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National Comparative Audit of Blood Transfusion

NHS Blood and Transplant

National Comparative Audit of the Use of Fresh Frozen Plasma

Full Report

February 2009

Reference Copy Only

St. Elsewhere's Hospital

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EXECUTIVE SUMMARY

Key Findings

Participation and use of guidelines

- 181 centres* (175 NHS and 6 Independent) returned completed organisational audit questionnaires.

- Of these, 80% (145/181 reported the existence of guidelines for FFP use in adults and 57% (104/181 reported the existence of guidelines for paediatric use. 90% (162/181 of centres stated that they had guidelines for the management of massive haemorrhage.

- Of 181 centres, 88% (160/181) stated that they used methylene blue treated FFP for children <16yrs. 6 stated that they used only solvent detergent treated plasma.

- 183 centres (178 NHS and 5 Independent) provided clinical data on 5032 FFP transfusion events for analysis in this audit. 63 FFP transfusion events were to patients with thrombotic thrombocytopenic purpura, which were excluded from further analysis.

- The remaining 4969 transfusion events comprised 4635 (93.3%) in patients aged 16 years or over, 114 (2.3%) in children aged 1-15 years and 220 (4.4%) in infants aged less than one year.

Clinical use of FFP and bleeding

- The more common clinical groups for FFP use in adults were warfarin reversal, liver disease and surgery (including cardiac).

- Of all FFP transfusions in adults, 43% respectively were given in the absence of any documented bleeding.

- 14% of all FFP transfusions in adults were given for warfarin overanticoagulation reversal. Of these, 56% were given to patients who were not bleeding.

- In children and infants, 48% and 62% of FFP transfusions were given in the absence of any documented bleeding.

- For 28% of adults the reason for transfusion was not documented in the case notes, with a similar result for children (24%) and for infants (17%).

Laboratory testing

- 8% of adults did not have INR or prothrombin time (PT) documented before FFP was administered, whilst for children and infants this increased to 16% and 14% respectively.

- Following FFP transfusion, coagulation results were not documented for 14% of transfused adults and for about a quarter of patients under age 16 (24% of children and 29% of infants).

- 27% of adults, 48% of children and 42% of infants without documented bleeding who received FFP transfusions and who had INR tested before FFP transfusion had an INR of ≤ 1.5. Similar proportions of adults, children and infants (23%, 45% and 31%) without bleeding and with pre-transfusion PT tested had a PT of <16 seconds.

- The effect of FFP, as recorded by the difference between the first recorded post-transfusion INR or PT result and the pre-transfusion result, was very small in the majority of cases. Reduction for the three groups (adults, children and infants) ranged from 0.1 to 0.2 for INR and 1.2 to 1.9 seconds for PT.

FFP Dose

- The median overall dose of FFP administered in adults, children and infants was 11, 12 and 14 ml/kg respectively

- In 40% of adults, 24% of children and 20% of infants the dose was less than 10ml/kg.

Use of Cryoprecipitate

- Cryoprecipitate was also given to 10%, 13% and 15% of adults, children and infants within 24 hours of receiving the first FFP transfusion. Of these, 67% of adults, 64% of children and 35% of infants had fibrinogen levels of ≥ 1.0g/l.

*By centre we mean an NHS Trust, an Independent Hospital, an NHS Treatment Centre or hospitals in a Primary Care Trust

Recommendations

Use of guidelines and implementation

- Every Trust / Hospital must have guidelines for use of FFP or cryoprecipitate relevant to adult and paediatric patients

- These guidelines should also indicate where pathogen inactivated plasma (e.g. methylene blue FFP, solvent detergent treated FFP) should be used instead of FFP

- Trusts / Hospitals should empower transfusion laboratory staff to challenge medical staff about the issue of FFP where there is no clear clinical indication as defined by local guidelines.

Clinical use of FFP

- The dose of FFP should be at least 10-15 ml/kg (BCSH guideline recommendations).

- The indication for FFP use must be documented in the hospital case notes.

- The use of FFP should be guided by the results of standard coagulation tests or near patient haemostasis testing/point of care testing (e.g. thromboelastography) pre-and post transfusion.

- When reporting coagulation results on infants, appropriate neonatal ranges must be used.

- Cryoprecipitate should be used when the fibrinogen level is less that 1 g/l.

- In a massive haemorrhage setting a more pragmatic approach may be indicated as results of coagulation testing may not be readily available, and FFP and cryoprecipitate may need to be issued in an empirical manner based on the clinical severity of bleeding. This practice must be confined within recommendations as stated in a local Trust / Hospital guideline.

- Prothrombin Complex Concentrate (PCC) should be used in accordance with BCSH guideline recommendations as the treatment of choice for emergency warfarin reversal. If unavailable, then FFP should only be used for the reversal of oral anticoagulation in the event of life threatening haemorrhage. Trusts / Hospitals must review their arrangements for provision of a ready stock of PCC with a local guideline for appropriate reversal of oral anticoagulant therapy that also includes the appropriate use of vitamin K.

Recommendations for further work

- The widespread use of FFP for prophylaxis in non bleeding patients needs careful scrutiny. This audit has shown that many non bleeding patients receive FFP with normal or only minor derangements of the prothrombin time (PT) or INR.

- This audit shows that much FFP use results in minimal or no improvement or correction in coagulation abnormalities. This raises important questions around cost and risk implications and the effective use of FFP transfusion. Only high quality trials with clinical outcomes will address the issue of which patients really benefit from FFP administration. Such studies are needed to evaluate the risk-benefit profile for use of FFP, which has been described as one of the more 'high risk' blood components in relation to adverse events.

- Although the majority of cases in this audit report evaluated FFP transfusion practice for adults, a smaller number of FFP transfusion events to children and infants were available for analysis. The findings were broadly similar for these groups of patients and the general recommendations of the audit report should also apply to children and infants.

- Pending further clinical trials, the BCSH guidelines should be revised with a view to influencing practice and in particular reducing FFP use in adults and paediatric patients without overt bleeding.

Introduction

There is evidence that Fresh Frozen Plasma (FFP) may be associated with high rates of inappropriate transfusion with some studies indicating rates of up to 50% non compliance with established guidelines.[1] The current British Committee for Standards in Haematology (BCSH) guidelines on the use of FFP aim to reinforce the message regarding avoidance of its inappropriate use.[2] A systematic review of all randomised trials involving FFP found an overall lack of evidence to support benefit in all clinical areas apart from TTP. [3]

FFP is not without risk and indeed may be amongst the most 'high risk' of all blood components in relation to transfusion reactions. [4] The 2005 SHOT report [5] highlighted that 24 of 69 reported transfusion reactions occurred following FFP. It was of particular concern that in 8 of these 24 adverse reactions (33%), including 1 fatality and 2 cases of serious morbidity, there did not appear to be a good clinical indication for FFP use. The SHOT report from 2007 [6] further emphasised that there was inappropriate use in 6 of 20 cases of FFP transfusion associated with an acute transfusion reaction.

The Health Service Circular Better Blood Transfusion: Safe and Appropriate Use of Blood (HSC 2007/001) promotes the appropriate use of all blood components including FFP with avoidance of unnecessary transfusion. [7]

Aims of the audit

- To audit the clinical use of FFP against BCSH guidelines.
- To determine dosage of FFP used.
- To determine if standard coagulation testing is performed pre and post administration of FFP.
- To assess changes in standard coagulation testing after the administration of FFP.
- To evaluate the clinical use of FFP in infants and paediatric patients.

Method

All NHS Trusts, NHS Treatment Centres and Independent Hospitals in England were invited to participate in the audit. The target sample for each participating centre was 40 consecutive patients receiving FFP, or if less than 40 transfusions was likely, then all patients within a 3 month period (April to June 2008). All patients, regardless of age or gender, were eligible for inclusion in the sample. Participants had the choice of collecting data on a prospective or recent retrospective basis, depending on their operational preferences. Data entry for the patient clinical audit was directly onto the audit tool webpage designed for the purpose. The organisational audit tool was not made available online, but was printed and sent to the Consultant Haematologist with responsibility for blood transfusion in NHS hospitals, and the Hospital Manager in independent hospitals.

Standards for the use of FFP and cryoprecipitate were obtained from respective BCSH guidelines on the use of FFP [2], oral anticoagulation [8], on management of massive haemorrhage [9] and on transfusion guidelines for infants and older children [10].

National results are presented in this report as percentages for categorical data and as median and inter-quartile range (IQR) for numerical data. Missing data are reflected by variation in patient denominators.

Individual hospital results are shown alongside the national results, to facilitate benchmarking. Some of the 'Your site' results are based on small numbers of patients and hospitals need to take account of this when interpreting their own results.

Sample characteristics

Eligible centres (by centre we mean an NHS Trust, an Independent Hospital, an NHS Treatment Centre or hospitals in a Primary Care Trust) comprised 248 NHS Hospitals (of which 6 were Children's Hospitals) and 61 Independent Hospitals. Of those 309 centres, the response rate from NHS Hospitals was 75% (186/248), and the response rate from Independent Hospitals was 16% (10/61), the response being returning clinical and/or organisational data. 59% (181/309) returned data on their organisational arrangements and 59% (183/309) returned clinical data on transfusions of FFP. The clinical data comprises information on 5032 cases, with a median 28 cases (Inter-quartile range 16-40 cases) per centre. Some hospitals returned organisational data but not clinical data and vice versa. This explains the changing denominators throughout this report.

Your site contributed 40 cases.

The overall sample contained 63 cases involving plasma exchange including 18 cases of Thrombotic thrombocytopenic purpura (TTP). These were excluded from further analyses because the rationale and use of FFP for these disorders is very different and the main objective of this audit was to evaluate the wider use of FFP in hospital practice.

Your site had 3 plasma exchange cases.

The remaining 4969 FFP transfusion cases formed the basis of the analysis in this report.

PRINCIPAL FINDINGS

Guidelines for FFP use

Standard: Trusts / Hospitals should have local guidelines for use of FFP based on relevant national guidance.

Results:

Local guidelines for FFP use in adults

Of 181 centres who responded to the organisational audit, 80% (145/181 [of which 133 (92%) were NHS Hospitals]) had guidelines for FFP use in adults and 16% (29/181) did not have guidelines. 6 centres were specialist Children's Hospitals and 7 stated that they did not know about the presence of local FFP guidelines.

Local guidelines for paediatrics

Of 181 centres, 57% (104/181 [96 (92%) of which were NHS hospitals]) had local guidelines for paediatric use and 39% (70/181) did not have guidelines (7 centres stated 'not known').

Massive haemorrhage guidelines

90% (162/181) of centres (155 NHS and 7 Independent) stated that they had guidelines for management of massive haemorrhage. 43% (77/181) of centres (all NHS) also had specific guidelines for management of massive obstetric haemorrhage. 15% (28/181) (26 NHS and 2 Independent) had guidelines for massive haemorrhage in theatres or in relation to surgery, while 5% (9/181) (all NHS) had guidelines for traumatic massive haemorrhage and 5% (9/181) (all NHS) had them for acute gastro-intestinal haemorrhage.

Choice of plasma product for use in children <16years

Of 181 centres, 88% (160/181) stated that they used methylene blue FFP for children <16yrs. 6 centres (3%) stated that they used solvent detergent treated plasma. The remaining 9% said that they did not treat patients in this age group or did not state clearly the type of component used.
3 NHS Hospitals stated that they were not using MB FFP

Patient data

The age distribution of the remaining sample of 4969 cases is shown below. 93.3% (4635) were aged 16 years or over (adults), 2.3% (114) aged 1-15 years (children) and 4.4% (220 cases) aged less than one year (infants).

Your site contributed 36 case(s) aged 16 years and over, 0 case(s) aged 1-15 years and 1 case(s) aged less than one year.

Figure 1: Age in years at initial FFP transfusion

The remaining results are stratified by these age groups. A cut-off of age 16 was selected because the National Blood Service provides specialised blood components up to the age of 16.

Where FFP was given in the three age groups

FFP transfusions to adults were given most frequently in theatres/recovery (23%), or Intensive Treatment Unit / High Dependency Units (32%), or on medical wards (22%). Most FFP transfusions to children and infants were given in neonatal/paediatric Intensive Care Units (33% in children and 80% in infants), or theatres/recovery (35% in children and 14% in infants).

The underlying medical or surgical conditions and the reasons for FFP transfusion

BCSH guidelines include the following groups of clinical indications: single coagulation factor deficiencies, multiple coagulation factor deficiencies e.g. Disseminated Intravascular Coagulation (DIC), Thrombotic Thrombocytopenic Purpura (TTP), reversal of warfarin overanticoagulation, vitamin K deficiency in the intensive care unit, liver disease, surgical bleeding and massive transfusion. These groups formed the basis of the subdivisions used in this audit report. For paediatric / neonatal use, additional indications have been included as below, reflecting the specific guidelines.

Table 1: Underlying medical or surgical conditions

Q6 What was the underlying medical or surgical condition?	Age 16+ years[1]				Age 1-15 years[2]				Age < 1 year[3]			
	National (4635)		Your site (36)		National (114)		Your site (0)		National (220)		Your site (1)	
Warfarin reversal	14%	669	3%	1	3%	3	%		-	0	0%	0
Disseminated Intravascular Coagulopathy (DIC)	3%	148	0%	0	9%	10	%		6%	14	0%	0
Massive haemorrhage (as defined in your hospital)	13%	590	3%	1	3%	3	%		3%	7	0%	0
Cancer	10%	451	28%	10	12%	14	%		2%	5	0%	0
Liver disease	19%	886	47%	17	4%	5	%		5%	12	0%	0
Cardiac surgery	13%	587	0%	0	15%	17	%		20%	43	0%	0
Other surgery	21%	974	17%	6	24%	27	%		8%	18	0%	0
Trauma	3%	158	0%	0	5%	6	%		-	0	0%	0
Other*	18%	812	%	5	34%	39	%		57%	126	100%	1

*The 977 patients in the Other category for the 3 age groups were sub-grouped as follows:

812 patients aged > 16+ years: Bleeding - but not massive haemorrhage (298) where bleeding site included gastrointestinal - 196, intracranial/subdural - 37, related to childbirth - 24 and other sites - 41; Sepsis (193), Renal failure (52), Cardiac failure/post cardiac arrest (34), other gastrointestinal conditions e.g. colitis, bowel obstruction (67), Others (121).

39 patients aged 1 - 15 years: Sepsis (14), burns (6), renal impairment (6), others (13)

126 patients aged <1yr : Sepsis (33), prematurity (24), unspecified coagulopathy/deranged clotting (28), bleeding – intraventricular haemorrhage, necrotising enterocolitis or unspecified (17) There was one reported case of FFP use for haemorrhagic disease of the newborn/vitamin K deficiency, one for haemophilia, and others (22).

COMMENT:
The more common groups of patients for FFP use in adults were warfarin reversal, liver disease and surgery (including cardiac).

Table 2: Main reasons for FFP transfusion

To understand better the clinical rationale for FFP administration, responses were sought about the main reasons for FFP transfusion

Q8 Which (one) of these best describe the reasons for giving this initial FFP transfusion?	Age 16+ years				Age 1-15 years				Age < 1 year			
	National (4635)		Your site (36)		National (114)		Your site (0)		National (220)		Your site (1)	
Bleeding	54%	2503	17%	6	44%	50	%		36%	80	0%	
Before invasive procedure or surgery, with abnormal coagulation	23%	1069	53%	19	16%	18	%		6%	14	0%	
During invasive procedure or surgery, with abnormal coagulation but no bleeding	8%	360	8%	3	14%	16	%		13%	29	0%	
Abnormal coagulation with no bleeding	12%	575	19%	7	18%	21	%		42%	93	100%	1
Other	1%	34	3%	1	4%	4	%		1%	2	0%	
Not documented / not known / blank	2%	94	0%		4%	5	%		1%	2	0%	

COMMENT

43% of all FFP transfusions were given to adult patients in the absence of any documented bleeding. In children and infants 48% and 62% of FFP transfusions respectively were given in the absence of any documented bleeding. Where FFP was given for bleeding, it was not possible to differentiate between minor or more severe grades of bleeding in this audit.

Use of FFP for warfarin reversal

Standard: BCSH guidelines on administration of FFP and BCSH guidelines on oral anticoagulation state that the reversal of anticoagulation in patients with major bleeding requires administration of a prothrombin complex concentrate. FFP has only a partial effect, is not the optimal treatment and should never be used for the reversal of warfarin over-anticoagulation in the absence of severe bleeding.

89% (161/181) had guidelines for management of over-anticoagulation with warfarin, while 9% (17/181) did not have guidelines. (Not known for 3 sites).

Table 3: FFP given for Warfarin reversal

	Age 16+ years with Warfarin reversal				Age 1-15 years with Warfarin reversal			
	National (669)		Your site (1)		National (3)		Your site ()	
% non-bleeding*	56%	374/667	100%	1/1	33%	1/3	%	/0

*Non-bleeding patients: Before/during invasive procedure/surgery with abnormal coagulation, or abnormal coagulation with no bleeding

There were no warfarin reversal cases for patients aged less than one year.

