

Joint UKBTS Professional Advisory Committee ⁽¹⁾

Summary Sheet

1. Paper for the JPAC meeting on:	12 November 2015
2. Date submitted:	09 November 2015
3. Title (including version no.):	Review of the shelf life of fresh frozen plasma components following thawing
4. Author(s):	Dr Laura Green and Dr Rebecca Cardigan for the SAC on Blood Components
5. Brief summary:	<p>The new BCSH guideline on the management of major bleeding, recommends that blood banks seeing major haemorrhage due to trauma should consider having pre-thawed plasma on standby to allow FFP to be immediately available for the management of major bleeding. Some centres are already doing this by operating a pre-thawed FFP policy, but this results in wastage of FFP due to the limited (24 hour) shelf-life of thawed FFP.</p> <p>We have therefore reviewed the available data on FFP with a view to possible extension of post-thaw shelf-life to enable rapid clinical provision without excessive wastage, and have made specific recommendations for consideration by JPAC.</p>
6. Action required by the Joint Professional Advisory Committee: (What do you want JPAC to do in response to this paper?) e.g. <ul style="list-style-type: none"> • endorse a specific recommendation • advise where there is a choice of possible actions • advise on priorities within the work plan • provide a steer on policy 	<p>Endorse the recommendation that:</p> <ol style="list-style-type: none"> 1) the shelf life of thawed MB FFP should remain the same (i.e. 24 hours) and not be extended 2) the shelf life of thawed FFP be extended to 5 days to permit use of extended thawed plasma according to BCSH guidelines. Possible options for clinical indications of extended-thawed FFP include management of major bleeding associated with trauma only, or management of any unexpected major bleeding. 3) clinical indications for extended-thawed FFP and re-issue when out of controlled storage (30 minute rule) need to be included in BCSH guidelines. 4) further data on FFP wastage, and the effect of the changes recommended in this paper on both wastage and speed at which plasma can be provided are gained <p>Data on the component and the importance of risk mitigation for bacterial contamination will need to be communicated to hospitals if these recommendations are accepted by JPAC, and SHOT will need to be notified of this change.</p>
7. Any other relevant information:	<p>This paper should be reviewed together with the previous JPAC papers:</p> <ul style="list-style-type: none"> • JPAC 11.59: November 2011 • JPAC 13.48: July 2013 • JPAC 15-37 Position statement

⁽¹⁾ Joint United Kingdom Blood Transfusion Services Professional Advisory Committee

Review of the shelf life of fresh frozen plasma components following thawing

Laura Green and Rebecca Cardigan on behalf of SACBC

1. Background

The British Committee for Standards in Haematology (BCSH) guidelines (O'Shaughnessy *et al*, 2004), and the Guidelines for the UK Blood Transfusion Services (2013) recommend that fresh frozen plasma (FFP) be used as soon as possible after thawing, or within 24 hours of thawing if stored at 4°C. However, the thawing process and the transit time needed to deliver FFP may lead to significant delays in its availability, particularly detrimental during emergencies such as major haemorrhage. JPAC were previously asked to review whether the shelf-life of FFP following thawing should be extended beyond 24 hours (extended-thawed FFP here after), a summary of which is given below.

1.1 Summary of previous recommendations from the UK Joint Professional Advisory Committee (JPAC)

1.1.1. Considerations for extending the shelf life of FFP to 5 days (JPAC 11.59)

In 2011 the UK Standing Advisory Committee on Blood Components (SACBC) was asked by JPAC to review the current evidence on whether the shelf life of standard FFP following thawing can be extended from 24 hours to 5 days in order to:

- 1) reduce the wastage of plasma
- 2) improve timely availability of FFP for urgent use, e.g. trauma
- 3) pilot the remote supply of plasma to hospitals by NHSBT

To this end the literature was reviewed with 2 main issues in mind: (1) the efficacy of the components; and (2) the risk of bacterial contamination and other side effects.

Recommendations

JPAC recommended that the shelf life of FFP following thawing should **not be changed** because:

- the laboratory data showed that coagulation factors declined during storage and therefore there is a possibility that their efficacy would also decline
- there are no clinical studies evaluating the use of FFP which have been thawed and stored for 5 days
- it would not be possible for hospitals to label plasma beyond 24 hours of thawing as a separate component, since this would require them to hold a manufacturing license from the Medicines and Healthcare Regulatory Authority (MHRA) under the Blood and Safety Quality Regulations.
- there may be a new recommendation from the Advisory Committee on the Safety of Blood Tissues and Organs (SaBTO) in 2012 for the type of FFP to be used in the UK
- it was felt that there wasn't a strong clinical drive for extending the shelf life of FFP

1.1.2. Considerations for extending the shelf life of FFP to 48 or 72 hours (JPAC 13.48)

In March 2012, the National Blood Transfusion Committee requested that JPAC examine the evidence on efficacy and safety of extending the shelf life of thawed FFP to 48-72 hours. The following were reviewed:

- a. coagulation factor content of FFP at 48-72 hrs;
- b. clinical demand and potential reduction in FFP wastage through a national questionnaire: should thawed FFP be extended to 48-72hrs?

Recommendations

JPAC recommended that the shelf life of FFP following thawing should **not be changed** because:

- There was an unknown effect of extended storage of thawed plasma on the clinical efficacy of the component since clinical studies on thawed plasma are lacking
- Several laboratory studies showed that FVIII levels reduce significantly at Day-2 or Day-3; this reduction does not meet the European/UK requirements for FFP.
- The questionnaire results showed that:
 - the majority of participants were satisfied with FFP delivery times but there is still room for improvement.
 - Half of the respondents had concerns about the possible loss of efficacy with extended-thaw FFP, and just over a third would definitely use it for treating major haemorrhage.
 - Only a minority predicted significant wastage reduction.
- The use of extended thawed plasma could not easily be restricted to selected patient groups as the component is not labelled as a separate product.

