasma

Product name	Donor source	Company name	Country
LyoPlas	Single donor	German Red Cross	Germany
French lyophilized plasma	Pooled donors	French Military Blood Institute	France
Bioplasma FDP	Pooled donors	National Bioproducts Institute	South Africa

Table 5: ABO compatibility of different FDP products

FDP product	ABO compatibility	Comment
FLYP	Universal <sup>42</sup>	
LyoPlas	Requires ABO compatibility <sup>42</sup>	LyoPlas is made from AB donors (universal plasma donor group) <sup>59</sup>
Bioplasma FDP	Universal <sup>48</sup>	

## ABO compatibility

As previously discussed, to our knowledge, there are three countries manufacturing FDP. These products undergo different processing that affect their ABO compatibility properties. FDP made from pooled donors enables the product to be ABO universal, whereas a product made from a single donor remains type specific. As table 5 highlights, FLYP and Bioplasma FDP are universal while LyoPlas requires ABO compatibility.

## Product administration and preparation time

Table 6 highlights some of the comparative storage logistic requirements between FFP, ELP and FDP.

FDP is kept in a vial and requires approximately 200ml of sterile water to reconstitute the plasma powder. This takes 5-10 minutes.

Difficulties with reconstitution of FDP have been reported. These were related to user error that most likely can be mitigated with appropriate training.<sup>20</sup> Clinicians who use FDP regularly suggest to first **swirl** the mixed content to avoid frothing.

### Does FDP have a logistic advantage?

Nguyen et al demonstrated that FDP was transfused faster compared with FFP (10-25 vs 70-145 minutes) and the time to meet the 1:1 ratio (RBC:plasma) is shorter in the FDP group compared with the FFP group.<sup>39</sup>

Flaumenhaft et al noted that FDP doesn't have complex logistics or time-consuming thawing. They also suggested it may be suitable for rapid treatment of coagulopathies with a logistic advantage over FFP.<sup>58</sup>

FDP may not have a logistic advantage over ELP if ELP and FDP are equally available (that is, a major trauma centre that has an ELP program). However, FDP may suit regional and rural and austere environments, especially in locations of limited or no plasma stores.

**Conclusion:** FDP can be stored at room temperature, is easily transportable and able to be prepared and administered rapidly when compared with FFP. FFP requires cold storage (minus 25-30°C). This means it is held at a blood bank. It also needs to be thawed. Thawing takes 30 minutes and then it needs to be transported to the POC, such as the emergency department. FDP appeared to have logistical advantages over FFP, especially in the clinical environment. However, it may not have logistic advantages when ELP and FDP are equally available.

**Table 6: Storage and logistic properties for FFP, ELP and FDP**

Values	FFP	ELP	FDP
Preparation time	30-40 minutes	Immediate	10-20 minutes for reconstitution
Shelf life	12 months	5-7 days	2 years
Pathogen inactivation	no	no	yes
Storage	≤ -25°C in blood banks	2-6°C point of care (POC)	Room temperature POC
ABO compatibility	Yes	Yes	LyoPlas – yes FLYP – no Bioplasma – yes
Blood service inventory management	Yes (defrosting/dispensing)	Yes (defrosting/dispensing)	No, can be kept at POC

## Cost to the health system

Table 7 suggests FDP can cost approximately twice as much as whole blood FFP. However, apheresis FFP is much closer in price.

A cost comparison analysis done by the South African Department of Health concluded that FDP was cheaper when taking other pragmatic factors into account such as storage and shelf life, crossmatching, thawing and wastage.<sup>60</sup>

**Conclusion:** From the information available and with the current exchange rate, FDP appears to cost twice as much as standard whole blood FFP. However, the per-year cost is likely to be lower for FDP compared with FFP and ELP when pragmatic factors of FFP and ELP management are considered.