There were 374 cases identified for whom FFP was given for warfarin reversal in the absence of bleeding:

- 298 (79%) of these 374 cases were treated in 117 sites that had warfarin guidelines, 25 in 8 sites without guidelines and 52 in sites where it was not known if guidelines existed.
- 291 (78%) of these 374 cases were treated in 115 hospitals that used PCC, 41 in 12 sites that did not use PCC and 43 in 9 sites where it was not known if PCC was used.

Comment
In adults 14% (669/4635) of all FFP transfusions were given for warfarin reversal. Of these, 56% (374/667) were given to patients who were not bleeding.

Documentation in case Notes

Standard: The reason for transfusing FFP should be recorded in the patient's medical records.

Table 4: Documentation in case notes

Q21 Is the reason for this initial FFP transfusion documented in the patient's records?	Age 16+ years				Age 1-15 years				Age < 1 year			
	National (4635)		Your site (36)		National (114)		Your site (0)		National (220)		Your site (1)	
Yes	71%	3274	78%	28	75%	86	%		81%	179	100%	1
No	28%	1279	22%	8	24%	27	%		17%	37	0%	
Blank=Not known	2%	82	0%		1%	1	%		2%	4	0%	

Comment
For adults just over a quarter of patients did not have the reason for FFP transfusion documented in the case notes, with a similar proportion for children. Around 1 in 6 infants did not have the reason documented (a total of 37 cases from 24 hospitals).

Dose of FFP given

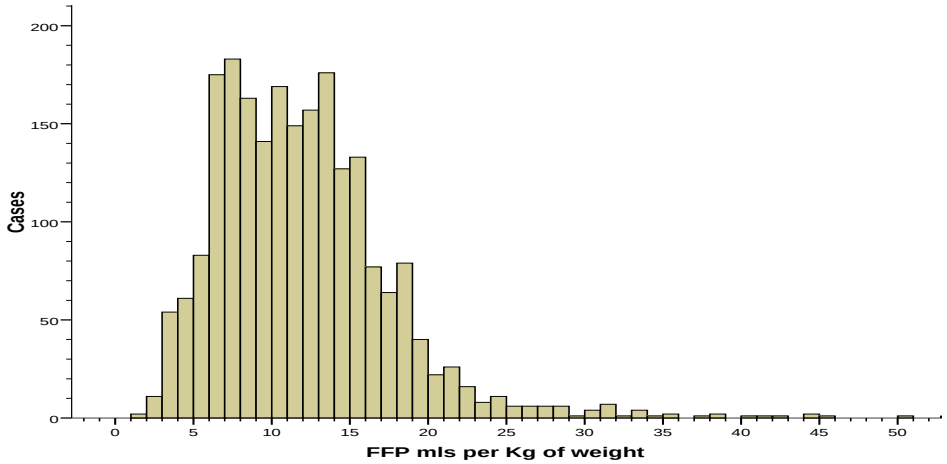
Standard: BCSH guidelines refer to a standard dose of 10-15ml/kg although this may be exceeded in massive haemorrhage.

The distribution of doses by weight for patients where this data is available is shown in the histograms below.

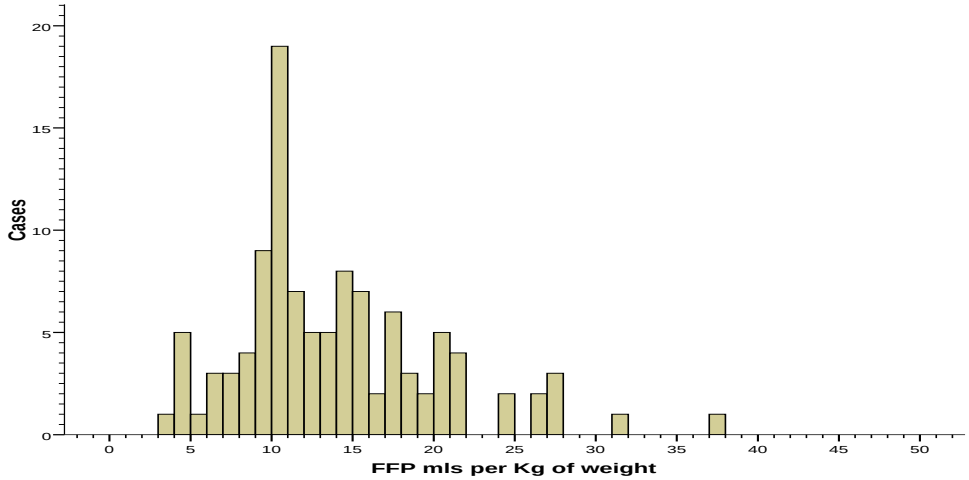
Comment
There was wide variation in the dose of FFP transfused by weight.
The median overall dose in adults, children and infants was 11ml/kg, 12ml/kg and 14ml/kg respectively.
In 40% of adults (873/2186) the dose was less than 10ml/kg.

Figure 2 : FFP (mls) per Kg of weight

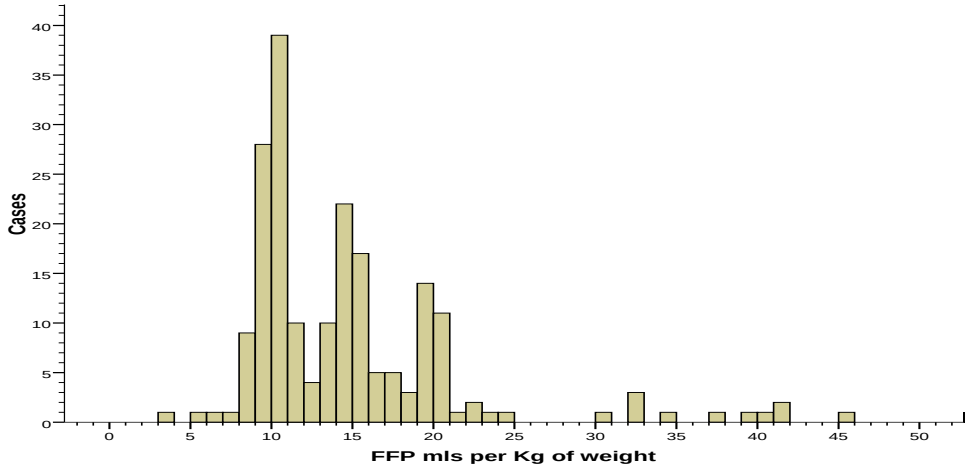
16 + years



1-15 years



<1 year



11 outliers (5 if <1 year, 6 if 16+ years) of >50 mls/Kg were omitted from the figure.
FFP per Kg was known for 203/220 if <1 year, 104/114 for 1-15 years, 2188/4635 if 16+ years.

The use of coagulation screening tests (PT or INR)

Standard: BCSH guidelines indicate that when FFP is given, the degree of correction of laboratory coagulation tests should be documented. The laboratory response to FFP transfusion could be monitored either using standard laboratory coagulation tests (e.g. PT) or through point of care testing.

Table 5: Reporting of standard coagulation screen tests: PT and/or INR

Either INR or PT test reported	Age 16+ years				Age 1-15 years				Age < 1 year			
	National (4635)		Your site (36)		National (114)		Your site (0)		National (220)		Your site (1)	
Before FFP was given	92%	4287	100%	36	84%	96	%		86%	190	100%	1
<24 hours after FFP given	86%	3977	89%	32	76%	87	%		71%	157	100%	1

Comment
8% of adults did not have INR or PT reported before FFP was given, whilst for children and infants this increased to 16% and 14% respectively. Following FFP transfusion, hospitals were unable to provide coagulation results for 14% of adults, and for 26% of patients under aged 16.

Degree of abnormality of coagulation testing before FFP transfusion in non-bleeding patients

The table below summarizes information on coagulation testing in patients with no documented bleeding. Patients with bleeding were excluded from this analysis because the management of such patients, particularly in the emergency setting, may need to be empirical in the absence of ready availability of coagulation test results.

Table 6: Degree of abnormality of coagulation testing before FFP transfusion in non-bleeding patients

	Age 16+ years				Age 1-15 years				Age < 1 year			
Pre FFP	**National (2004)***		**Your site (29)**		**National (55)***		**Your site (0)**		**National (136)***		**Your site (1)**	
INR ≤ 1.5	27%	381/1409	33%	1/3	48%	10/21	%	/0	42%	28/67	%	/0
PT <16 sec	23%	319/1416	41%	12/29	45%	18/40	%	/0	31%	30/98	0%	0/1

*Non-bleeding patients: Before/during invasive procedure/surgery with abnormal coagulation, or abnormal coagulation with no bleeding.

Comment
27% of adults, 48% of children and 42% of infants without bleeding who received FFP transfusions and who had INR tested had INR ≤ 1.5. Similar proportions (23%, 45% and 31%) without bleeding and with PT tested had PT <16 seconds.

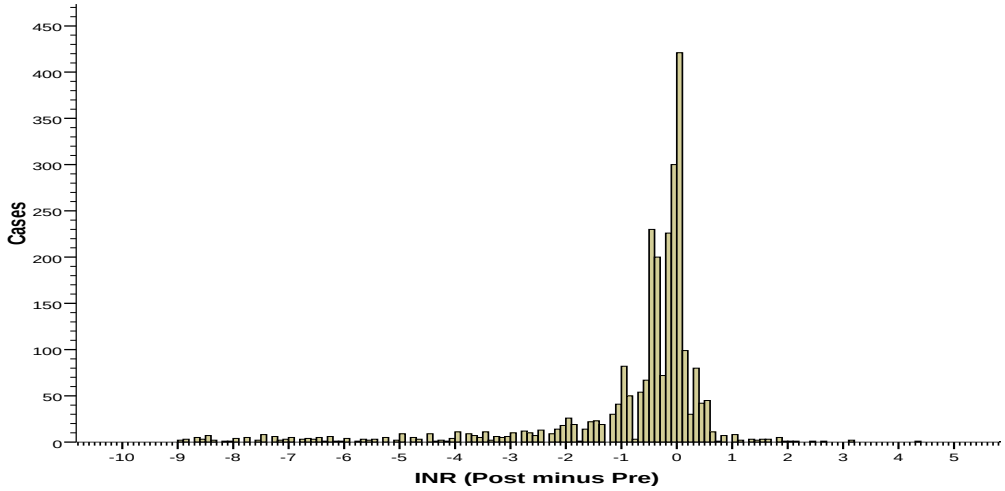
Changes in PT and INR after FFP administration

The following three histograms illustrate the level of correction of INR (i.e. pre minus post transfusion) for all patients in the three different age groups. Similar histograms were obtained for the analysis of data for correction of PT.

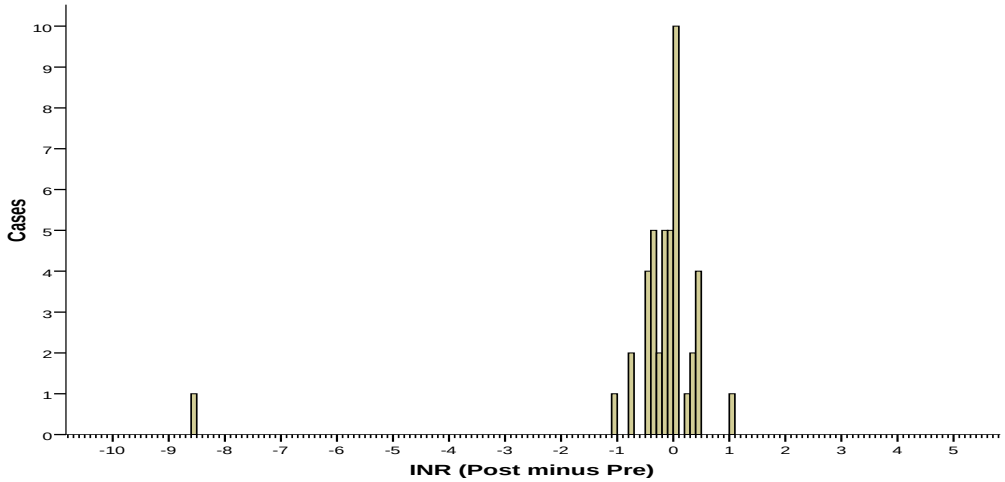
Comment
The effect of FFP, as recorded by the difference between the first recorded post-transfusion INR or PT result and the pre transfusion result was very small in the majority of cases.
For patients without documented bleeding, the median reduction in INR was 0.3 and in prothrombin time was 2 seconds.

Figure 3: (Post minus pre) INR results

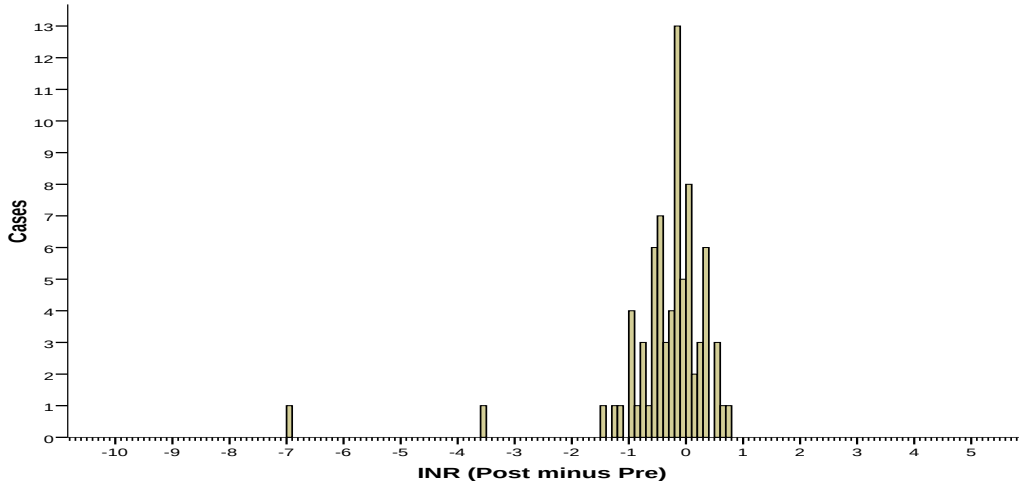
16 + years



1-15 years



<1 year



2 outliers (both16+ years) of >5 were omitted from the figure.
(Post minus Pre) INR was known for 76/220 if <1 year, 43/114 for 1-15 years, 2543/4635 if 16+ years.

Reference ranges for neonatal patients

Standard: Results for neonatal patients should be compared to a specific paediatric reference range and not adult ranges, due to physiological differences.

Table 7: Separate laboratory reference range for neonatal patients

	National (171 sites)*		Your site
Separate laboratory reference range for neonatal patients	32%	56/176	Yes

*excludes 5 hospitals that do not treat children

Comment
Hospitals should review their reference ranges used for reporting neonatal coagulation results: it is inappropriate to use adult ranges for interpreting results in this patient group.

Use of Cryoprecipitate

Standard: BCSH guidelines on massive haemorrhage state that cryoprecipitate is indicated if the fibrinogen level is <1.0g/l.

Table 8: Use of Cryoprecipitate

Cryoprecipitate given with the initial FFP episode and/or in following 24 hours	Age 16+ years				Age 1-15 years				Age < 1 year			
	National (4635)		Your site (36)		National (114)		Your site (0)		National (220)		Your site (1)	
% patients treated with FFP who received Cryoprecipitate	10%	470	17%	6	13%	15	%		15%	33	0%	0
% patients with a pre FFP Fibrinogen <1.0 g/l if Cryoprecipitate given	33%	111/336	50%	3/6	36%	5/14	%	/0	65%	17/26	%	/0
% patients treated with cryoprecipitate if pre FFP Fibrinogen <1.0 g/l	49%	111/228	75%	3/4	56%	5/9	%	/0	39%	17/44	%	/0

Comment
Of all patients receiving FFP transfusion, cryoprecipitate was also given to 10%, 13% and 15% of adults, children and infants respectively. In many of these patients receiving cryoprecipitate (67% of adults, 64% of children and 35% of infants) the fibrinogen was ≥ 1.0g/l. Conversely, only 49% of adults, 56% of children and 39% of infants who had fibrinogen <1.0g/l were reported as having received cryoprecipitate transfusion.

Discussion

The aim of this audit was to evaluate use of FFP by comparison to current BCSH guidelines. The analysis of data from 5032 FFP events ensures that the report is based on a sufficiently large and representative sample of practice. The findings therefore have the credibility to promote meaningful multidisciplinary discussion on appropriate use of FFP to bring about a change in practice.

One of the main findings from the audit was the high proportion of FFP use for patients without documented bleeding. Many non-bleeding patients continue to receive FFP with only minor derangements of their prothrombin times or INR or even with normal coagulation results. The findings also indicate that use of FFP results in only minimal or no improvement or correction in prothrombin time or INR. Hospitals should empower transfusion laboratory staff to question medical staff about the use of FFP where there is no clear clinical indication for its use in adult and paediatric patients without overt bleeding.