1.2 Reasons for revisiting the shelf life of thawed FFP

1.2.1. Increase availability of FFP for management of major bleeding of trauma

Recently, a randomised controlled study (The PROPPR - Pragmatic, Randomized Optimal Platelet and Plasma Ratios) compared outcomes in patients with severe trauma and major bleeding. For selected post-hoc analyses, the early administration of plasma, platelets, and RBC in a 1:1:1 compared with a 1:1:2 ratio reduces death due to exsanguination at 24 hours, albeit with no significant differences in mortality at 24 hours and 28 days (Holcomb *et al*, 2015). The results of this study informed the new BCSH guideline on the management of major bleeding, which recommends that FFP be given empirically and early in the initial resuscitation process in a high dose ratio of 1:1 with red cells, before coagulation test results are available (Hunt *et al*, 2015a). For other major haemorrhage however, the guideline recommends that FFP be administered in a ratio of 1:2 with the red cells (Hunt *et al*, 2015b). Currently the National Institute for Health and Care Excellence (NICE) has distributed a draft clinical guideline for consultation on the assessment and management of major trauma: the draft document recommends that in adults and children a ratio of 1 unit of plasma to 1 unit of red cell should be used to replace fluid volume of patients who develop major bleeding (NICE 2015 draft guideline). In order to fulfil these guideline recommendations, major trauma centres will need to make FFP readily available for the management of major bleeding in trauma.

However, findings from a prospective observational study at 22 hospitals in the UK, including both major trauma centres and smaller trauma units, indicated that for patients who received plasma, the median time to first FFP transfusion was 87 min after arrival; for patients with more severe bleeding (massive haemorrhage) the timing was slightly faster at 68 min. Therefore, it is clearly important to look at the pathways of timely transfusion support and consider all options to support rapid administration of blood component.

1.2.2. Reduce FFP wastage

Some hospitals are pre-emptively thawing FFP and storing it for 24 hours (the current maximal shelf-life): this approach, however, is leading to significant FFP wastage. Since SACBC and JPAC last reviewed the shelf life of thawed FFP in 2012, it is believed that FFP wastage has increased significantly.

Until recently, data on FFP wastage has been scant as this was not collected by the Blood Stocks Management Scheme. From August 2015, BSMS hospitals have been submitting data on all types of component wastage, but data on FFP is not yet available for many hospitals. Recent FFP wastage

rates (Aug-Oct 2015) reported to NHSBT is variable and ranges from 1% - 86% of adult FFP issued, with an average wastage rate of 13%. For Adult FFP, in those hospitals providing pre-thawed plasma, (mainly trauma centres) the wastage range is 1% - 45%, with an average wastage rate of 14%. During Aug-Oct this represents over 1500 units - approximately a third of all FFP wastage. Intelligence and feedback from hospitals indicates that there is an upward trend for FFP wastage, especially for those centres providing pre-thawed plasma for trauma which anecdotally may be as high as 50%.

Wastage data for FFP overall for SNBTS for 2014/15 is 18%. The wastage rate in 2014/15 for WBS for thawed & returned unused FFP was 12% which has increased from 7% in 2010/11. In discussions with hospitals supplied by WBS their most challenging issue is the requirement for maintaining the cold chain – as if this is out of Blood Bank control for > 30 minutes and returned it is discarded.

1.3 Aims of current paper

In light of new clinical evidence, NHSBT has asked JPAC to re-evaluate the shelf life of thawed FFP and methylene blue treated FFP (MB FFP) beyond 24 hours (and up to 5 days). The literature review on the *in vitro* characteristics of the coagulation factors within thawed plasma during storage have been described in a previous paper (Cardigan & Green, 2015). For the current paper we will summarise the most recent NHSBT laboratory data and use it as the starting point for considering extending the shelf life of thawed FFP. In this paper we will not discuss solvent detergent FFP (Octaplas) as this is a licensed medicinal product and therefore its shelf-life following thawing is governed by the manufacturer (Octapharma) – currently 8 hours at 20-25°C and 24 hours at 2-8°C.

Data relating to MB FFP following thawing were reviewed by JPAC in 2006 in order to extend the shelf-life from 4 to 24 hours (JPAC 06-55). The data presented from NHSBT showed almost a doubling of thrombin generation between 24 and 48 hours. The reason for the increase in could be due to cold activation of plasma occurring beyond 24 hours post-thaw and is consistent with data from Germany showing an increase in activation of FVII and FX after 7 days storage of thawed MB FFP. It is unclear why this occurs with MB but not standard FFP. Currently we are not aware of any countries using thawed MB FFP, or indeed any PI FFP, beyond 24 hours of thawing. Due to the increased thrombin generation profile on extended post-thaw storage, the known reduction in clotting factors due to the initial PI treatment, and a desire to take a precautionary approach to minimising exposure of neonates to DEHP, we do not recommend that the shelf-life of thawed MB FFP be extended beyond 24 hours. MB FFP is thus not considered further here, and all subsequent discussion relates to untreated single donor FFP.

Liquid (never frozen) plasma is not considered within. A separate paper will be presented to JPAC in March 2016 with data and a specification for this component, dependent upon the outcome from phase 1 studies ongoing in NHSBT.

2 Data on coagulation factor content of standard FFP once thawed

The most recent data from FFP produced by NHSBT using current production processes are given in Tables 1, 2 and 3. These studies focused on the loss of factors V, VII and VIII and protein S as previous studies have identified these as being those most affected by storage following thawing.

SACBC also considered data in between day 1 and day 5, but due to the conclusions reached regarding the acceptability of data at day 5, these data are not presented to JPAC to simplify the paper.