**Table 7: Cost comparison between FFP, ELP and FDP**

Product	Dose	Volume	Cost
Whole blood FFP	1 unit	295ml +/-10%	\$157.55
Apheresis FFP	1 unit	295ml +/-10%	\$242.92
ELP	1 unit	295ml +/-10%	Same as FFP
FDP (LyoPlas)	1 vial	200ml	Approximately \$300

## Summary of key findings – literature review

Table 8: Summary of the key findings for FDP

Endpoints	Evidence	Summary
Mortality	Low-quality evidence	FDP has comparable affects on mortality outcomes when compared with FFP
Intensive care unit and hospital length of stay	No studies were found that reported on ICU or hospital length of stay for FDP	
Need for additional blood products	Low-to-moderate quality evidence	FDP and FFP are comparable
Safety profile	Low-to-moderate quality evidence	No evidence that FDP is superior, or inferior, to FFP regarding adverse reactions and infectious risk
Efficacy	Low-to-moderate quality evidence	FDP is comparable to FFP regarding affects on coagulation parameters
	Low-quality evidence	In initial trauma resuscitation, FDP achieves more rapid improvements in coagulation parameters than FFP. This is likely to be attributed to FDP's logistic ability to be administered faster than FFP.
Availability	N/A	FDP is used in several countries, mostly in Europe for civilian, prehospital and military use. FDP is not available in Australia
Cost to the health system	N/A	FDP appears to cost twice as much as standard whole blood FFP. Per-year costs are likely to be lower for FDP than FFP or ELP when pragmatic factors are considered
ABO compatibility	N/A	There is variability between the different FDP products. Two of the three producers manufacture a universal FDP
Storage, administration and preparation time	Low to moderate	FDP appeared to have logistical advantages over FFP. FDP can be stored at room temperature, is easily transportable and able to be prepared and administered faster when compared with FFP



## What are the potential implications for NSW?

ITIM has considered the current evidence of FDP and the implication for the NSW trauma system.

- The current low-level evidence for FDP is acknowledged. However, there may be enough evidence and decades of international experience within advanced healthcare and trauma systems to support the introduction and usage of FDP into the NSW trauma system.
- FDP is likely to be most beneficial in the rural, remote and other austere conditions, especially in the prehospital environment with long transport times.
- FDP may be beneficial in achieving balanced RBC to plasma ratios in initial MTP activation, and in reducing excessive wastage of FFP and cryoprecipitate.
- FDP's logistic benefits, such as long shelf life, easy storage and transportability, may allow it to be stockpiled for rapid deployment to disaster and major incidents, including rural and remote locations. This is an advantage when there are high demands for plasma with reduced stocks.

This is the expert consensus regarding the answer to the question: In traumatic critical bleeding, is FDP a reasonable alternative to FFP?

- ITIM has considered FDP's efficacy, safety profile, logistic advantages and longstanding overseas usage. It considers FDP a reasonable alternative to FFP in traumatic critical bleeding. This may also apply to other conditions with critical bleeding.

- ITIM would support FDP use in environments where trauma patients do not have access to plasma products, particularly in rural and regional areas and medical retrieval transports.
- Any implementation of FDP is best conducted under controlled conditions, such as research or quality improvement. It would need use, adverse events and outcomes to be closely monitored by the NSW Trauma Registry.

## Next steps

To progress the adoption of FDP to treat people with traumatic critical bleeding, key stakeholders need to be identified to address:

- implementing a risk/benefit analysis for FDP
- the economic feasibility of FDP
- develop a research framework to determine FDP's viability and suitability for NSW trauma.