FFP also continues to be used for reversal of warfarin over-anticoagulation, and in many patients without bleeding, and this raises important issues about the appropriate use of vitamin K and prothrombin complex concentrates.

Although the majority of cases in this audit report evaluated FFP transfusion practice for adults, there were a number of FFP transfusion events in children and infants also available for analysis. The findings appeared broadly similar for these groups of patients and the general recommendations of the audit report therefore apply to adult and paediatric patients.

Supplementary Findings

Introduction

The following three sections provide additional details for selected results from the audit. These results have been presented separately for:

- adults (starting below, page 23),
- children (starting page 37), and
- infants (page 68).

All three sections include some common findings already reported in the main summary report, so that the individual sections can also be read as separate papers.

Section A - Adults aged 16 years and over (n=4635)

Overview

The median (IQR) age was 67 (52-77) years. Weights were known for 47% (2188/4635), median (IQR) of 73 (62-85) Kg.

Table A1: Where FFP was given

Q1 - Where was patient when FFP administered?	National (4635)	
Theatres/recovery	23%	1048
A&E	6%	284
Surgical ward	13%	584
Medical ward	22%	1011
Intensive Treatment Unit / High Dependency Unit	32%	1465
Haematology/oncology	2%	86
Day care	0.2%	10
Don't know	1%	50
Other	2%	97

Summary Box
32% FFP transfusions were used in Intensive Treatment Unit / High Dependency Units, 23% in theatres/recovery and 22% on medical wards.

The underlying medical or surgical conditions and the main reasons for FFP transfusion

BCSH guidelines (2004) include the following groups of clinical indications: single coagulation factor deficiencies; multiple coagulation factor deficiencies e.g. Disseminated Intravascular Coagulation (DIC); Thrombotic Thrombocytopenic Purpura (TTP); reversal of warfarin effect; vitamin K deficiency in intensive care; liver disease; surgical bleeding; and massive transfusion. These groups formed the basis of the subdivisions used in this section of the audit report, alongside further questions addressing the use of FFP for either bleeding, or prior to surgery or an invasive procedure.

- **Selected BCSH guideline recommendations**
- FFP and other components are not routinely indicated if patient has Disseminated Intravascular Coagulation (DIC) without bleeding
- FFP has only a partial effect, is not the original treatment and should never be used for the reversal of warfarin anticoagulation in the absence of severe bleeding
- FFP is advocated by some for the prevention of bleeding in patients with liver disease and a prolonged Prothrombin Time (PT), although the response may be unpredictable: available evidence suggests that patients with liver disease and a raised PT are unlikely to benefit from FFP

Table A2: The underlying medical or surgical conditions

Q6 - What was the underlying medical or surgical condition?	**National (4635)**	
Reversal of warfarin over-anticoagulation	14%	669
Disseminated Intravascular Coagulopathy (DIC)	3%	148
Massive haemorrhage (as defined in your hospital)	13%	590
Cancer	10%	451
Liver disease	19%	886
Cardiac surgery	13%	587
Other surgery	21%	974
Trauma	3%	158
Other*	18%	812

Multiple answers were possible - 621 had two conditions stated, 42 had more than two stated. 68 had none stated.

*812 patients aged over 16 years : **A.** Bleeding (but not massive haemorrhage): n=298, including Gastrointestinal – 196 Intracranial/subdural – 37; Related to childbirth (but not MOH) -24; and other sites - 41. **B**. Sepsis -193. **C**. Renal failure – 52. **D**. Cardiac failure/post cardiac arrest – 34. **E**: Other gastrointestinal conditions (e.g. colitis, bowel obstruction, etc) – 67. **F:** Others; n=121.

To understand better the clinical rationale for FFP administration, responses were then sought about the main reasons for FFP transfusion.

Table A3: The main reasons for giving FFP

Q8 - Which (one) of these best describe the reasons for giving this initial FFP transfusion?	National (4635)	
Bleeding	54%	2503
Before invasive procedure or surgery, with abnormal coagulation	23%	1069
During invasive procedure or surgery, with abnormal coagulation	8%	360
Abnormal coagulation with no bleeding	12%	575
Other	1%	34
Not documented / not known / blank	2%	94

Underlying medical or surgical condition

Based on the results of question 8 (Table A3), it was possible to subdivide patients receiving FFP into two broad groups: those with any documented bleeding, and those without bleeding, encompassing the use of FFP before or during invasive procedure/surgery with abnormal coagulation, or for abnormal coagulation with no bleeding.

These main reasons for initial FFP transfusion were then applied to the categories of underlying medical or surgical conditions, shown in Table A2. The underlying diagnoses with the highest proportions of FFP use in non-bleeding patients were cancer, warfarin anticoagulation reversal and liver disease. Although some cases of apparent massive haemorrhage were recorded as non-bleeding, this may reflect differences in the actual timing of the audited FFP transfusion in relation to on-going bleeding, and in some cases other underlying conditions were documented

Table A4: Medical or surgical condition in conjunction with bleeding

	Q8: Reason for initial FFP			
Q6 underlying medical or surgical condition	Bleed		Non-bleed*	
Warfarin reversal	44%	293	56%	374
Disseminated Intravascular Coagulopathy DIC	52%	77	48%	71
Massive haemorrhage	95%	560	5%	30
Cancer	39%	169	61%	263
Liver disease	44%	389	56%	486
Cardiac surgery	68%	381	32%	181
Other surgery	55%	528	45%	429
Trauma	67%	105	33%	51
Other **	48%	371	52%	421
Total	56%	2503	44%	2004

*Non-bleed: Before/during invasive procedure/surgery with abnormal coagulation, or abnormal coagulation with no bleeding

**Other includes 2 Trauma, 3 Liver, 1 other surgery, 1 warfarin & other surgery, 1 trauma and warfarin

Summary Box
The more common stated underlying conditions were warfarin reversal, liver disease and surgery (including cardiac).
A significant number (43%) of all FFP transfusions were given to adult patients in the absence of any recorded bleeding.
Although 54% of all FFP transfusions were given to adult patients with some documented bleeding, it was not possible to differentiate between more minor or more severe grades of bleeding in this audit.

Bleeding characteristics

Details of bleeding were requested for FFP transfusions related to clinical bleeding, and the responses are shown in table A5 below.

Table A5: Bleeding characteristics

Q10 If bleeding, which site(s)?	National (2503)	
Skin / subcutaneous	4%	93
Catheter / line	4%	102
Intracranial	3%	80
Nose / mouth	4%	107
Respiratory system	2%	62
Gastrointestinal system	47%	1181
Haematuria	3%	70
Gynae	4%	112
Vascular including cardiac	19%	479
Obstetric	4%	107
Musculoskeletal	5%	136
Other	1%	31
None of the above stated	7%	164

One site was stated for 2175, two sites for 126 and more than two sites for 38.

Summary Box
The commonest sites for bleeding were gastrointestinal and vascular

Procedures or surgery

Additional details of surgery and procedures were requested for FFP transfusions related to these interventions.

Table A6: Patients undergoing procedures or surgery

Q12-19 If patient underwent a procedure or surgery, please indicate which	National (4635)	
Biopsy	2%	115
Endoscopy	10%	470
Central line insertion /removal	8%	381
Cardiac surgery	12%	534
Liver surgery	1%	50
Other surgery*:	37%	1735
• Vascular surgery	4%	201
• Orthopaedics	4%	188
• Hysterectomy / gynaecology	1%	57
• Childbirth /ectopic /pregnancy /caesarean	1%	62
• Laparotomy	15%	703
• Other surgery (e.g. neuro, ENT, burns, debridement, drainage)	3%	151
• Other procedures (e.g. laparoscopy, tracheostomies, CT guided draining, chest drain, angiography, ascitic tap/drain)	7%	347
None of the above stated	33%	1496

*Other sub-categories were derived from the dataset and were not options listed on the audit tool

Summary Box
The more common types of surgery associated with FFP transfusion included laparotomy and cardiac surgery.
The more common types of procedures included endoscopy and central line insertion/removal.

Table A7: Documentation in case notes

Q21 Is the reason for this initial FFP transfusion documented in the patient's records?	Age 16+ years National (4635)	
Yes	71%	3274
No	28%	1279
Blank=Not known	2%	82

FFP dose in relation to weight

BCSH guidelines refer to a traditional dose of 10-15 ml/kg for adults, although this may be exceeded in massive bleeding. Dose per Kg weight was known for 47% (2186). Total median dose (IQR) per Kg was 11 (8-15).

Note that dose variation by whether weight was known or not was very similar suggesting that the dose per weight values recorded here are representative of the whole.

Table A8: FFP volume by whether weight known

	Weight known (2188)		**Weight not known (2447)**	
≤1 unit (≤273mls)	5%	102	5%	131
>1 but ≤2 units (274-586mls)	33%	730	37%	909
>2 but ≤3 units (587-819mls)	18%	400	14%	345
>3 but ≤4 units (820-1092mls)	37%	812	38%	922
>4 units (>1092mls)	6%	142	5%	120
Volume not known	0.1%	2	1%	20

The distribution of doses by weight for patients 16+ years, where this data was available, is shown in figure 2 on page 15 of this report.

Summary Box
There was wide variation in the dose of FFP transfused, by weight.
The median overall dose was 11 ml/kg.
In 40% (873/2186) of cases the dose was less than 10 ml/kg, and in 76% (1651/2186) the dose was less than 15ml/kg.

The use of coagulation screen tests (INR or PT)

Standard: BCSH guidelines indicate that if FFP is given to correct laboratory abnormalities, the degree of correction should be recorded. The laboratory response to FFP transfusion should be monitored either using laboratory tests or through point of care testing.

Table A9: Reporting of coagulation screen tests: PT and/or INR

Either INR or PT test reported	National (4635)	
Before FFP was given	92%	4287
<24 hours after FFP given	86%	3977

Summary Box
INR or PT was recorded as undertaken prior to FFP transfusion in 92% of cases.
The INR was reported as the only coagulation test for 22% (1039/4635) of all adults; 45% (2108/4635) reported both INR and PT.
86% had INR or PT results documented up to 24 hours after FFP transfusion

Laboratory Coagulation Tests including PT
The standard laboratory coagulation tests including PT were originally developed to investigate coagulation factor deficiencies in patients with a bleeding history, by providing an end-assessment of thrombin generation by fibrin formation. However, the important issue of their applied clinical value in different clinical settings continues to be raised. PT results are dependent on reagent and laboratory quality controls and processes, and may be abnormal for a number of reasons not associated with bleeding risk. Some laboratories in this audit reported the INR only, but the INR was developed to monitor warfarin therapy, by standardising results to account for different sensitivities of thromboplastins. The extrapolation of PT to INR may only be valid for those patients stably anti-coagulated with vitamin K antagonists, and may not be appropriate for many other patients, with, for example, liver disease. *Please note that results for APTT have not been presented in this report.*

The degree of abnormality of coagulation testing before FFP transfusion

Tables A10 and A11 and histograms below summarize the range of results for INR or PT prior to FFP transfusion in adults. The data in the Tables has been divided into groups of patients, based on the responses to questions 6 and 8, which allow us to present the findings for:

- patients with any recorded bleeding;
- patients without bleeding, i.e. for whom FFP was transfused before or during invasive procedure/surgery with abnormal coagulation, or abnormal coagulation with no bleeding;
- patients for warfarin over-anticoagulation reversal.

Table A10: The degree of abnormality of coagulation testing before FFP transfusion

	INR (Pre FFP)			PT (Pre FFP)		
	median	**IQR**	**n**	**median**	**IQR**	**n**
With bleeding	1.6	1.2-2.3	1667	18	14-24	1747
Without bleeding	1.9	1.5-2.7	1409	20	16-28	1416
Warfarin reversal	3.2	2.2-5.3	575	40	27-69	374

NOTE: The organisational audit asked about limits of normal for prothrombin times (PT) for adults. The site median for the upper limit of normal was 13.8, IQR 12.7 to 15.0, range 11.0 to 19.0, n=147 sites. A cut-off of 16 and 25 seconds in the table below broadly reflects INR thresholds of 1.2 and 1.8.

Table A11	**Q8 Reason for initial FFP**			
% With:	**Bleeding**		**Non-bleeding***	
Pre FFP INR <=1.5	48%	802/1667	27%	381/1409
Pre FFP INR >1.5 but <=2.0	21%	354/1667	32%	445/1409
Pre FFP PT < 16 sec	38%	662/1747	23%	319/1416
Pre FFP PT 16-24 sec	39%	682/1747	46%	653/1416
Pre FFP PT >= 25 sec	23%	403/1747	31%	444/1416

*Before/during invasive procedure/surgery with abnormal coagulation, or abnormal coagulation with no bleeding

Summary Box

There is a wide range of INR and/or PT results prior to the FFP administration.

The median INR prior to FFP administration in patients with bleeding was 1.6 (IQR 1.2 – 2.3).

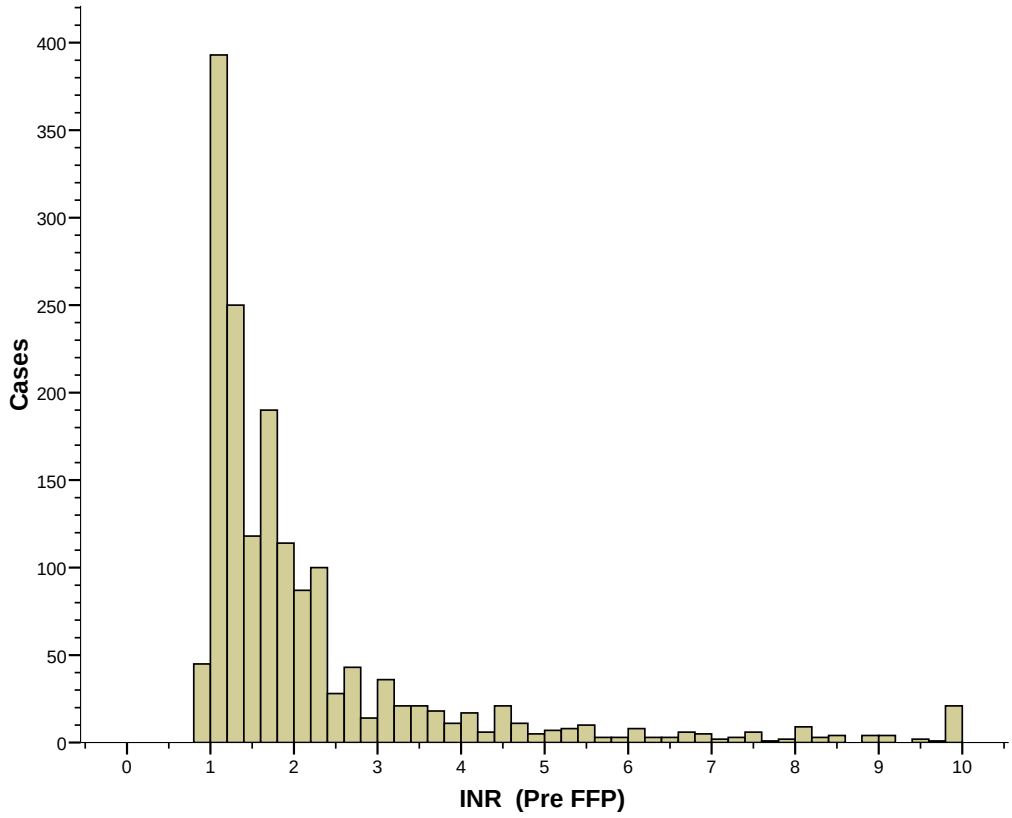
The median INR prior to FFP administration in patients with no recorded bleeding was 1.9 (IQR 1.5 – 2.7)

The median INR prior to FFP administration in patients for Warfarin overanticoagulation reversal was 3.2 (IQR 2.2 – 5.3).

23% and 27% of patients without bleeding (recorded as before or during invasive procedure/surgery with abnormal coagulation, or abnormal coagulation with no bleeding) who received FFP transfusions had normal levels of PT or INR respectively (defined as PT<16s and INR<=1.5).

46% and 32% of patients without bleeding (recorded as before or during invasive procedure/surgery with abnormal coagulation, or abnormal coagulation with no bleeding) who received FFP transfusions had only mild abnormalities of PT or INR respectively (defined as PT 16-24s and INR 1.5 -1.9).