Table 1. Coagulation factors in FFP at days 1 and 5 after thawing – NHSBT data

Clotting factor tests	Pre freeze	post thaw (T0)	24 hours post thaw	% change T0 vs. D1	D5 (120 hours) post thaw	% change T0 vs. D5	p-value (ANOVA)
PT (ratio)	1.02 ±0.05	1.03 ±0.05	1.06 ±0.06	2.4 ±1.4	1.13*** ±0.05	9.5 ±1.5	<0.0001
APTT (ratio)	1.14 ±0.04	1.17 ±0.05	1.23 ±0.05	5.0 ±2.0	1.26*** ±0.05	8.2 ±2.4	<0.0001
Fg (g/L)	2.55 ±0.35	2.57 ±0.40	2.60 ±0.46	0.7 ±5.7	2.61 ±0.39	1.80 ±5.9	0.4
FII (IU/mL)	0.91 ±0.08	0.91 ±0.09	0.88 ±0.07	-3.5 ±3.4	0.84*** ±0.06	-7.7 ±4.2	<0.0001
FV (IU/mL)	0.87 ±0.13	0.85 ±0.13	0.81 ±0.12	-5.1 ±4.0	0.74*** ±0.11	-12.9 ±4.6	<0.0001
FVII (IU/mL)	0.94 ±0.14	0.97 ±0.17	0.95 ±0.16	-2.5 ±4.5	0.79*** ±0.13	-18.3 ±4.8	<0.0001
FVIII (IU/mL)	0.85 ±0.19	0.82 ±0.20	0.62 ±0.16	-23.6 ±3.5	0.57*** ±0.14	-30.7 ±3.7	<0.0001
FXI (IU/mL)	0.90 ±0.16	0.94 ±0.17	0.89 ±0.15	-5.1 ±2.9	0.87* ±0.16	-7.2 ±3.9	<0.0001
FXII (IU/mL)	1.04 ±0.18	1.06 ±0.19	1.05 ±0.19	-1.2 ±4.3	1.03* ±0.17	-2.5 ±4.2	0.0014
Free PS (%)	99.0 ±14.3	98.2 ±12.9	96.3 ±14.0	-2.0 ±3.9	94.0** ±13.9	-4.4 ±3.5	<0.0001
PS activity (%)	89.4 ±15.2	84.6 ±13.9	82.3 ±13.6	-2.5 ±5.7	72.5*** ±11.7	-14.0 ±6.8	<0.0001
PC (%)	94.7 ±9.64	95.6 ±9.56	94.5 ±9.54	-1.1 ±2.4	93.8 ±9.90	-1.9 ±2.7	0.01

Results are given as Mean ±Standard deviation n=x, from a pool of n=2 units pooled and split
 One-way ANOVA performed with *post test comparing 1 day post thaw versus 5 days post thaw ONLY*, significant differences shown as * P<0.05 ** P<0.01 *** P<0.001.
 P value shown is from overall ANOVA, not post test.

Data in Table 1 from NHSBT show that for all factors studied, except protein C, there is a statistically significant decrease between 24 and 120 hours (5 days) after thawing. Previous studies have shown that most of the loss of FVIII occurs within the first 24 hours following thawing, and then the rate of loss decreases. For other factors the loss of activity is more linear during storage once thawed. However, with the exception of FVIII, mean levels remain above 70% of normal at day 5. Levels of FVIII and vWF in FFP are highly dependent upon ABO blood group, with the lowest values in group O donors. Therefore levels of FVIII at day 5 will vary by ABO group: in group A plasma mean levels are approximately 68% of normal. This is relevant as the current BCSH guidelines recommend the use of group A plasma as the universal group for the treatment of major haemorrhage due to trauma (Hunt *et al*, 2015b).

Data on thrombin generation from NHSBT (Table 2) suggests that extending the storage time from 24 hours to 5 days results in a small increase in the time to initiate thrombin generation, but no effect on the overall capacity of plasma to generate thrombin (ETP).

Data on markers of contact activation (cleavage of the amidolytic substrate S2302 and FXIIa:C1-inhibitor complexes) as well as levels of C1-inhibitor do not suggest that there is measurable

contact activation occurring during storage for up to 7 days, although we have only assessed a relatively small number of units and cold activation of plasma is known to be highly variable between donations. NHSBT is currently assessing a larger number of units of liquid plasma to confirm that this finding is reproducible in a larger data set.

Table 2. Thrombin generation, ROTEM and activation markers following thawing and storage of FFP for up to 7 days

	Time following thawing				
	Pre-freeze	0	1	5	7
Lag (min)	2.32 ±0.41	2.51 ±0.34	2.71 ±0.41	2.87* ±0.41	2.93 ±0.44
Peak (nM/L)	367 ±65.7	370 ±36.4	335 ±37.3	314 ±61.0	301 ±59.6
ETP (nM/min)	1813 ±412.1	1878 ±263.6	1851 ±259.5	1825 ±432.7	1757 ±440.6
ttPeak (min)	4.58 ±0.61	4.93 ±0.55	5.42 ±0.68	5.92*** ±0.85	6.05 ±0.95
CT (sec)	41.9 ±4.12	43.5 ±4.20	45.2 ±3.82	48.4* ±6.06	51.5 ±6.54
MCF (mm)	21.2 ±3.45	21.8 ±3.63	19.1 ±3.25	21.9*** ±3.41	20.5 ±4.53
AA (deg)	79.4 ±2.15	79.5 ±2.38	77.8 ±2.36	78.7* ±2.54	78.7 ±2.96
C1INH (%)	100 ±11.9	101 ±14.9	101 ±15.4	101 ±10.7	99 ±15.9
C1INH-FXIIa (IU/mL)	2.92 ±1.86	2.19 ±2.08	2.13 ±2.17	2.21 ±2.26	2.14 ±2.29
S-2032 (max V)	1.6 ±0.5	1.5 ±0.5	1.5 ±0.4	1.4 ±0.5	1.4 ±0.5

Thrombin generation, ROTEM and activation markers of FFP at various time points: pre-freeze, immediately post thaw, 1 day (current shelf life), 5 day and 7 days post thaw. Mean ±SD. Right: Percentage change of immediately post thaw versus 1, 5 and 7 days post thaw. One-way ANOVA performed with post test comparing 1 day post thaw versus 5 days post thaw ONLY, significant differences shown as * P<0.05 ** P<0.01 *** P<0.001.

In 2014, Newcastle upon Tyne Hospital tested 40 units of group A pre-thawed FFP for fibrinogen, FVII, FVIII, and signs of leakage at 24, 72 and 120 hours. Similar to the NHSBT data, their results show that the % reduction in fibrinogen was insignificant up to 120 hours, whilst FVII and FVIII levels reduced significantly (Table 3, data courtesy of Dr Jonathan Wallis). They also noted a decrease in FV by 72 hours, which is consistent with the most recent data from NHSBT.