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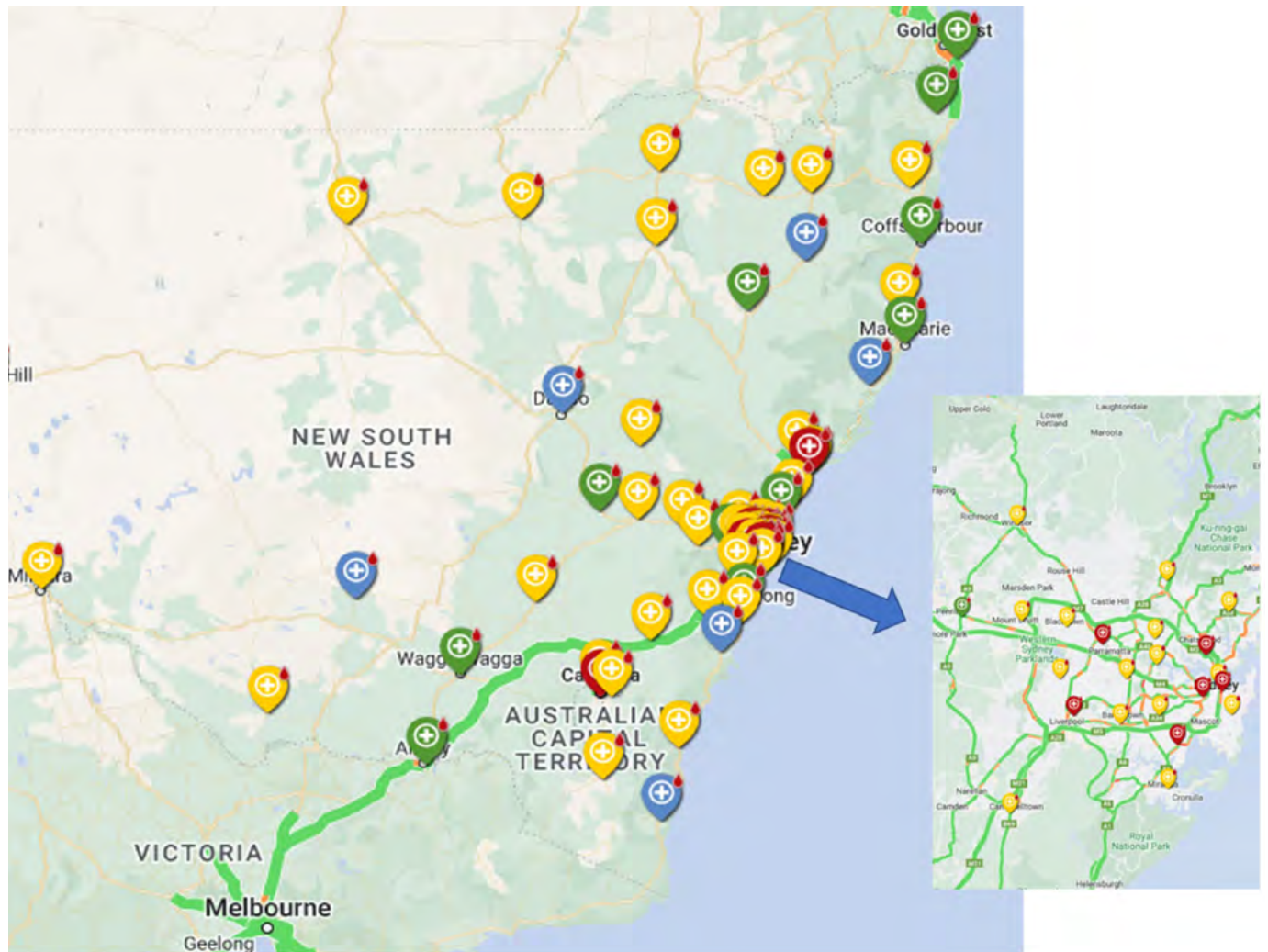
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# Appendix 1: Hospitals in NSW that store fresh-frozen plasma



# Glossary

ABO	ABO blood group system is used to match the blood type of the donor to the person receiving the transfusion.
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.
Austere environment	For the purpose of this document, the term austere environment refers to a location where the medical services are relatively scarce compared with a location such as a major trauma centre. An austere environment may include a prehospital accident scene or a small rural or remote health facility without the medical equipment or skills to manage a critical trauma patient.
ELP	Extended life plasma. Thawed fresh-frozen plasma that can be stored between 2-6°C for up to five days.
FC	Fibrinogen concentrate. A pasteurised drug stored as a lyophilised powder at room temperature, used to supplement plasma fibrinogen.
FDP	Freeze-dried plasma. A pasteurised drug stored as a lyophilised powder at room temperature, used to supplement plasma.
FFP	Fresh-frozen plasma. A unit of blood product that contains all of the coagulation factors.
HIV	Human immunodeficiency virus
ICU	Intensive care unit
ITIM	Institute of Trauma and Injury Management. An institute within the NSW Agency for Clinical Innovation, ITIM oversees, coordinates and supports the NSW trauma system. ITIM is supported by five committees of senior trauma clinicians, one of them being the TIC.
LyoPlas	A form of freeze-dried plasma produced by German Red Cross.
Massive transfusion	Defined in adults as replacement of >1 blood volume in 24 hours or >50% of blood volume in four hours. Adult blood volume is approximately 70mL/kg.

## Glossary (cont.)

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 that 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.
PAMPer trial	Prehospital Air Medical Plasma. An American trial determining the effect of prehospital infusions during air transport of two units of AB plasma on 30-day mortality in patients with haemorrhagic shock, as compared with conventional care.
RBC	Red blood cells
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. This procedure applies to patients in the care of NSW Ambulance specialist medical teams who are in the inter-hospital or prehospital phase.
TIC	Trauma Innovation Committee. 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.
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



# Acknowledgements

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## 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 FDP.

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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.

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