Figure A1 - INR/PT results prior to FFP transfusion in adult patients with bleeding



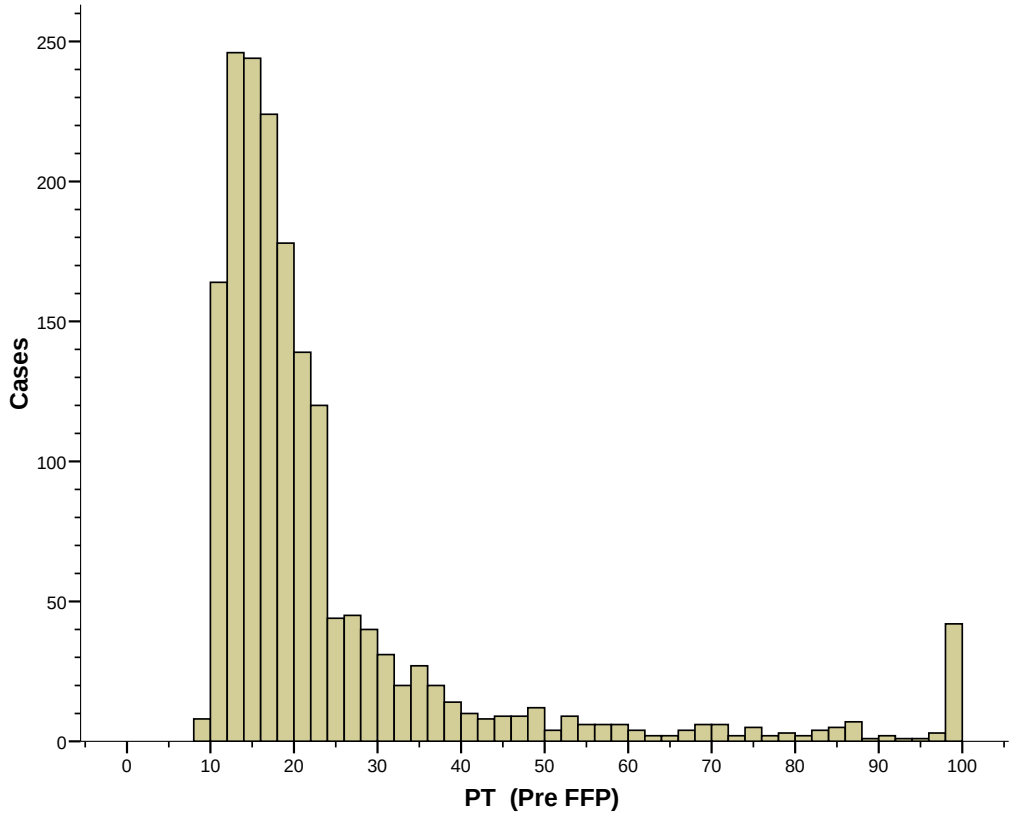
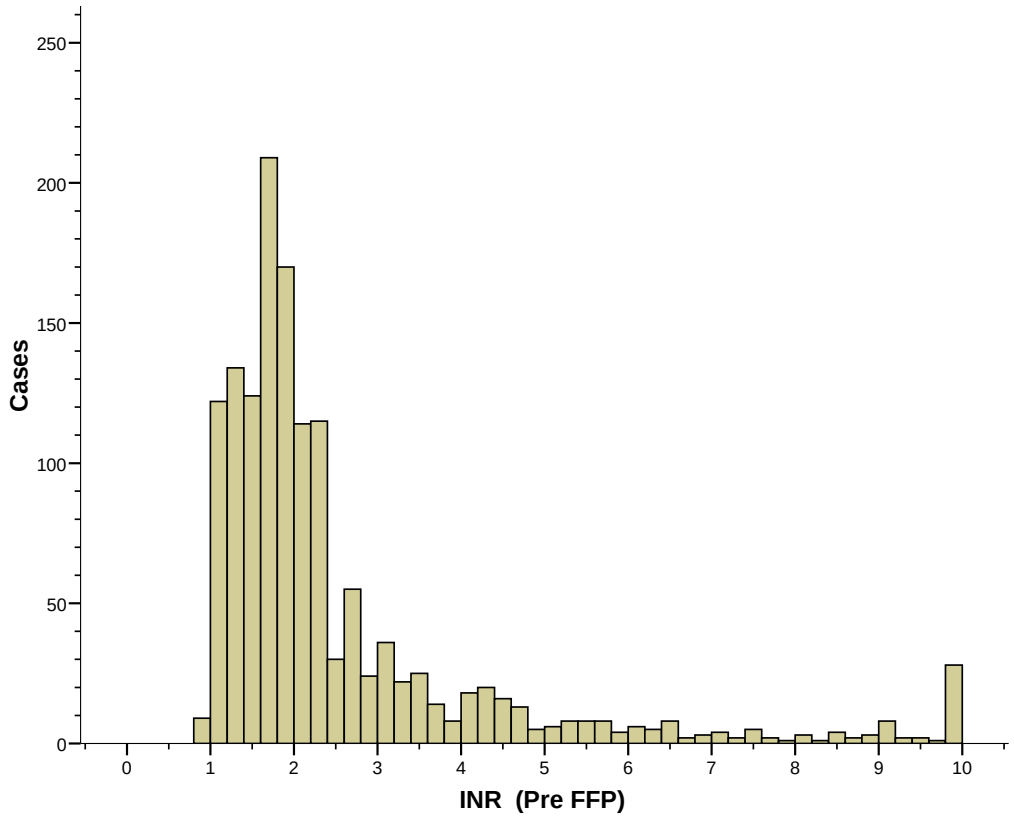


Figure A2 - INR/PT results prior to FFP transfusion in adult patients without bleeding



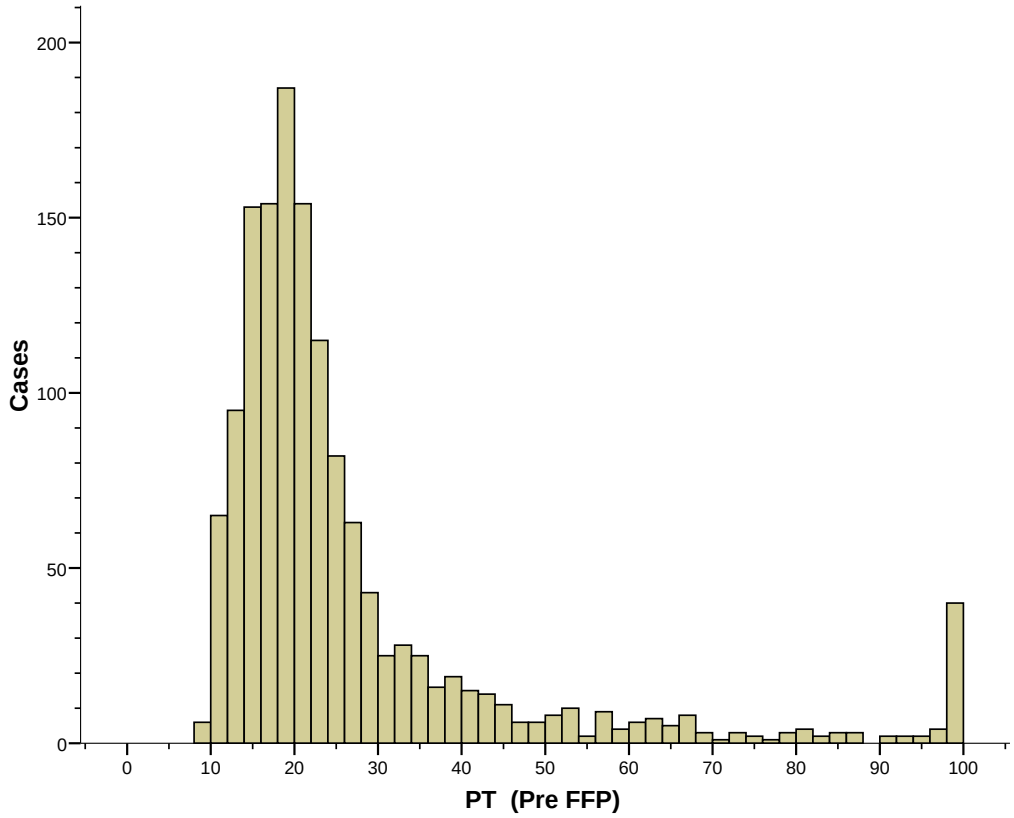
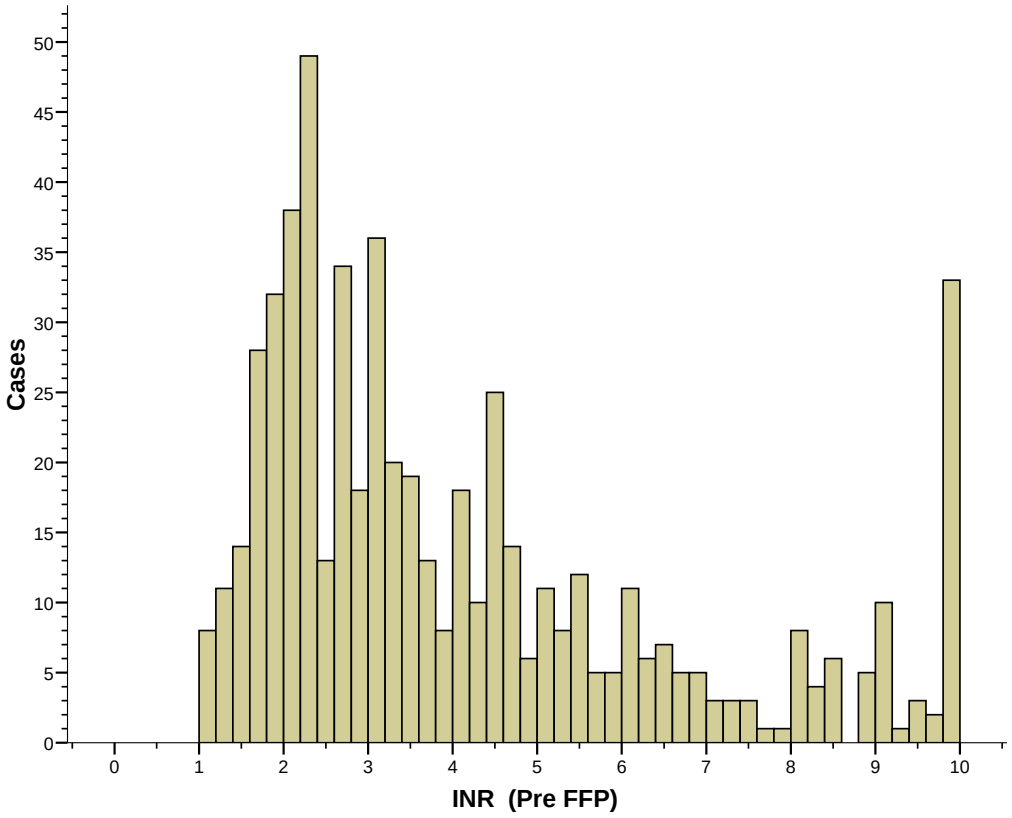
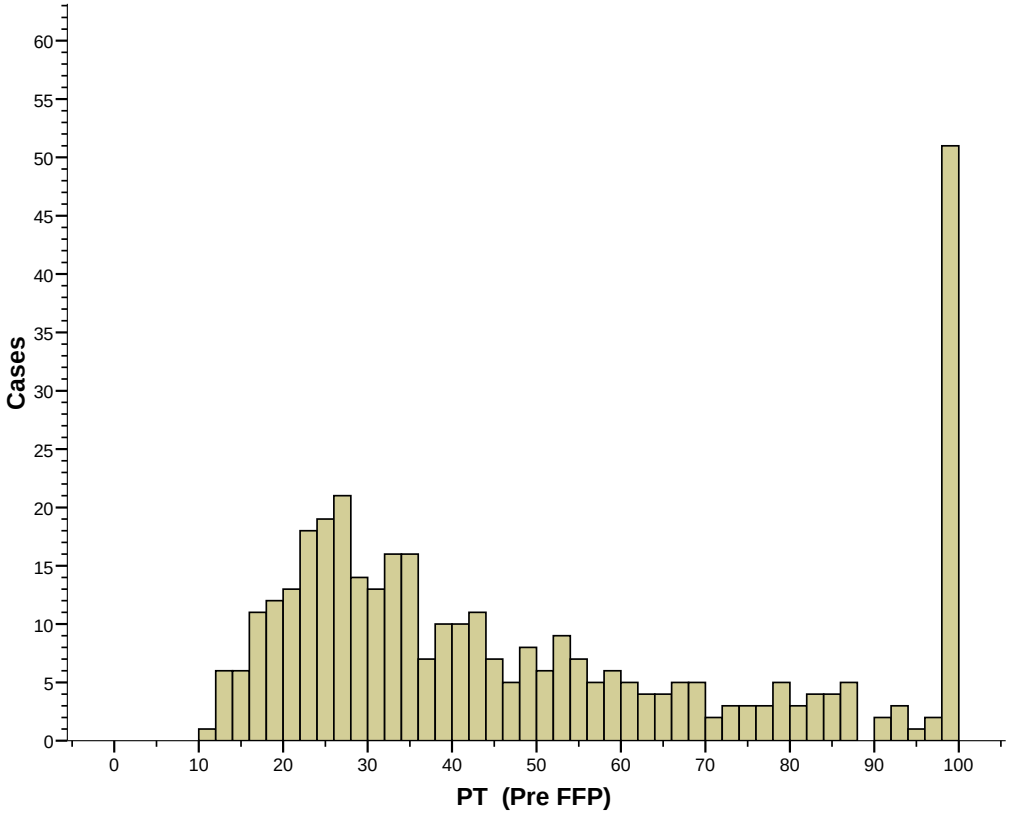


Figure A3 - INR/PT results prior to FFP transfusion in adult patients with warfarin related over-anticoagulation





The effect of FFP administration: changes in INR or PT

❖ **BCSH guideline recommendation**

➢ If FFP is given to correct abnormal coagulation parameters, the degree of correction should be recorded.

The effect of FFP administration on changes in the standard coagulation tests (INR or PT) for adult patients is summarised below:

Table A12: Change in INR or PT	National
INR (Post minus Pre FFP)	
• Median	-0.20
• IQR	-0.70 to 0.00
• Cases	2543
PT *seconds* (Post minus Pre FFP)	
• Median	-1.90
• IQR	-5.90 to +0.10
• Cases	2701

These changes were also analysed by category of patient group according to underlying medical or surgical condition (Question 6) and to the reasons for giving the FFP transfusion (Question 8; subdividing patients receiving FFP into two main groups: those with recorded bleeding, and those without, i.e. for whom FFP was transfused before or during invasive procedure/surgery with abnormal coagulation, or abnormal coagulation with no bleeding), as described in Table A13 on the following page.

Summary Box

The effect of FFP, as recorded by the difference between the first recorded post-transfusion INR or PT result and the pre-transfusion result was very small when results for all adults were evaluated.

The median reduction in INR was 0.2 and in PT was 1.9 seconds, and the IQR for both tests included 0.

The effect of FFP, as recorded by the difference between the pre-transfusion result and the first recorded post-transfusion INR or PT result within 24 hours was also very small in all underlying medical conditions, including those without documented bleeding, with the exception of patients requiring warfarin anticoagulation reversal.

In patients with warfarin overanticoagulation requiring reversal, the net reductions in INR or PT were more marked although FFP use in this context may have been inappropriate.