Table 3. Post Thaw FFP Coagulation Factor levels over time

	24hrs post thawing					72 hours post thawing					120 hours post thawing				
	FI	FV	FVII	FVIII	Leakage/ integrity check	FI	FV	FVII	FVIII	Leakage/ integrity check	F1	FV	FVII	FVIII	Leakage/ integrity check
Average	2.288	94.173	110.39	75.308	No Leakage or floculation observed.	2.333	88.373	101.3	68.08	No Leakage or floculation observed.	2.2775	82.568	94.148	66.78	No Leakage or floculation observed.
Max	3.44	128.5	180.7	125.4		3.4	122.5	180.7	102		3.11	128.5	164.9	93.7	
Min	1.63	63.4	66.3	37.6		1.65	50.7	63.6	11.3		1.52	50.7	58.6	35.7	
SDEV	0.9162	32.566	57.699	44.045		0.882	35.915	59.78	45.83		0.79529	39.111	54.113	29.02	
MEDIAN	2.26	95	109.74	73.5		2.23	90.6	101.5	68.74		2.28	82.084	90.75	65.4	

Data from Newcastle upon Tyne Hospital (provided by Dr Jonathan Wallis). Data are based on 40 units of group A FFP from NHSBT as expressed as a % of pooled normal plasma.

To put the data on thawed plasma into context we have included data on pathogen inactivated plasma components for comparison (Table 4). PI-treatment of plasma, by any of the available methods, results in a reduction in clotting factors, the magnitude of which is dependent upon the PI method and clotting factor in question. For some factors there is a 30-40% loss of activity following PI. However, these plasmas are used in Europe for the same indications as FFP with the exception of the treatment of TTP (MB is thought to have reduced efficacy).

The large majority of FFP units transfused are given to support patients with major haemorrhage, either obstetric, surgical or traumatic. FFP is less commonly used to treat coagulopathy in sick patients with liver disease prior to invasive procedures, DIC and rarely to treat single factor deficiencies or thrombotic thrombocytopenic purpura (TTP). FFP usage in adults is always given as multiples of units, generally a minimum of 4 (1 litre). As such any variation in factor content between individual donor units, bar that associated with blood group type, is averaged out to give final levels similar to those in the table above. In small children a clinically effective dose may be as little as a single whole unit (220-290 mLs). For such patients' variation in factor content in individual donor units may therefore be clinically significant. These patients are also mandated to receive plasma from a source with a low risk of vCJD. Currently hospitals use either SD FFP or MB FFP for this indication. FFP is also used to correct certain single factor deficiencies where concentrates are not available (Factor V, factor XI). For these uses it is recommended that patients should receive pathogen inactivated plasma. In most centres this is interpreted as SD-treated pooled plasma. A minority of patients may receive MB treated single donor plasma, and in the future, possibly single donor PI plasma. These usages can be excluded from the current analysis in that they are generally less acute demands, will usually use a non standard FFP and are overall very small volume use.

FFP may be used to treat TTP. SD pooled plasma is recommended and MB plasma is not recommended. Untreated standard FFP may be used and in the absence of testing of ADMANTS13 levels post thaw should be used within 24 hours of thaw as at present.

The evidence for use of FFP to support coagulation in non bleeding patients is weak. It is therefore difficult to make any firm recommendations with regard to type of plasma or length of storage. However, if either SD or MB treated plasma is considered suitable, then prolonged storage thawed standard FFP may be considered equivalent given the equivalent factor levels.

Table 4. Data on thawed FFP in comparison to PI-treated plasma

* Internal data from NHSBT Component Development Laboratory, ** data reproduced in part from Backholer et al Vox Sanquinis 2016 Jan 12. doi: 10.1111/vox.12368. [Epub ahead of print], *** data from product insert

	Thawed FFP*				MB**	Intercept**	Octaplas LG***
	post thaw (T0)	24 hours post thaw	120 hours post thaw	168 hours post thaw	post thaw (T0)	post thaw (T0)	post thaw (T0)
PT (ratio)	1.03 ±0.05	1.06 ±0.06	1.13 ±0.05	1.15 ±0.06	1.06 (0.04)	1.08 (0.04)	
APTT (ratio)	1.17 ±0.05	1.23 ±0.05	1.26 ±0.05	1.26 ±0.05	1.40 (0.04)	1.34 (0.05)	
FibC (g/L)	2.57 ±0.40	2.60 ±0.46	2.61 ±0.39	2.63 ±0.43	1.70 (0.15)	2.05 (0.17)	2.6 ± 0.1
FII (IU/mL)	0.91 ±0.09	0.88 ±0.07	0.84 ±0.06	0.82 ±0.07	0.90 (0.07)	0.90 (0.07)	1.01 ± 0.07
FV (IU/mL)	0.85 ±0.13	0.81 ±0.12	0.74 ±0.11	0.74 ±0.10	0.73 (0.05)	0.77 (0.05)	0.76 ± 0.05
FVII (IU/mL)	0.97 ±0.17	0.95 ±0.16	0.79 ±0.13	0.72 ±0.11	1.08 (0.12)	1.05 (0.14)	1.09 ± 0.05
FVIII (IU/mL)	0.82 ±0.20	0.62 ±0.16	0.57 ±0.14	0.54 ±0.14	0.61 (0.08)	0.58 (0.08)	0.80 ± 0.07
FXI (IU/mL)	0.94 ±0.17	0.89 ±0.15	0.87 ±0.16	0.90 ±0.17	0.42 (0.05)	0.58 (0.06)	0.88 ± 0.04
FXII (IU/mL)	1.06 ±0.19	1.05 ±0.19	1.03 ±0.17	1.03 ±0.18	0.81 (0.07)	0.80 (0.09)	1.04 ± 0.08
Free ProS (%)	98.2 ±12.9	96.3 ±14.0	94.0** ±13.9	92.7 ±13.6	74 (6)	75 (6)	
Pro S (activity %)	84.6 ±13.9	82.3 ±13.6	72.5*** ±11.7	68.8 ±12.7	NA	NA	0.63 ± 0.08
ProC (%)	95.6 ±9.56	94.5 ±9.54	93.8 ±9.90	94.4 ±9.94	95 (8)	95 (7)	86 ± 8
C1-INH	101 ±14.9	101 ±15.4	101 ±10.7	99 ±15.9			

3. Discussion

Determining how long to extend the post-thaw shelf life of FFP consists in getting the right balance of:

- a. Efficacy of the component
- b. Safety of component
- c. Practical consideration/challenges

a. Efficacy of the component – standard FFP

Clinical indications for FFP transfusion include: single coagulation factor deficiency (i.e. FV deficiency); reversal of warfarin effect in the presence of life-threatening bleeding (together with prothrombin complex concentrate); disseminated intravascular coagulation in the presence of bleeding; massive transfusion; coagulopathy prior to invasive procedures; and plasma exchange for thrombotic thrombocytopenic purpura (O'Shaughnessy *et al*, 2004). With the exception of the last, the recommendations on FFP for the other clinical indications are based on expert opinion rather than randomised control studies.

Efficacy of FFP can be estimated by its haemostatic properties and the clinical impact of these properties on patients' outcome (i.e. correction of haemostasis and improved morbidity and mortality).

Haemostatic properties

Currently we do not know the levels of individual clotting factors (or inhibitors) in FFP which are necessary for its efficacy or safety in different clinical indications. Our data demonstrate a decrease in clotting factors in thawed FFP over time, meaning that insofar as haemostatic properties are concerned, extended-thawed FFP (both at days 3 and 5) is inferior to thawed FFP stored for 24 hours. However, despite this decrease, the average of all clotting factors (excepting FVIII) remain >70% of normal at Day 5, although no clinical studies have compared the efficacy and safety of extended-thawed FFP with that stored for 24 hours. There is no evidence from usage in other countries that a reduction to these levels reduces clinical efficacy of FFP in helping to correct haemostasis in the setting of bleeding patients.

Any reduction in haemostatic efficacy of extended-thawed FFP might be balanced by its usage enabling transfusion of FFP earlier in the course of major bleeding. Benefit of this was demonstrated in the PROPPR study, whereby the early use of FFP reduces death from exsanguinations (although the average shelf life of thawed FFP in this study remains unknown). Further, in the case of bleeding trauma patients, FVIII levels do not drop significantly in the first 24 hrs (Frith & Brohi, 2012); thus, it could be argued that the use of extended-thawed FFP would be satisfactory (despite containing lower levels of FVIII), since the replacement of FVIII at the onset of bleeding may be relatively less critical. Furthermore, dependent on the volume of thawed plasma individual hospitals hold, the volume of plasma stored >24hours given to any individual is limited.

Having optimum levels of clotting/inhibitor factors in plasma determines not only the efficacy but also its safety. For example, in the past low levels of protein S and alpha2 antiplasmin (anticoagulants) in solvent-detergent treated (SD) plasma has resulted in increased risk of thrombotic complications (Yarranton *et al*, 2003;Magner *et al*, 2007). Further, in 2010 an increase in thromboembolic events was also reported following Octagam (intravenous immunoglobulin) administration in both the US and the EU (2010) due to increased levels of FXIa. Currently, the finished product for Octaplas LG is tested for coagulation factors V, VIII, and XI, and the inhibitors

protein C, protein S, and plasmin inhibitor: a minimum of 0.5 IU/mL is obtained for each of the three coagulation factors, whereas the inhibitor levels are guaranteed equal or higher than 0.7, 0.3, and 0.2 IU/mL respectively (*Octapharma: product insert for Octaplas LG*). Our results show that the mean level for Protein S/C and FXI remain within the normal range at day 5. This is not surprising when we consider that FFP in the UK is produced from male donors (protein S/C levels are higher than women), and that our plasma is not pathogen inactivated (Protein C and S are labile towards solvent detergent treatment).

Other properties

Some authors have also suggested that the efficacy of FFP may in part be due to its effect in promoting vascular stability. The *in vitro* impact of FFP on vascular endothelium have been discussed in a recent review (Cardigan & Green, 2015), and the overall conclusion is that the effect of FFP on endothelium is lessened when FFP is thawed and stored for 5 days, although clinical data are needed to confirm these findings. FFP also contains adiponectin which is known to have vascular protective function. In one study –using a haemorrhagic shock mouse model - FFP resuscitation reversed the lung vascular damage-induced by haemorrhagic shock and this was shown to be partly attributable to adiponectin (Deng *et al*, 2015). Currently, we do not know what happens to adiponectin levels in FFP after prolonged storage once thawed.

International experience

Extended thawed FFP is used in several countries, with the shelf life varying between 5 and 14 days. Examples are:

- some centres in the USA (shelf life 5 days, labelled as a separate component to FFP)
- the Dutch Military Blood Bank in Leiden, Netherlands (for up to 7 days)
- the Academic Hospital Leiden, Netherlands (stored for up to 14 days; the average time at usage is 3 days post-thaw)
- some centres in Germany (stored for 7 days following thawing)
- Canada (5 days post-thaw shelf life)
- Australia (5 days following thawing if used to treat coagulopathies other than FVIII deficiencies)
- Some centres in Sweden (7 or 14 day shelf-life)

An EU survey was carried out in 2015 as part of the recent EU Symposium on plasma. Of the 13 countries that responded, only 2 are using thawed FFP beyond 24 hours of storage (i.e. 7-14 days) (data provided by Dr Sheila MacLennan). The current Council of Europe Guide states that FFP should be used immediately on thawing. Although there was no immediate agreement to change this, following the symposium a group is being set up to consider this issue with a view to recommending what should be in the next edition.

In the PROPPR study (in USA), out of the 12 trial sites that participated in the study, 11 used extended thawed FFP (shelf life 5 days), and only one site used liquid plasma with the shelf life of 26 days (Novak *et al*, 2015).

b. Safety

Two main safety considerations are:

- a. Bacterial contamination
- b. Levels of Phthalates

Bacterial contamination

The risk of bacterial transmission of FFP is very small, and to date there has been no SHOT report of infections arising from plasma. The two main junctures where bacterial contamination could be introduced for FFP are during blood donor phlebotomy or the FFP thawing process in hospitals. The most significant concern is bacterial growth when plasma is removed from the cold environment.

The risk of bacterial contamination arising from donors and proliferating during subsequent extended post thaw storage at 4°C is very small, and in the worst case scenario we can assume that this is equal to that of red cells. In the case of red cells, between 1995 and 2014, data on organisms implicated in bacterial transmissions identified six incidents reported to NHSBT from approximately 40 million units, giving an estimated incidence of transmission of 1 in 6 million (*JPAC paper 15-54: Deviations from 4°C temperature storage for red cells: effect on viability and bacterial growth, May 2015*).