Table A13 - The effect of FFP administration: changes in INR or PT in different clinical situations

Underlying condition	Reason for FFP		FFP dose per Kg			INR (Post minus Pre FFP)			PT (Post minus Pre FFP)		
		N	median	IQR	n	median	IQR	n	median	IQR	n
Warfarin reversal	Bleed	293	11	7-15	93	-2.1	-3.9 to -0.9	181	-25	-51 to -11	127
	Non-bleed*	374	11	8-14	148	-1.0	-2.8 to -0.4	277	-13	-39 to -4	162
Disseminated Intravascular Coagulopathy (DIC)	Bleed	77	10	7-15	28	-0.4	-0.8 to -0.1	36	-5	-9 to -1	59
	Non-bleed*	71	10	7-13	33	-0.2	-0.5 to 0.0	31	-1	-6 to 0	54
Massive haemorrhage	Bleed	560	13	8-17	202	-0.1	-0.4 to +0.1	283	-1	-4 to +2	347
	Non-bleed*	30	12	8-15	10	-0.2	-0.4 to 0.0	17	0	-2 to +3	23
Cancer	Bleed	169	11	7-14	84	-0.2	-0.8 to +0.1	80	-2	-7 to +1	89
	Non-bleed*	263	11	8-14	125	-0.2	-0.6 to 0.0	136	-2	-6 to -0	136
Liver disease	Bleed	389	12	9-17	132	-0.2	-0.5 to 0.0	213	-2	-6 to -1	243
	Non-bleed*	486	10	7-14	252	-0.2	-0.4 to -0.1	246	-2	-4 to 0	280
Cardiac surgery	Bleed	381	11	8-15	324	0.0	-0.2 to +0.2	225	-1	-2 to +2	225
	Non-bleed*	181	12	8-16	153	0.0	-0.2 to +0.1	90	0	-2 to +1	95
Other surgery	Bleed	528	12	8-15	277	-0.1	-0.3 to +0.2	276	-1	-4 to+2	341
	Non-bleed*	429	12	8-15	189	-0.3	-0.6 to -0.1	233	-2	-6 to 0	272
Trauma	Bleed	105	12	8-18	25	-0.1	-0.5 to 0.1	60	-2	-6 to +1	58
	Non-bleed*	51	12	8-15	19	-0.2	-0.9 to 0.0	32	-2	-5 to 0	26
Other	Bleed	371	10	7-14	126	-0.2	-1.1 to 0.0	213	-2	-7 to 0	206
	Non-bleed*	421	12	8-15	162	-0.3	-1.2 to -0.1	247	-3	-10 to -1	234
Total	**Bleed**	**2503**	**11**	**8-15**	**1146**	**-0.2**	**-0.6 to +0.1**	**1357**	**-2**	**-5 to +1**	**1489**
	Non-bleed*	**2004**	**11**	**8-15**	**978**	**-0.3**	**-0.9 to -0.1**	**1124**	**-2**	**-6 to 0**	**1139**

* Non-bleed: Before/during invasive procedure/surgery with abnormal coagulation, or abnormal coagulation with no bleeding

Additional FFP and Cryoprecipitate use

The following table summarises the responses to questions seeking information about the use of additional FFP transfusions and cryoprecipitate:

Table A14: Additional FFP and Cryoprecipitate use

		National (4635)
Q65 Additional units of FFP given within 24 hours following initial FFP transfusion	19%	900
Q66 Cryoprecipitate given with the initial FFP episode and/or in following 24 hours	10%	470
• If yes the % Pre FFP Fibrinogen <1.0 g/l	33%	111/336
• If yes the % 1st Post FFP Fibrinogen <1.0 g/l	19%	64/332

❖ **BCSH guideline recommendation**

➢ Cryoprecipitate is indicated if plasma fibrinogen is less than 1 g/l

Notable subgroups with higher (≥15%) rates of cryoprecipitate use included patients with DIC, massive haemorrhage, requiring obstetric surgery or procedures, with multiple bleeding sites or obstetric and gynaecological bleeding, or pre-fibrinogen levels < 1g/l.

Summary Box

In 19% of cases, additional units of FFP were given within 24 hours following the initial FFP transfusion.

Cryoprecipitate was also given to 10% of patients either with the initial FFP transfusion and/or in the following 24 hours.

Cryoprecipitate use appeared more common in patients with DIC, massive haemorrhage, undergoing surgery and with multiple bleeding sites.

Many cases of cryoprecipitate use were patients in whom fibrinogen levels were not less than 1g/l.

Section B - Children aged 1 to 15 years (n=114)

Overview

The median (IQR) age was 6 (2-12) years. Weights were known for 91% (104/114), median (IQR) of 20 (13-31) Kg.

Table B1: Where FFP was given

Q1 - Where was patient when FFP administered?	National (114)	
Theatres/recovery	35%	40
A&E	4%	5
Surgical ward	4%	5
Medical ward	14%	16
Intensive Treatment Unit / High Dependency Unit	33%	38
Neonatal unit	-	0
Haematology/oncology	3%	3
Day care	4%	5
Don't know	1%	1
Other	1%	1

Summary Box
Most FFP transfusions to children were given in paediatric intensive care units or theatres/recovery.

The underlying medical or surgical conditions and the main reasons for FFP transfusion

The BSCH guidelines (2004a, 2004b) refer to paediatric use of FFP. Similar broad categories of groups of clinical indications exist for older children as for adults (see page 9), including: single coagulation factor deficiencies; multiple coagulation factor deficiencies e.g. DIC; TTP; reversal of warfarin effect; vitamin K deficiency in intensive care; liver disease; surgical bleeding (including cardiac); and massive transfusion. These groups formed the basis of the subdivisions used in this section of the audit report, alongside further questions addressing the use of FFP for either bleeding, or prior to surgery or an invasive procedure.

Table B2: Underlying medical or surgical conditions

Q6 What was the underlying medical or surgical condition?	National (114)	
Warfarin reversal	3%	3
Disseminated Intravascular Coagulopathy (DIC)	9%	10
Massive haemorrhage (as defined in your hospital)	3%	3
Cancer	12%	14
Liver disease	4%	5
Cardiac surgery	15%	17
Other surgery	24%	27
Trauma	5%	6
Other*	34%	39

Multiple answers were possible - 11 had two conditions stated. 1 had none stated.
*39 patients aged 1 – 15 years : Sepsis (14); other conditions reported included burns (6), renal impairment (6).

Summary Box
The more common groups of underlying medical or surgical conditions for FFP use in children were surgery (including cardiac), cancer and sepsis.

Table B3: The main reasons for FFP transfusion, and details of bleeding, procedures and surgery

To understand better the clinical rationale for FFP administration, responses were sought about the main reasons for FFP transfusion

Q8 Which (one) of these best describe the reasons for giving this initial FFP transfusion?	National (114)	
Bleeding	44%	50
Before invasive procedure or surgery, with abnormal coagulation	16%	18
During invasive procedure or surgery, with abnormal coagulation	14%	16
Abnormal coagulation with no bleeding	18%	21
Other	4%	4
Not documented / not known / blank	4%	5

Table B4: Bleeding characteristics

Details of bleeding were requested for FFP transfusions related to clinical bleeding, and are shown in below.

Q10 If bleeding, which site(s)?	National (50)	
Skin / subcutaneous	6%	3
Catheter / line	4%	2
Intracranial	8%	4
Nose / mouth	6%	3
Respiratory system	6%	3
Gastrointestinal system	16%	8
Haematuria	2%	1
Gynae	-	0
Vascular	26%	13
Obstetric	-	0
Musculoskeletal	24%	12
Other	-	0
None of the above stated	8%	4

One site was stated for 44, two sites for 1 and 3 sites for 1.

Table B5: Patients undergoing procedures or surgery

Details of surgery and procedures were requested for FFP transfusions and are shown in below.

Q12-19 If patient underwent a procedure or surgery, please indicate which	National (114)	
Biopsy	7%	8
Endoscopy	2%	2
Central line insertion /removal	6%	7
Cardiac surgery	13%	15
Liver surgery	2%	2
Other surgery*:	33%	38
• Vascular surgery	1%	1
• Orthopaedics	11%	13
• Hysterectomy / gynaecology	1%	1
• Laparotomy	5%	6
• Other surgery (e.g. neuro, ENT, burns, debridement, drainage)	7%	8
• Other procedures (e.g. laparoscopy, tracheostomies, CT guided draining, chest drain, angiography, ascitic tap/drain)	4%	5
None of the above stated	43%	48

*Other categories were derived from the dataset and were not options listed on the audit tool

Summary Box
A significant number (just under half) of all FFP transfusions were given to children in the absence of any recorded bleeding.
Where FFP is used prior to surgery, this is primarily for cardiac surgery and orthopaedic surgery.

Table B6: Documentation in the case notes

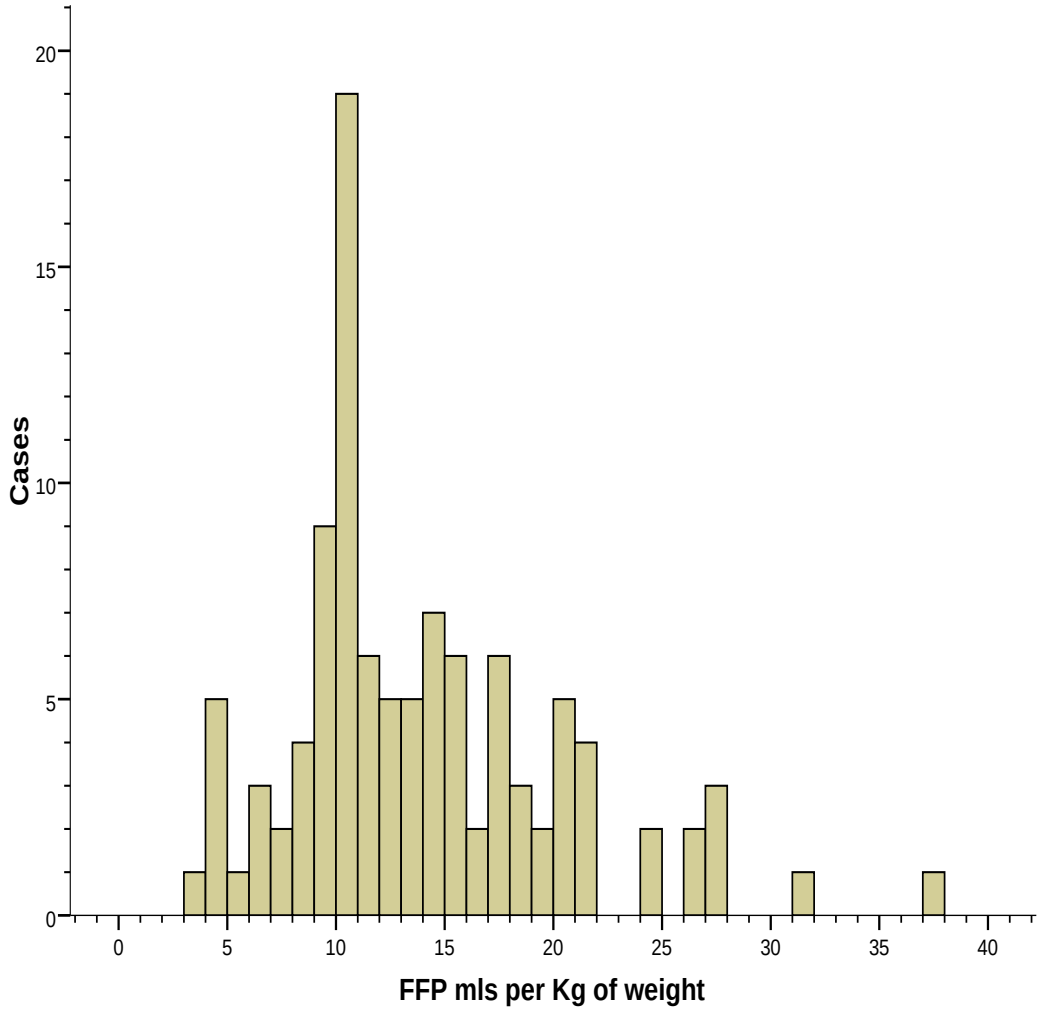
Q21 Is the reason for this initial FFP transfusion documented in the patient's records?	National (114)	
Yes	75%	86
No	24%	27
Blank=Not known	1%	1

Summary Box
The reason for FFP transfusion was documented in three quarters of cases

FFP Dose in relation to weight

Dose per Kg weight was known for 91% (104). Median (IQR) per Kg was 12 (10-18).
The distribution of doses by weight is shown by the histogram below:

Figure B1



Summary Box
There was wide variation in the dose of FFP transfused, by weight
The median dose was 12 ml/kg
In 24% (25/104) of cases the dose was less than 10 ml/kg

Use of coagulation tests

Table B7: Reporting of coagulation screen tests: PT and/or INR

Either INR or PT test reported	National (114)	
Before FFP was given	84%	96
<24 hours after FFP given	76%	87

Summary Box
Values for INR pre-FFP were reported by 47% (54/114) of cases.
The INR was reported as the only coagulation test for 12% (14/114) of children; 35% (40/114) reported both INR and PT.
The coagulation tests, whether INR or PT, were recorded as undertaken prior to FFP transfusion in 84% of cases.

Laboratory Coagulation Tests including PT
The standard laboratory coagulation tests including PT were originally developed to investigate coagulation factor deficiencies in patients with a bleeding history, by providing an end-assessment of thrombin generation by fibrin formation. However, the important issue of their applied clinical value in different clinical settings continues to be raised. PT results are dependent on reagent and laboratory quality controls and processes, and may be abnormal for a number of reasons not associated with bleeding risk. Some laboratories in this audit reported the INR only, but the INR was developed to monitor warfarin therapy, by standardising results to account for different sensitivities of thromboplastins. The extrapolation of PT to INR may only be valid for those patients stably anti-coagulated with vitamin K antagonists, and may not be appropriate for many other patients, with, for example, liver disease. *Please note that results for APTT have not been presented in this report.*

The degree of abnormality of coagulation testing before FFP transfusion

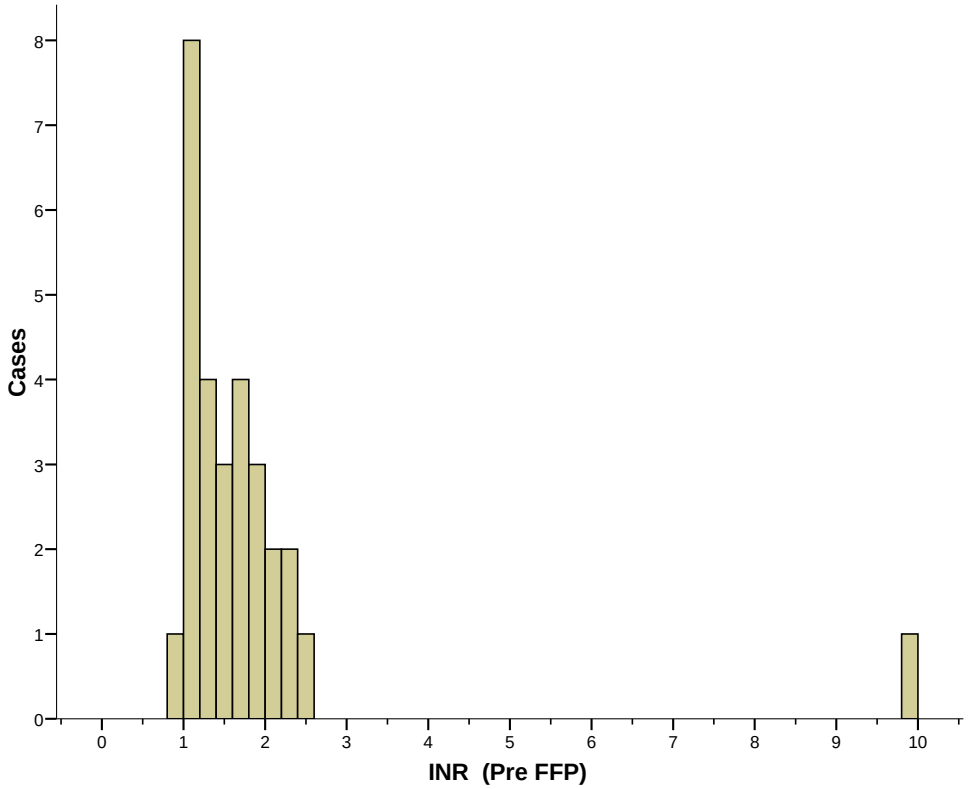
Based on the responses to question 8, it was possible to subdivide infants receiving FFP into two main groups, those with any recorded bleeding, and those without, i.e. for whom FFP was transfused before or during invasive procedure/surgery with abnormal coagulation, or abnormal coagulation with no bleeding.

The table below and the histograms shown on the next page summarize the range of results for INR or PT prior to FFP transfusion.

Table B8: The degree of abnormality of coagulation testing before FFP transfusion

	INR (Pre FFP)			PT (Pre FFP)		
	median	IQR	n	median	IQR	n
With bleeding	1.5	1.2-1.9	29	16	13-21	38
Without bleeding	1.6	1.2-1.8	21	17	13-21	40
Warfarin reversal	2.3	1.7,2.3,10.0	3	17		1

Figure B2: INR/PT results prior to FFP in children with bleeding



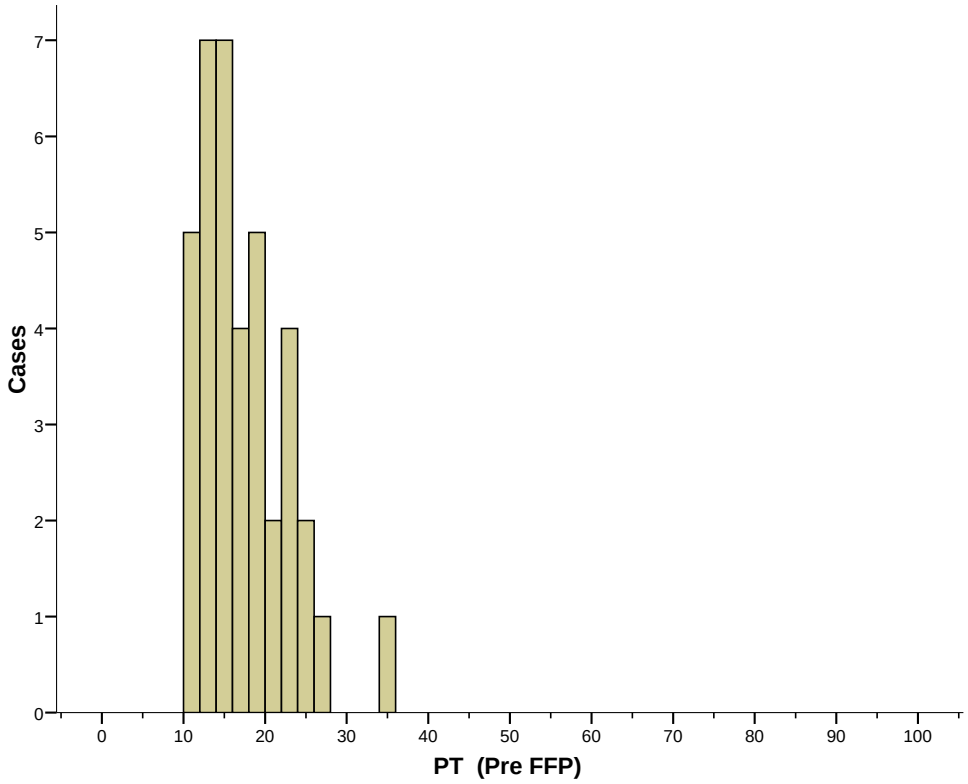
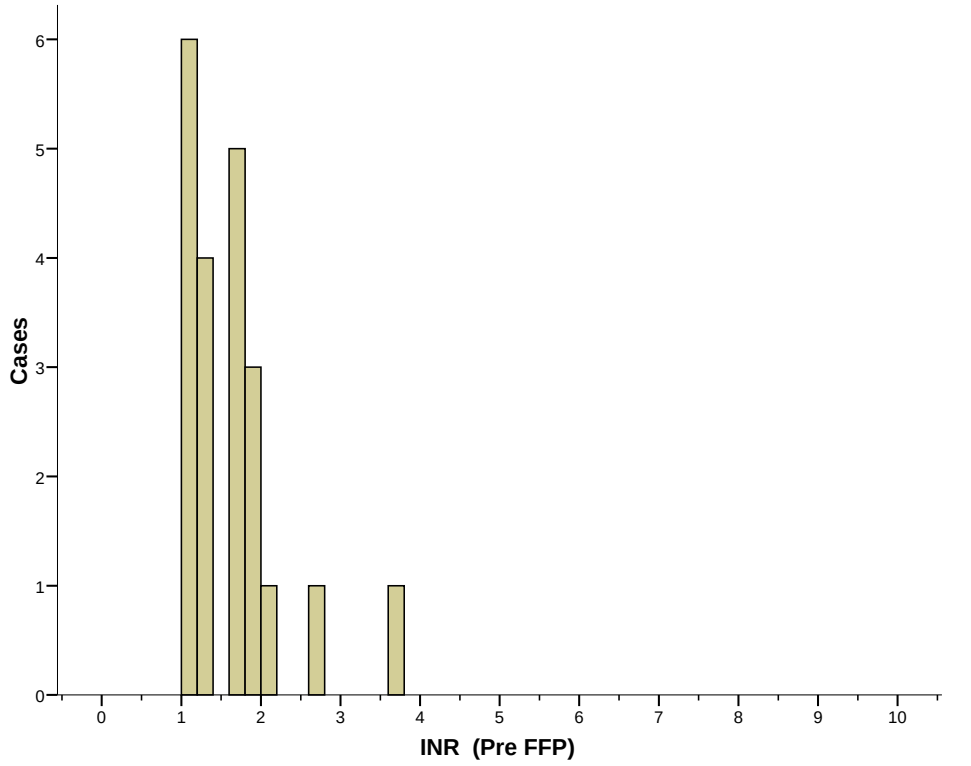


Figure B3: INR/PT results prior to FFP in children without bleeding



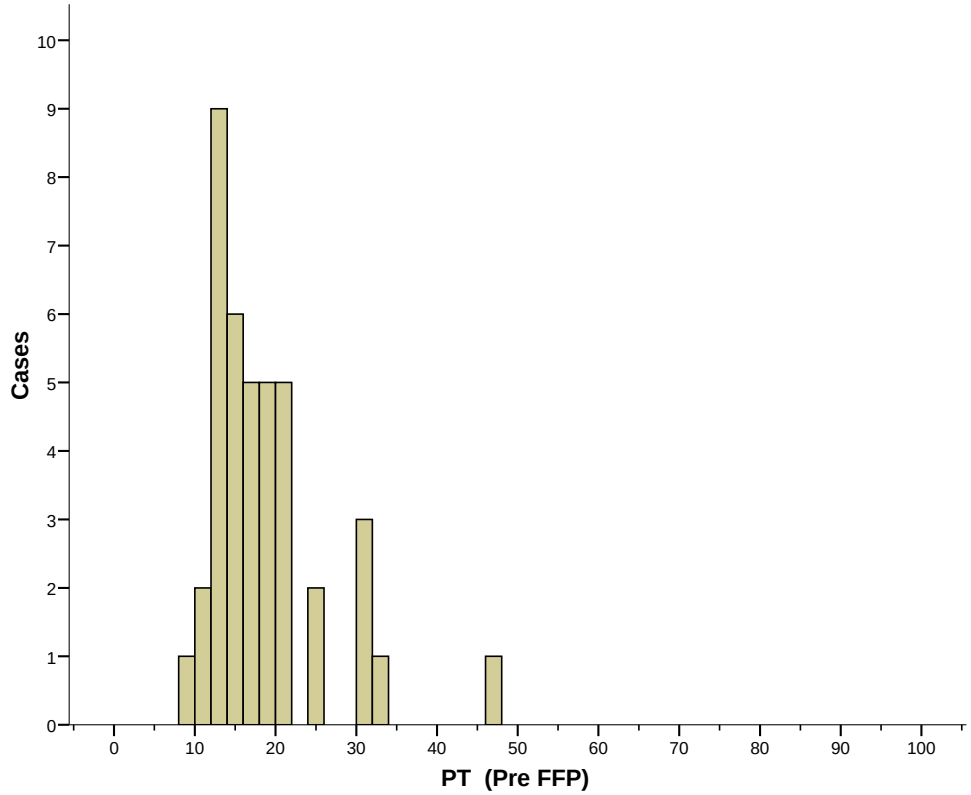


Table B9: Degree of abnormal coagulation in bleeding and non-bleeding children prior to FFP

		Q8 Reason for initial FFP		
% WITH:		Bleeding	Non-bleeding*	
Pre FFP INR ≤1.5	52%	15/29	48%	10/21
Pre FFP INR >1.5 but ≤2.0	34%	10/29	38%	8/21
Pre FFP PT < 16 sec	50%	19/38	45%	18/40
Pre FFP PT 16-24 sec	42%	16/38	40%	16/40
Pre FFP PT ≥ 25 sec	8%	3/38	15%	6/40

*Before/during invasive procedure/surgery with abnormal coagulation, or abnormal coagulation with no bleeding

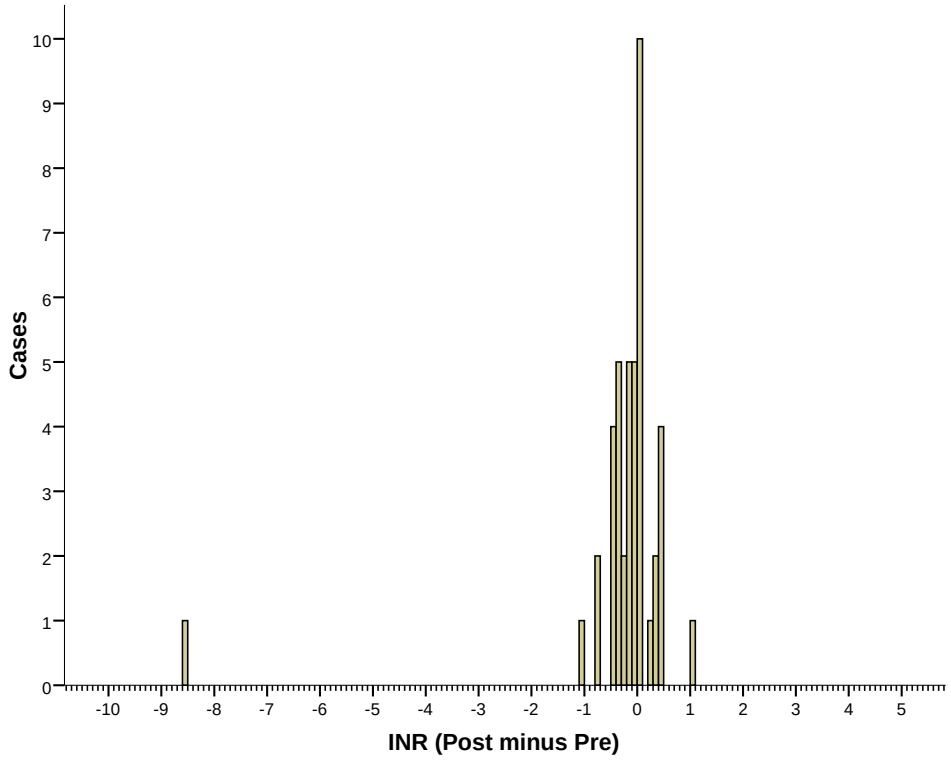
Summary Box
There is a wide range of INR and/or PT results prior to FFP administration.
The median INR prior to FFP administration in children with bleeding was 1.5 (IQR 1.2 -1.9).
The median INR prior to FFP administration in children with no recorded bleeding was 1.6 (IQR 1.2 -1.8).

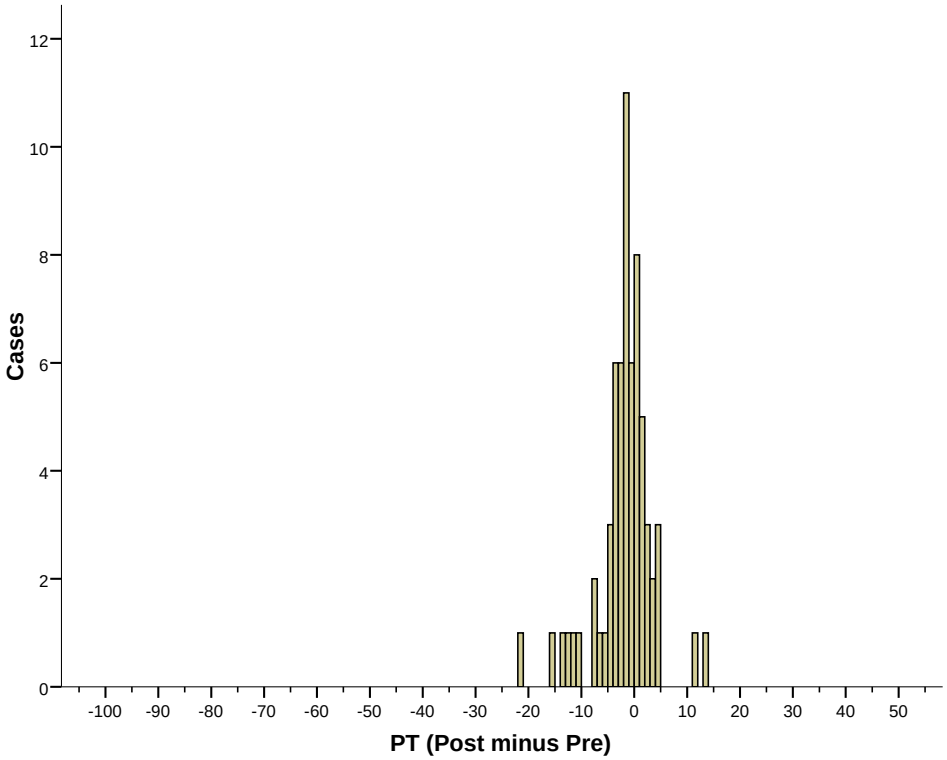
Table B10: The effect of FFP administration: changes in INR or PT

Change in INR or PT	National
INR (Post minus Pre FFP)	
• Median	-0.10
• IQR	-0.32 to +0.10
• Cases	43
PT (Post minus Pre FFP)	
• Median	-1.20
• IQR	-3.60 to +0.55
• Cases	65

Summary Box
In nearly all cases, the effect of FFP, as recorded by the difference between the first recorded post-transfusion INR or PT result and the pre-transfusion result, was very small. The median reduction in INR was 0.1 and in PT was 1.2 seconds, and the IQR for both tests included 0.

Figure B4: INR and PT results post minus pre-transfusion





Use of additional FFP and cryoprecipitate use

Table B11: Additional FFP and Cryoprecipitate use

	National (114)	
Q65 Additional units of FFP given within 24 hours following initial FFP transfusion	25%	28
Q66 Cryoprecipitate given with the initial FFP episode and/or in following 24 hours	13%	15
• If yes the % Pre FFP Fibrinogen <1.0 g/l	36%	5/14
• If yes the % 1st Post FFP Fibrinogen <1.0 g/l	15%	2/13

❖ **BCSH guideline recommendation**

➢ Cryoprecipitate is indicated if plasma fibrinogen is less than 1 g/l

Summary Box

In 25% of cases, additional units of FFP were given within 24 hours following the initial FFP transfusion.

Cryoprecipitate was also given to 13% of children either with the initial FFP transfusion and/or in the following 24 hours.

Section C – Infants (aged less than 1 year) (n=220)

Overview

Two-thirds of those cases where age was less than 1 year (66%, 145/220) were stated as being aged less than one month.

Of those less than one month, 21% (31/145) had a gestational age less than 27 weeks (the cut-off for neonatal intensive care units in the UK at level 1). 41% (59/145) had a gestational age of 36 weeks or more (term).

Weights were known for 96% (212/220), and the distribution of weights is shown below:

Figure C1 – Weight in infants in Kg.

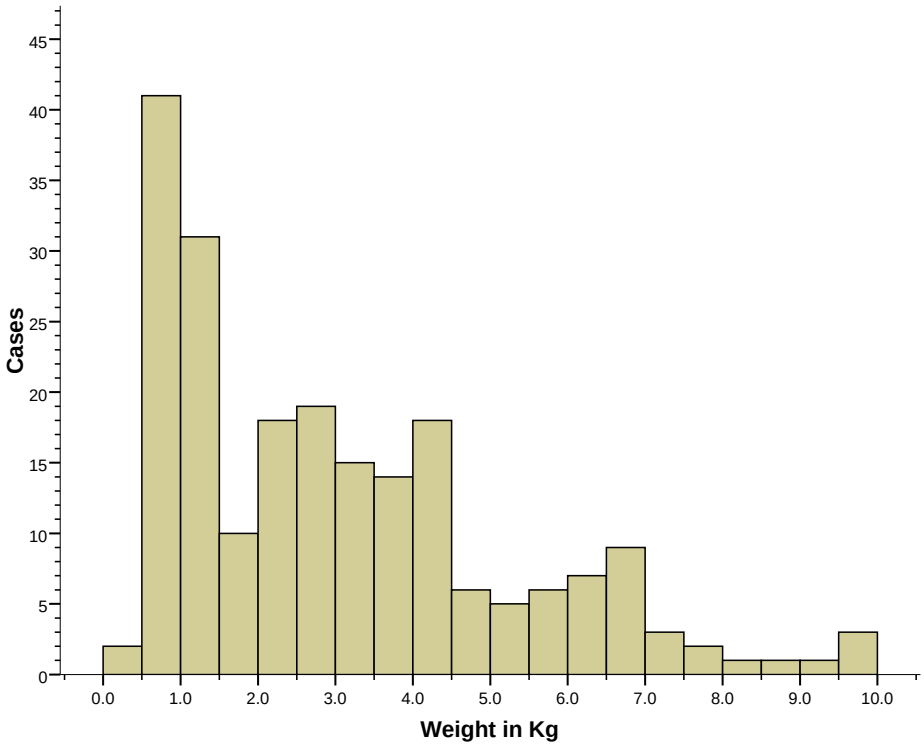


Table C1: Where FFP was given

Q1 - Where was patient when FFP administered?	National (220)	
Theatres/recovery	14%	31
A&E	1%	3
Surgical ward	0.5%	1
Medical ward	4%	8
Intensive Treatment Unit / High Dependency Unit	20%	44
Neonatal unit	60%	132
Haematology/oncology	0.5%	1
Day care	-	0
Don't know	-	0
Other	-	0

Summary Box
Most FFP transfusions to infants were given in neonatal/paediatric intensive care units, or theatres.

BSCH guidelines (2004a, 2004b) refer to paediatric use of FFP, including specifically use in neonates. The main categories of groups of clinical indications include: inherited coagulation factor deficiencies; multiple coagulation factor deficiencies e.g. DIC; haemorrhagic disease of the newborn/vitamin K deficiency in intensive care; liver disease; surgical bleeding (including cardiac); and massive transfusion. These groups formed the basis of the subdivisions used in this section of the audit report, alongside further questions addressing the use of FFP for either active bleeding, or prior to surgery or an invasive procedure with acquired deficiencies of one or more coagulation factors.