The risk of bacterial contamination arising during the process of thawing and subsequent extended storage remains unknown. Some of the potential risks that could increase the likelihood of contamination during thawing include:

- The presence of pinholes or cracks in the packs: this could be visible or invisible
- Leaking or burst bag
- Dirty thawing equipment
- Prolonged thawing process
- Fluctuations of temperatures during thawing

In 2011 SACBC and JPAC reviewed the variations in practice during thawing of plasma and concluded that the thawing temperature of all frozen plasma components be changed from 37°C to 33-37°C (*JPAC 11-58*). The risk of bacterial contamination could be reduced by ensuring there is no direct contact of FFP with water, that thawing devices are kept clean and regulatory decontaminated, and that there is careful visual inspection of units following thawing and prior to administration. All UK Blood Services provide FFP in a vacuumed packed outer container, and thus FFP should not come into direct contact with thawing devices.

Canada, Australia and the USA have not reported any cases of bacterial sepsis associated with extended thawed plasma (personal communication Dana Devine, Joanne Pink, Louis Katz). In excess of 750,000 units of FFP have been issued in Canada since introducing a 5 day thawed product (2011) and over 700,000 units of FFP in Australia since 2010. The latest published data available from the USA (AABB Blood Survey Report 2013) suggests that 53% of all plasma transfused is thawed plasma, an increase from 24.5% in 2011. However, it is not known at what time post thaw (up to the maximal 5 day shelf-life) that most extended-thawed FFP is actually transfused in these countries. Within Australia, only a small number of laboratories currently use pre-thawed plasma. These are predominantly large metropolitan and regional laboratories that support hospitals with major surgical, intensive care, emergency and trauma services; and normally hold between 2 and 8 units of pre-thawed group A and/or AB FFP.

Phthalates

Plasticisers such as di(2-ethylhexyl)phthalate (DEHP) added to blood bags can leach out of the bags into the blood component and therefore be transfused to patients. Since DEHP is lipophilic, there is a potential for increased levels due to leaching into plasma during storage at 4°C. Concerns about DEHP have been discussed in the recent review (Cardigan & Green, 2015), and it is acknowledged that levels of DEHP in plasma thawed and stored for 5 days are two-fold higher than that in red cells and platelets at the end of their shelf-life. This issue is of most concern for patients receiving

massive transfusion, chronic transfusion and neonates.

c. Practical consideration/challenges

The main practical considerations for extended thawed FFP are:

- Labelling of the components
- Clinical indication (the best way to control this)
- Management of FFP wastage
- Timing of 'out of controlled temperature'
- Quality monitoring

Labelling of the components

In the USA and Australia, once thawed, FFP is relabelled as a different component after 24 hours ('thawed plasma' or 'extended thawed plasma'). Some centres use standard 24 hour thawed FFP and extended-thawed FFP interchangeably, others do not.

Given the data on component quality, extended-thawed FFP should be labelled as a different component to standard thawed 24 hour FFP. However, the vast majority of hospitals in the UK do not hold a blood establishment licence so if extended-thawed FFP is to be introduced, they cannot introduce new labels to the blood component once thawed. Thus the only possible option for how to manage an extension to storage following thawing is to change the post-thaw shelf life in the Red Book for FFP from 24 hours to a new agreed extended-thawed shelf-life. An example of how the wording could be changed is given below, the exact wording would be notified through a change notification.

From

'Once thawed, the component must not be refrozen and should be transfused as soon as possible. If delay is unavoidable, the component may be stored and should be used within 4 hours if maintained at 22 ± 2 °C or 24 hours if stored at 4 ± 2 °C, but it should be borne in mind that extended post-thaw storage will result in a decline in the content of labile coagulation factors'

To

- *'Once thawed, the component must not be refrozen and should be transfused as soon as possible. If delay is unavoidable, the component may be stored and should be used within 4 hours if maintained at 22 ± 2 °C or 24 hours if stored at 4 ± 2 °C. For management of major bleeding, thawed FFP that has been stored at 4 ± 2 °C can be used for up to 5 days, but it should be borne in mind that extended post-thaw storage will result in a decline in the content of labile coagulation factors'*

There is a precedent for having a shorter shelf-life of a component for some clinical indications than is given on the label. This currently applies for Red Cells in Additive Solution, Leucocyte depleted for Large Volume Transfusion of Neonates/Infants, where the component should be used in < 5 days for neonates and infants, but for other indications it has a shelf life of 35 days.

When thawing FFP, hospitals would write on the expiry date/time of thawed units as they do now, and put this in their LIMS system. The extended thaw option would require that hospitals are extra vigilant in identifying any safety issue relating to the component, as well as, ensuring its appropriate use.

The main disadvantage of this option is that extended-thawed FFP will not be labelled as a separate component and as such there are risks that:

- any safety concerns may not be identified
- the manual entry of new expiry date and time could lead to component being used beyond its recommended shelf life - because of mismanagement of stocks or because of human error when entering information. Some hospitals have indicated that regardless of shelf-life having the final expiry of the component on the label when issued from UKBTS (as is the case for red cells and platelets) is attractive as it ensures (through LIMS) units are not used after expiry once thawed.

3.2 Clinical indications for extended-thawed FFP

If JPAC approves the use of extended-thawed FFP, there will have to be clear clinical indications for its use. These should be recommended by the BCSH FFP guideline, currently being revised.

Possible clinical indications for extended thawed FFP are: a) management of major bleeding associated with trauma only; or b) management of any major bleeding; or 3) all current indications for standard FFP. Extended-thawed FFP would not be appropriate for situations where pathogen inactivated FFP is recommended, e.g. for patients who have a single factor deficiency, thrombotic thrombocytopenic purpura.

SACBC have discussed these options. SACBC members were in agreement that as well as excluding single factor deficiency or therapeutic plasma exchange, extended thawed FFP should not be used for children/neonates. The latter is a precautionary approach to reduce exposure to DEHP and because there is little clinical experience with its use in these patients - most other centres that use thawed plasma exclude its use in neonates. There was less consensus on which FFP recipients extended-thawed FFP would be suitable for. SACBC concluded that extended-thawed FFP could be used in trauma based on evidence from the PROPPR study. They also felt that it might be reasonable to extrapolate from usage in trauma to other situations of major haemorrhage, although the pathophysiology is different. SACBC were less confident that extended-thawed FFP should be used for other less urgent indications. Therefore in the first instance SACBC suggest that the use of extended thawed FFP be restricted to clinical indications where immediate availability will improve timely supply to the bedside with documented clinical benefits, and the extended post thaw shelf life will help to reduce wastage.