❖ **Selected BCSH guideline recommendations**

- FFP and other components are not routinely indicated if patient has Disseminated Intravascular Coagulation (DIC) without bleeding
- FFP is indicated for sick infants with hypoxia, hypotension, sepsis or liver disorders associated with significant coagulopathy and bleeding, or who are at risk of bleeding from an invasive procedure because of significant coagulopathy
- Prematurity may predispose to longer clotting times but on its own is not an indication for FFP
- FFP has not been proven to have clinical benefit when given to septic patients
- Shortening of the prolonged clotting times is unpredictable and should be checked following administration

Table C2: The underlying medical or surgical conditions

Q6 What was the underlying medical or surgical condition?	National (220)	
Warfarin reversal	-	0
Disseminated Intravascular Coagulopathy (DIC)	6%	14
Massive haemorrhage (as defined in your hospital)	3%	7
Cancer	2%	5
Liver disease	5%	12
Cardiac surgery	20%	43
Other surgery	8%	18
Trauma	-	0
Other*	57%	126

Multiple answers were possible - 8 had two conditions stated. 3 had none stated.

*126 infants : Sepsis (33), prematurity (24), unspecified coagulopathy/deranged clotting (28 cases), and bleeding (IVH, NEC or unspecified, 17). There was one reported case of FFP use for haemorrhagic disease of the newborn/vitamin K deficiency, two cases of use for Rhesus HDN, and one for haemophilia.

Summary Box
The more common category of underlying condition requiring FFP transfusion in infants was cardiac surgery.

Table C3: Reasons for giving FFP

Q8 Which (one) of these best describe the reasons for giving this initial FFP transfusion?	National (220)	
Bleeding	36%	80
Before invasive procedure or surgery, with abnormal coagulation	6%	14
During invasive procedure or surgery, with abnormal coagulation	13%	29
Abnormal coagulation with no bleeding	42%	93
Other	1%	2
Not documented / not known / blank	1%	2

Table C4: Bleeding characteristics

Q10 If bleeding, which site(s)?	National (80)	
Skin / subcutaneous	11%	9
Catheter / line	14%	11
Intracranial	14%	11
Nose / mouth	9%	7
Respiratory system	20%	16
Gastrointestinal system	15%	12
Haematuria	3%	2
Gynae	1%	1
Vascular	19%	15
Obstetric	-	0
Musculoskeletal	3%	2
Other	-	0
None of the above stated	10%	8

One site was stated for 61, two sites for 10 and 5 sites for 1.

Table C5: Patients undergoing procedures or surgery

Q12-19 If patient underwent a procedure or surgery, please indicate which	National (220)	
Biopsy	1%	2
Endoscopy	0.5%	1
Central line insertion /removal	10%	21
Cardiac surgery	16%	36
Liver surgery	-	0
Other surgery*:	16%	35
• Vascular surgery	-	0
• Orthopaedics	-	0
• Hysterectomy / gynaecology	-	0
• Childbirth /ectopic /pregnancy /caesarean	-	0
• Laparotomy	8%	18
• Other surgery (e.g. neuro, ENT, burns, debridement, drainage)	2%	4
• Other procedures (e.g. laparoscopy, tracheostomies, CT guided draining, chest drain, angiography, ascitic tap/drain)	4%	9
None of the above stated	60%	131

*Other categories were derived from the dataset and were not options listed on the audit tool.

Summary Box
The most common clinical reason for FFP transfusion in infants is coagulopathy in the absence of bleeding (and not prior to surgery or invasive procedure).
Where FFP is used prior to surgery, this is primarily for cardiac surgery. 10% is used prior to central line insertion or removal.

Table C6: Documentation in case notes

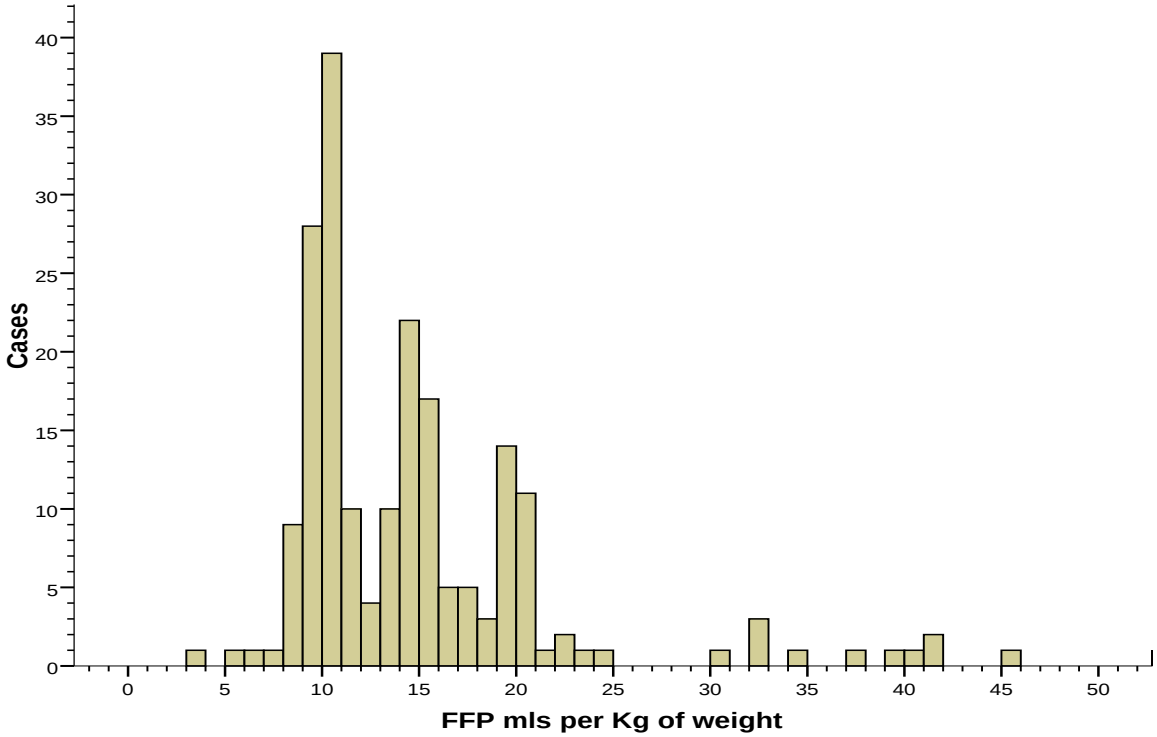
Q21 Is the reason for this initial FFP transfusion documented in the patient's records?	National (220)	
Yes	81%	179
No	17%	37
Blank=Not known	2%	4

Summary Box
The reason for FFP transfusion was documented in 81% of cases

FFP dose in relation to weight

Dose per Kg weight was known for 92% (202). Median (IQR) dose per Kg was 14 (10-18). The distribution of doses by weight is shown by the histogram below:

Figure C2: FFP mls per Kg of weight



5 outliers above 50 have been removed from the graphic.

Table C7: Doses of FFP per Kg.

		National
Bleeding	Median Dose/Kg	15
	IQR Dose/Kg	10-19
	Cases	75
Non-bleeding*	Median Dose/Kg	12
	IQR Dose/Kg	10-16
	Cases	125

*Before/during invasive procedure/surgery with abnormal coagulation, or abnormal coagulation with no bleeding

Summary Box
There was wide variation in the dose of FFP transfused, by weight, with a suggestion of modal patterns at 10 ml/kg and 20 ml/kg.
The median dose was 14 ml/kg and for 20% (41/202) of infants the dose was less than 10ml/kg.

The use coagulation screen tests

- **BCSH guideline recommendation**
- If FFP is given to correct abnormal coagulation parameters, the degree of correction should be recorded.

Table C8: Reporting of standard coagulation screen tests: PT and/or INR

Either INR or PT test reported	National (220)	
Before FFP was given	86%	190
<24 hours after FFP given	71%	157
BOTH before and after FFP given	63%	139

Summary Box
INR or PT was recorded as undertaken prior to FFP transfusion in 86% of cases.
The INR was reported as the only coagulation test for 15% (34/220) of all infants; 32% (70/220) reported both INR and PT.
Please see page 42 (in section on Children) for further background information about the standard coagulation tests including PT and INR)

The degree of abnormality of coagulation testing before FFP transfusion

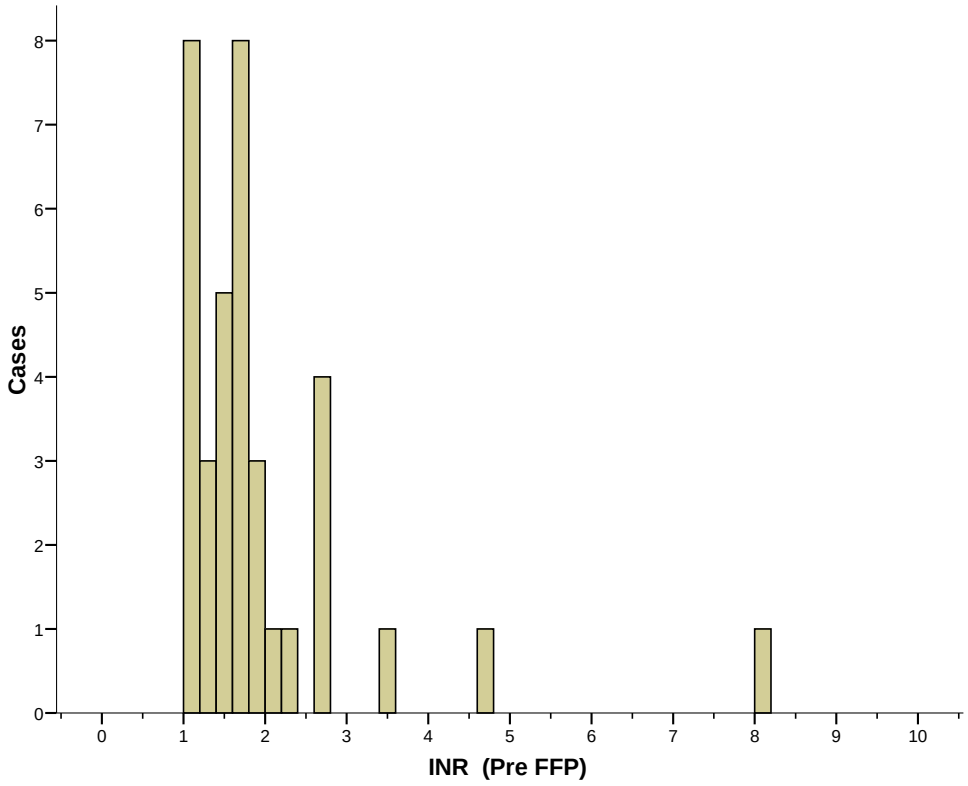
Based on the results of question 8, it was possible to subdivide infants receiving FFP into two main groups, those with any recorded bleeding, and those without, i.e. for whom FFP was transfused before or during invasive procedure/surgery with abnormal coagulation, or abnormal coagulation with no bleeding.

Table C9 and figures C3 and C4 below summarize the range of results for INR or PT prior to FFP transfusion.

Table C9: The degree of abnormality of coagulation testing before FFP transfusion

	INR (Pre FFP)			PT (Pre FFP)		
	median	IQR	n	median	IQR	n
With bleeding	1.6	1.3-2.1	36	18	15-28	56
Without bleeding	1.7	1.3-2.2	67	19	15-24	98

Figure C3: INR/PT results prior to FFP in infants under 1 year with bleeding



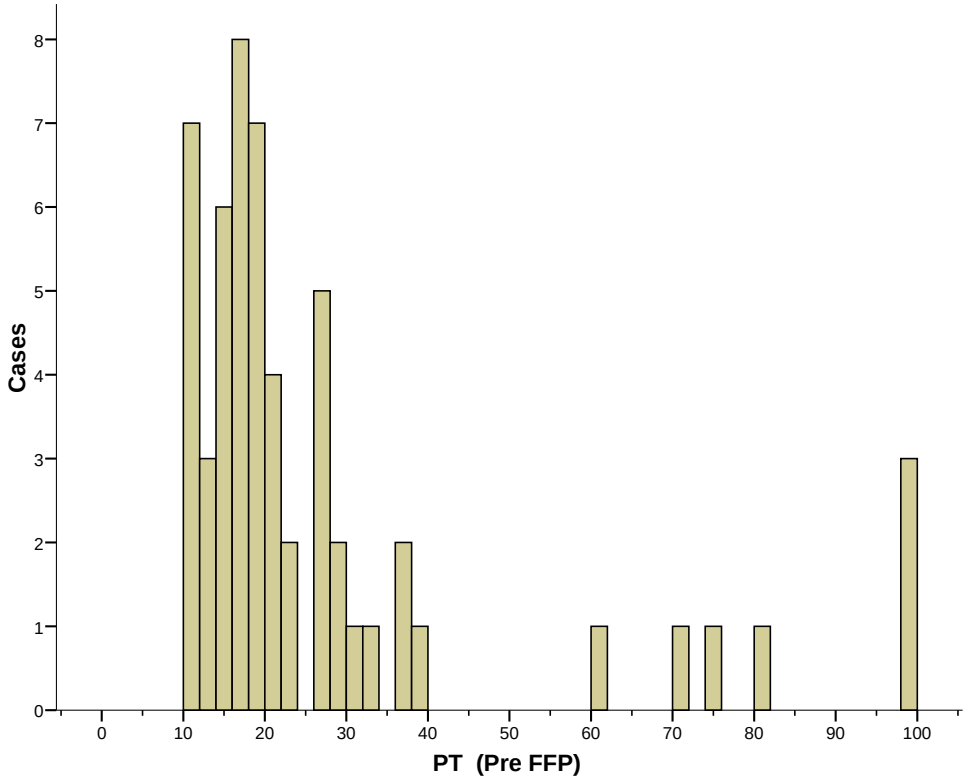
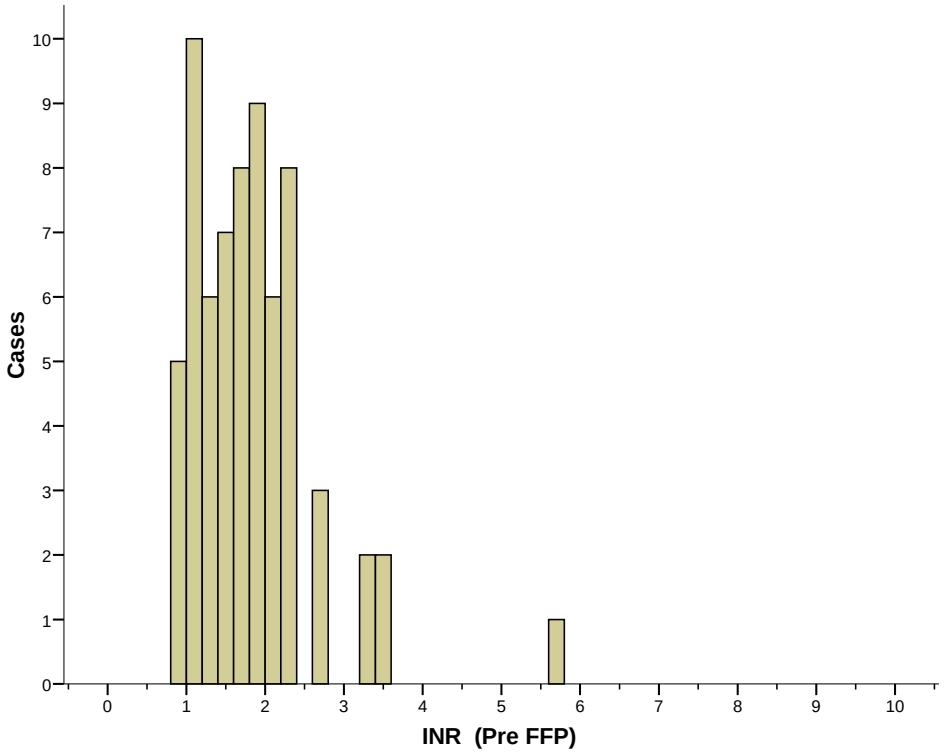