3.3 Other aspects

Management of FFP wastage

Reducing FFP wastage is one of the main drivers for extending the shelf life of thawed FFP, particularly for those hospitals who are pre-thawing FFP in anticipation of demand. Although it is difficult to predict by how much extending the shelf life of thawed FFP will reduce wastage, it seems uncontroversial that broadly speaking, the shelf life of thawed FFP is inversely related to the level of wastage experienced. It is also likely to be the case that by extending the use of thawed plasma from trauma to all major bleeding that the likelihood of plasma pre-thawed for use in trauma being re-issued to other patients would increase.

Currently the wastage rate in NHS hospitals varies widely (data provided by Blood Stocks Management Scheme, see Appendix). The quantity of attributable wastage will depend on:

- hospitals' ability to manage effectively the usage and wastage of plasma, with some being better than others.
- the size of the hospitals - the bigger the hospital the higher the chances of recycling the pre-thawed FFP to other non-trauma patients

- clinical indications - if BCSH guidelines restrict the clinical indication of extended thawed FFP, then it is unlikely that FFP wastage will be diminished.

From the PROPPR study, which used a shelf life of 5 days for thawed FFP - the average FFP wastage rate was between 1- 7% (Novak *et al*, 2015).

It should be acknowledged that it is not clear from the data that is currently available what effect introducing extended thawed plasma either for trauma or trauma plus other causes of major bleeding will have on wastage rates.

Maximum timing of extended thawed FFP out of controlled temperature

Another important practical consideration is the maximum timing that extended thawed FFP could be outside controlled temperature (i.e. 2-6°C). In the case of red cells (also stored at 2-6°C) the 30 minute rule applies, primarily to reduce risk of bacterial growth and to preserve the quality of red cells. For extended thawed FFP, in the absence of any data we recommend the same rule be applied and this would be mainly to prevent bacterial growth. Currently Canada and Australia also operate a 30 min rule for thawed plasma, while in the United States the guidance from the AABB is not clear. Canada is currently performing laboratory studies to ascertain whether this could be extended.

Some laboratory or blood tracking IT systems may limit time out of controlled temperature to a single programmable time for all components.

In order to reduce bacterial risk it will be important (via BCSH) to provide guidance to hospitals on time out of controlled temperature. The application of the 30 minute rule, whilst essential, may limit the amount of plasma that can be re-issued to other patients.

Quality monitoring

Currently for FFP, quality monitoring (QM) testing includes the measurement of FVIII levels in the component at the point of production. Apart from thawing, no further manufacturing process will be applied to extended thawed FFP, and thus no additional QM is required, assuming that the initial QM testing is adequate. However, better understanding of the impact of different thawing methods/processes used by hospitals, on the quality of extended-thawed FFP, would be advisable during any implementation of extended thawed FFP, since this is a variable that could influence final product quality that has not been assessed.

Summary

Following the results of the PROPPR study the BCSH guideline on the management of major bleeding, has recommended that for trauma patients who are bleeding, FFP should be given in the initial resuscitation process in a dose ratio of 1:1 with red cells, before coagulation test results are available.

Currently some hospitals are pre-emptively thawing FFP and storing it for 24 hours: this approach however is leading to significant FFP wastage.

In vitro data from NHSBT has shown that the longer the standard FFP is left after thawing, the lower the clotting factors are. However, the average level of clotting factors measured (except FVIII) remain >70% of normal at Day 5.

Currently, we do not know what the optimum level of individual clotting factors (or inhibitors) in FFP required for its efficacy or safety. In the PROPPR study, 11 of the 12 trial sites used extended

thawed FFP (shelf life of 5 days), although we do not know the average shelf life of FFP transfused in the study.

Recent data in animal models suggest that FFP may also be important in exerting a protective effect on the endothelium, and this is lessened in thawed plasma. The effect appears to be partly attributable to adiponectin, and it is not known what effect storage of thawed plasma has on this.

Extended thawed FFP is used in several countries (USA, some European countries, Australia and New Zealand), with the shelf life varying between 5 and 14 days.

The extension of shelf life of thawed FFP could theoretically increase the risk of bacterial proliferation, particularly if a water method is used for thawing, but steps could be taken to mitigate this risk.

Plasticisers such as di(2-ethylhexyl)phthalate (DEHP) added to blood bags can leach out of the bags into the blood component and therefore be transfused to patients. This is particularly of concern for children/neonates, massive transfusion and chronic transfusion. However for major haemorrhage, the benefit of early administration of plasma appear to outweigh theoretical toxicology concerns.

Recommendations from SACBC

MB FFP

- The shelf life of thawed MB FFP should remain the same (i.e. 24 hours) and not be extended

Standard FFP

- In light of new clinical evidence of benefit for giving FFP early in bleeding in trauma, we support the extension of the shelf life of thawed FFP to 5 days for enabling hospitals to reduce wastage while increasing availability.

If extension of shelf life of thawed FFP is approved the following would need to be considered:

- *Clinical indications* would need to be determined by the BCSH guideline, and this is currently being updated. Possible options for clinical indications of *extended thawed FFP* include: a) management of major bleeding associated with trauma only; or b) management of any major bleeding.
- *Labelling*: change the post-thaw shelf life in the Red Book for FFP from 24 hours to an agreed shelf-life: the wording in the specification could be changed in line with BCSH recommendations:

From

'Once thawed, the component must not be refrozen and should be transfused as soon as possible. If delay is unavoidable, the component may be stored and should be used within 4 hours if maintained at 22 ± 2 °C or 24 hours if stored at 4 ± 2 °C, but it should be borne in mind that extended post-thaw storage will result in a decline in the content of labile coagulation factors'

To

- *'Once thawed, the component must not be refrozen and should be transfused as soon as possible. If delay is unavoidable, the component may be stored and should be used within 4 hours if maintained at 22 ± 2 °C or 24 hours if stored at 4 ± 2 °C. For management of major*

bleeding, thawed FFP that has been stored at 4 ± 2 °C can be used for up to 5 days, but it should be borne in mind that extended post-thaw storage will result in a decline in the content of labile coagulation factors'

- *Quality monitoring: we do not recommend any extra quality monitoring*
- *Thawing process:* In order to reduce the risk of bacterial contamination/growth the following mitigating factors must be followed
 - Use thawing methods that do not directly expose FFP units to water
 - If water baths methods are used, hospitals need to ensure that direct contact of units with water is avoided (i.e. vacuum packs)
 - Ensure that plasma thawers are decontaminated on regular basis
 - There has to be visual inspection at the time of thawing and at the time of administration of FFP
- *30 minute rule:* If extended thawed FFP is taken out of the controlled temperature environment (i.e. 2-6°C), then it should be transfused within 4 hours and only be re-issued if returned to controlled storage within 30 minutes.

Future work:

It would be desirable to gain a better understanding of:

- FFP wastage management for hospitals, as the current data are limited but variable and suggest that there may be room to improve practice. Further, it is not known whether the change to extended thawed plasma would improve either the rapidity of provision of plasma or wastage rates and this could be examined as part of any implementation.
- The difference that different thawing methods/process have on quality of extended thawed FFP

NHSBT is concurrently assessing a never frozen plasma (or liquid plasma) component. SACBC is planning to submit a paper to JPAC in March 2016 containing phase 0/1 data on for approval of a specification for this component. Currently work is being undertaken to ensure that levels of RBC and WBC are sufficiently low to obviate the need to irradiate or RhD match this component. If in the future, both liquid plasma and extended thawed FFP are used by hospitals, further work is needed to assess their cost (both from NHSBT and hospital ends) and safety.

Appendix Table 1. Studies assessing levels of coagulation factors in thawed untreated plasma

No of units and ABO group	Length of time as WB prior to freezing and temp	LD?	Stored for up to	Key findings
4 (2A & 2O)	<3 hrs	no	28d	At d28 loss of 8% fibrinogen, 40% FV, 64% FVIII (39% by d3), 20% of FIX and FXI.
15 (5A, 5B, 5O)	Not stated	Not stated	5d	No loss of FII, V, VII, X or fibrinogen. 40% loss of FVIII.
20 (5 of each ABO)	24hr 4oC (FP24)	Not stated	5d	No increase in FVIIa
5 all O	Not stated but apheresis so probably short	Not stated	14d	At d14: 35% loss of FV, 45% loss FVIII, 8% loss fibrinogen.
18 apheresis, 19 from WB	For WB<8 hrs, plasma not frozen but 4oC	Yes	28d	At d28: 60-65% loss FVIII, 25% loss FV, no loss C1-INH, no increase in d-dimers
10 FFP (5A, 5O) 10 FP24 (5A, 5O)	<8 hrs <24 hrs at 4oC	Not stated	5d	No decrease in ADAMTS13 activity after 5d for either product
30 WB FFP (all A) 39 apheresis (Ab or A)	<8hrs <2hrs	Yes	42d	Change in prekallikrein, C1-INH and PC dependent upon donor. Kallikrein generation more predominant in females. No change in ATIII or d-dimers, increase in TATover 42d.
18 (5 of each A,B, O, + 3AB)	<24hr 4oC	Not stated	5d	At d5: minimal change in fibrinogen, FII, FVIII, ATIII, PC ro ADAMTS13. Loss of FV (34%), FVII (18%), FIX (11%), PS (31%). Increase in FXI (52%) and FXII (21%).
20 (5 of each ABO)	<1 hr (apheresis)	Yes	6d	Miminal changes in fibrinogen, FXII, FXIII, PS, PC, ATIII, vWF ag. Loss of FII (10%), FV (14%), FVII (36%), FVIII (38%), FIX (11%), FXI (16%).
15 (5A, 5B, 5O)	<8 hr <24hr 4oC	Mix	5d	For FP24: minimal changes in fibrinogen, FII, FIX, FX, vWFag, ATIII, PC. Loss of FV (31%), FVII (14%), FVIII (28%), vWF activity (17%), PS (15%).
15 (8A, 4O, 2B, 1AB)	<24 hr 'room temp'	Yes	7d	Minimal loss of fibrinogen, FX, ATIII, FXI, free PS, FV. At day 5 21% loss FVII and 25% loss FVIII
14 (O:non O 1:1.8) 16 (O:non O 1:1)	<8 hour <24 hour 4oC	Not stated	5d 5d	Reduced thrombin generation day 5 v day 1 (Increased lag time, reduced ETP and peak thrombin). ROTEG: alpha angle, maximum amplitude similar Day 0 v day 5, but increase in reaction time.
30 (13 O: 17 non-O)	< 8 hour	Not stated	5d	Thrombin generation/ROTEG results as above. 50% decrease in platelet microparticles day 5 v day 0 by flow cytometry. Filtration to remove MP reduces thrombin generation.
28 O & 26 non-O	<24 hr ambient temp	Yes	5d	
10 O thawed 37oC 10 O thawed 45oC	Not stated	Not stated	20d	Loss of FV and FVIII similar whether thawed at 37 or 45oC, but thawing times faster at the higher temperature. Loss of 25% FV and 39% FVIII at day 5, with further decline to day 20. A 20% increase in FVII by day 5.

Reproduced from (Cardigan & Green, 2015)

Table 2. Residual coagulation factor/inhibitor levels in untreated plasma 5 days following thawing (% of baseline immediately post-thaw)

Type of plasma	FFP	FFP?	FFP	FFP	FFP	FFP	FFP	FP24	FP24	FP24	FP24	RT-FP24	RT-FP24	NS	NS
Fibrinogen	97	95			95	99	99	92		100	102	96	100	100	
FII					90	97	94			97	99			80	
FV	74	80			86	79	70	75		66	69	97	80	66	75
FVII					64	67	91	81		82	86	78	91	72	119
FVIII	75	60			62	53	75	65		97	72	75	65	41-67	61
FIX					89	98	94	100		89	96				
FX					89	93	98				97	100		80	
FXI					84		97	100		152		100			
FXII					102		99			121					
FXIII					100		97								
VWF antigen					100	99	92				96				
VWF activity						92	84				83				
ATIII				100	100	97	100			95	104	96			
PC					100	100	100			94	102				
PS					100	93	87	36		69	85	100			
ADAMTS13		94	100						100	93					
Antiplasmin								100							

Reproduced from (Cardigan & Green, 2015)

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