Figure C4: INR/PT results prior to FFP in infants under 1 year without bleeding



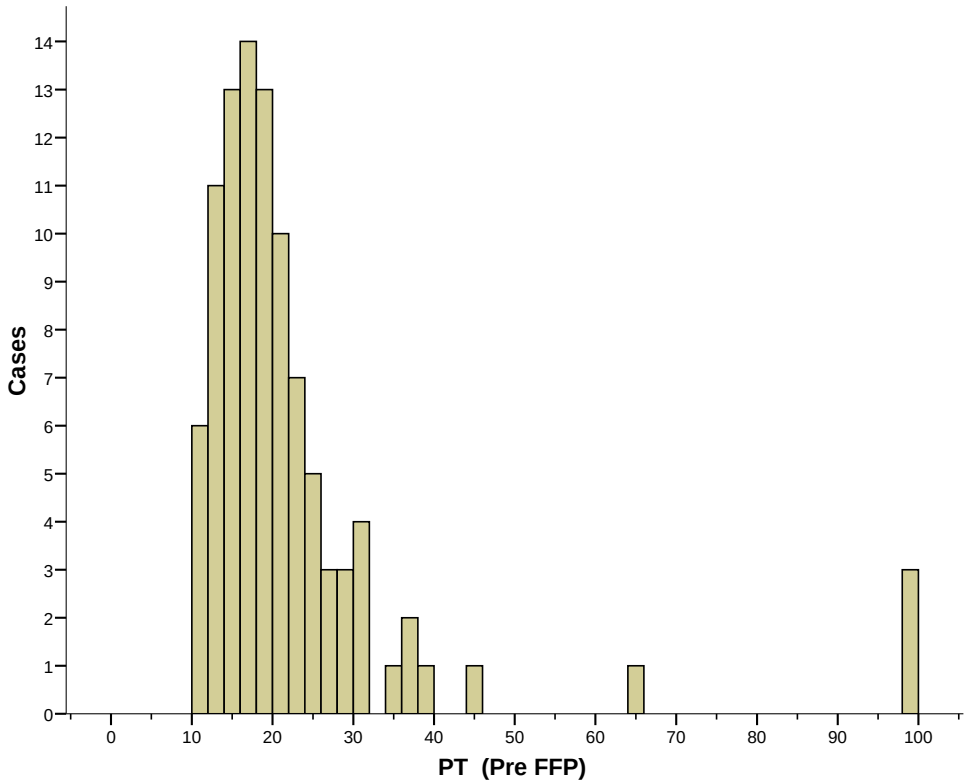


Table C10: Degree of abnormal coagulation in bleeding and non-bleeding infants given FFP

		Q8 Reason for initial FFP		
% with:		Bleeding	Non-bleeding*	
Pre FFP INR ≤1.5	44%	16/36	42%	28/67
Pre FFP INR >1.5 but ≤2.0	31%	11/36	27%	18/67
Pre FFP PT < 16 sec	29%	16/56	31%	30/98
Pre FFP PT 16-24 sec	38%	21/56	47%	46/98
Pre FFP PT ≥25 sec	34%	19/56	22%	22/98

*Before/during invasive procedure/surgery with abnormal coagulation, or abnormal coagulation with no bleeding

Summary Box
There is a wide range of INR and/or PT results prior to FFP administration.
The median INR prior to FFP administration in infants with bleeding was 1.6 (IQR 1.3 -2.1).
The median INR prior to FFP administration in infants with no recorded bleeding was 1.7 (IQR 1.3 - 2.2).

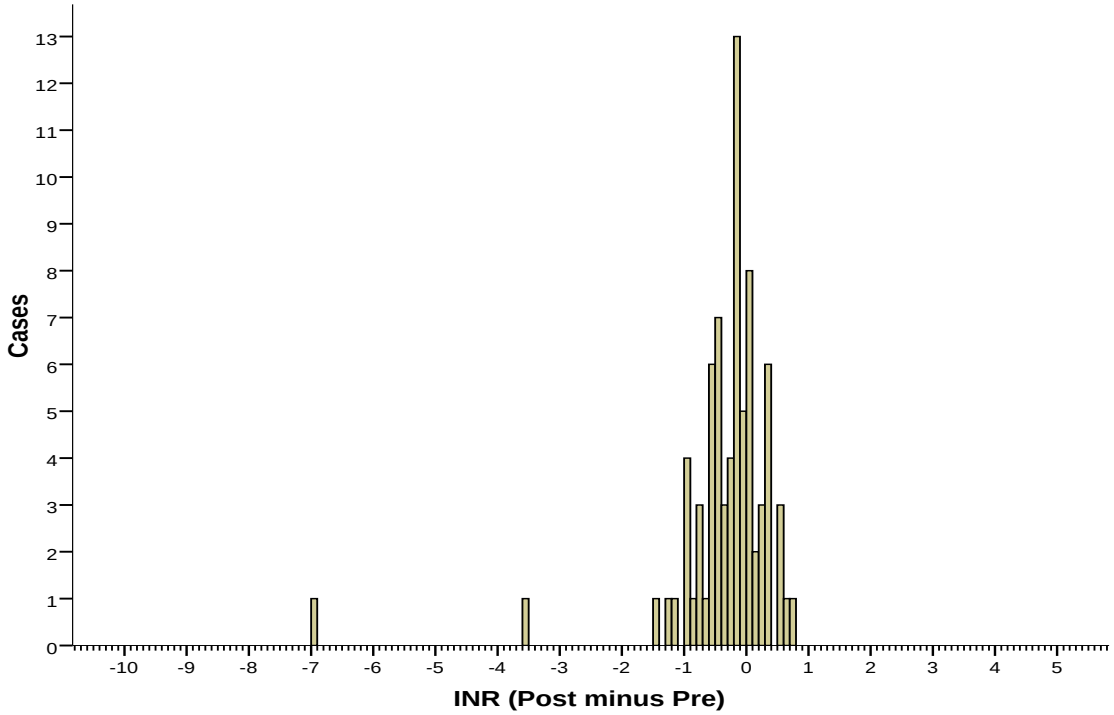
The effect of FFP administration on changes in the standard coagulation tests (INR or PT) is summarised in Table C11 and figure C5 on the next page:

Table C11: The effect of FFP administration: changes in INR or PT

Change in INR or PT	National
INR (Post minus Pre FFP)	
• Median	-0.20
• IQR	-0.55 to +0.10
• Cases	76
PT seconds (Post minus Pre FFP)	
• Median	-1.90
• IQR	-6.00 to +0.40
• Cases	104

Summary Box
In nearly all cases the effect of FFP, as recorded by the difference between the first recorded post-transfusion INR or PT result and the pre-transfusion result was very small.
The median reduction in INR was 0.2 and in PT was 1.9 seconds, and the IQR for both tests included 0.

Figure C5: INR and PT results post minus pre-transfusion



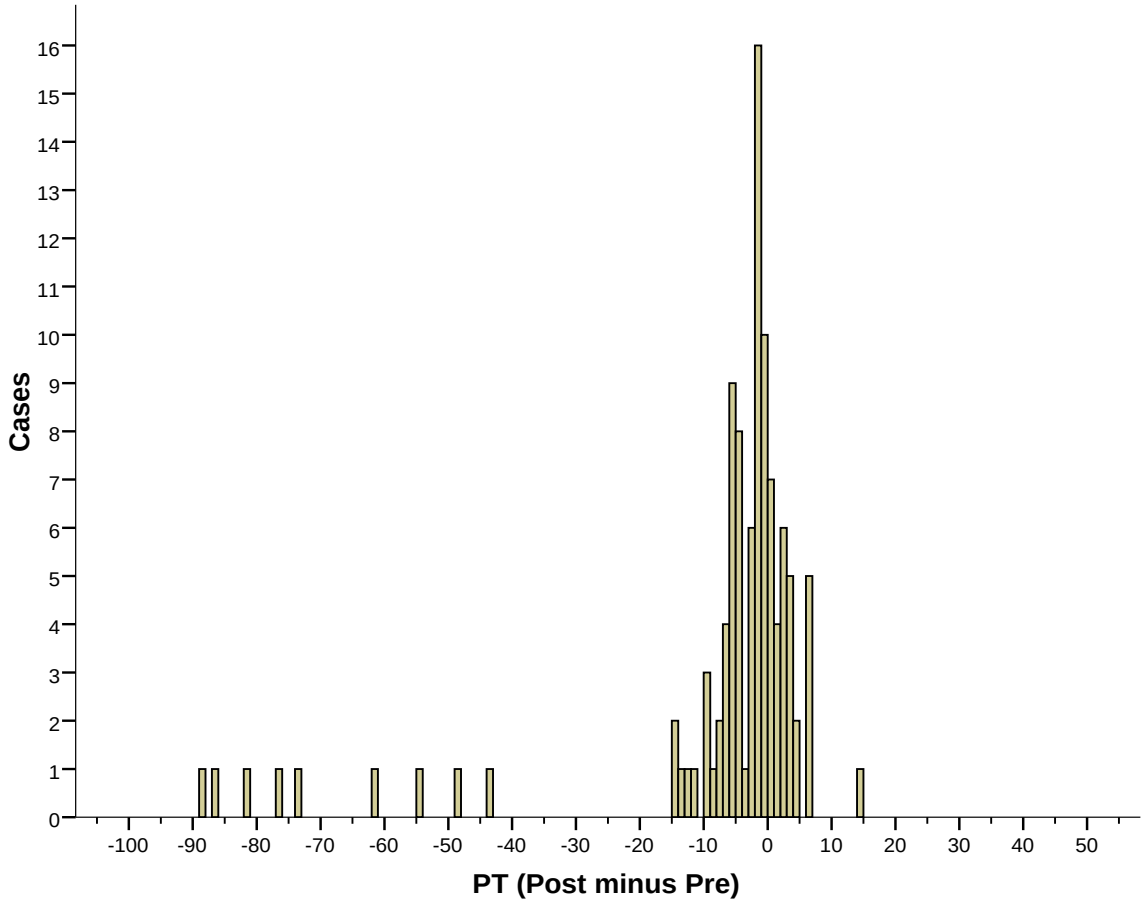


Table C12: Additional FFP and Cryoprecipitate use

		National (220)
Q65 Additional units of FFP given within 24 hours following initial FFP transfusion	20%	45
Q66 Cryoprecipitate given with the initial FFP episode and/or in following 24 hours	15%	33
• If yes the % Pre FFP Fibrinogen <1.0 g/l	65%	17/26
• If yes the % 1st Post FFP Fibrinogen <1.0 g/l	32%	8/25

Summary Box
In 45% of cases, additional units of FFP were given within 24 hours following the initial FFP transfusion.
Cryoprecipitate was also given to 33% of children either with the initial FFP transfusion and/or in the following 24 hours.

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Appendix 1 – Organisational Audit Questionnaire

Q1. How would you best describe your hospital?

Independent *DGH* *Teaching* *Specialist*

Q2. Do you have a (hospital or trust) guideline for use of FFP in:

Adults? *Paediatrics?*

Q3. Do you have a (hospital or trust) guideline for management of massive haemorrhage? Yes No

If yes, please state for which specific areas you have local guidelines

Q4. Do you have hospital or trust guideline for the management of over-anticoagulation with Warfarin? Yes No

Q5. Which plasma product do you use for children aged <16years?

MB FFP *Other – specify*

Q6. Do you use other pathogen inactivated plasma products?

None *Octaplas* *Other (specify)*

Q7. If you use other pathogen inactivated plasma products, please give clinical indications for use at your centre:

Thrombotic Thrombocytopaenic Purpura (TTP) *Yes* *No*

Other clinical indications (specify)

Q8. Do you use Prothrombin Complex Concentrate for warfarin reversal in your hospital? Yes No

Q9 Approximately how many times have you used PCC for warfarin reversal in your hospital over the last 6 months?

Q10. Which method does your laboratory use for measuring fibrinogen?

Clauss *PT derived*

Q11. What are your current laboratory's reference ranges for prothrombin time (PT) for adults?

PT

Q12 .What is the International Sensitivity Index (ISI) of the thromboplastin used by your coagulation laboratory?

ISI

Q13. Do you have separate laboratory reference ranges for neonatal patients? Yes No

Q14. Are these ranges stated when neonatal results are reported? Yes No

Q15. If you answered 'yes' to Q13, what is the source of these ranges?

Q16. Has the hospital undertaken any specific audits in relation to use of FFP?

Yes, within the last 2 years *Yes, within the last 5 years* *No*

If yes, was this a local or regional audit? *Local* ☐ *Regional* ☐

Other Notes

Appendix 2 – Patient Audit Tool

1. Where was the patient when the FFP was administered? *(Tick one option)*

Theatres/recovery; A&E ; Surgical ward ; Medical ward; Intensive Treatment Unit / High Dependency Unit; Neonatal Unit; Haematology/oncology ward; Day care; Don't know; Other (Give details)

2. Other

3. What is the patient's date of birth?

4 If age less than one month what was the gestational age at birth?

5. What is the patient's weight in Kg? **or** Not Recorded

6. What was the underlying medical or surgical condition? (tick all that apply)

Warfarin reversal; Disseminated Intravascular Coagulopathy (DIC); Thrombotic thrombocytopenic purpura (TTP); Massive haemorrhage (as defined in your hospital); Cancer; Liver disease; Cardiac surgery; Other surgery; Trauma; Other, (Give details)

7. Other

8. Which of these best describe the reasons for giving this initial FFP transfusion? (*tick one option):*

Bleeding; Before invasive procedure or surgery, with abnormal coagulation; During invasive procedure or surgery, with abnormal coagulation; Abnormal coagulation with no bleeding; Plasma exchange; Pending plasma exchange; Other, (Give details)

9. Other

10. If bleeding, specify site (Tick as many as apply)

Skin/subcutaneous; Sites of catheter / line insertion; Nose/mouth; Intracranial; Gastrointestinal system; Gynae; Haematuria; Musculoskeletal; Obstetric; Respiratory system; Vascular; Other, (Give details)

11. Other

If patient underwent a procedure or surgery, please indicate which:

12. Biopsy (state site *e.g. Liver, bone marrow, renal, other*)

13. Biopsy site

14. Endoscopy (State type *e.g., colonoscopy, ERCP, bronchoscopy*)

15. Endoscopy type

16. Central line insertion / removal

17. Cardiac surgery

18. Liver surgery

19. Other, *(Give details below)*

20. Other

21. Is the reason for this initial FFP documented in the patient's records?

22. What was the total volume of FFP transfused for this episode?

23. What was the date of this initial FFP transfusion?

24. What was the start time of this initial FFP transfusion?

25 to 32 – details of coagulation test results before transfusion

Date, Time, INR, PT, APTT, Thrombin time, Fibrinogen and Platelet count

33 to 64 - details of coagulation test results after transfusion

Date, Time, INR, PT, APTT, Thrombin time, Fibrinogen and Platelet count

65. Were any additional units of FFP given within the 24 hours following this initial FFP transfusion?

66. Was any cryoprecipitate given with the initial FFP episode and/or in the following 24 hours?

67. Did the patient receive Warfarin at any time in the 7 days prior to transfusion?

68. Did the patient receive vitamin K at any time in the 7 days prior to transfusion?

69. Was an adverse reaction to FFP noted in the case notes?

70. If yes, please describe

71. Did this patient die during this admission?

72. If yes, what was the date of death?

Appendix C - List of participating centres

Addenbrooke's Hospital
Airedale General Hospital
Arrowe Park Hospital
Barnet Hospital
Barnsley District General Hospital
Barts and The London NHS Trust
Basildon and Thurrock University Hospital NHS Foundation Trust
Basingstoke & North Hampshire Hospital
Bedford Hospital
Birmingham Women's Hospital
Bishop Auckland General Hospital
Blackpool Victoria Hospital
BMI Bath Clinic
BMI London Independent Hospital
BMI The Princess Margaret
BMI The Priory Hospital
Bradford Royal Infirmary
Bristol Royal Infirmary
Broomfield Hospital
Caerphilly District Miner's Hospital
Central Middlesex Hospital
Charing Cross Hospital
Chase Farm Hospital
Chelsea and Westminster Hospital
Chesterfield Royal Hospital
Christie Hospital
City Hospital Campus Nottingham
Colchester General Hospital
Conquest Hospital
Countess of Chester Hospital
County Hospital Hereford
Coventry & Warwickshire
Cumberland Infirmary
Darent Valley Hospital
Darlington Memorial Hospital
Derby Hospitals NHS Foundation Trust
Derriford Hospital
Dewsbury & District Hospital
Diana, Princess of Wales
Dorset County Hospital
Ealing Hospital
East Lancashire Hospitals NHS Trust
East Surrey Hospital
Eastbourne District General Hospital
Epsom Hospital
Freeman Hospital
Friarage Hospital
George Eliot Hospital
Glan Clwyd Hospital
Good Hope Hospital
Grantham and District
Great Ormond Street Hospital for Children
Guy's & St. Thomas' NHS Foundation Trust
Hammersmith Hospital
Harefield Hospital
Harrogate District Hospital
Hemel Hempstead General Hospital
Hexham General Hospital
Hinchingbrooke Hospital
Huddersfield Royal Infirmary
Hull Royal Infirmary
Ipswich Hospital
James Paget Hospital
Kent & Canterbury Hospital
Kettering General Hospital
King's College Hospital
Kings Mill Hospital
Kingston Hospital
Lincoln County Hospital
Lister Hospital
London Bridge Hospital
Macclesfield District General Hospital
Manchester Royal Infirmary
Mayday University Hospital
Medway Maritime Hospital
Morriston Hospital
Neath Port Talbot Hospital
Nevill Hall Hospital
New Cross Hospital
Newcastle General Hospital
Newham General Hospital
Norfolk & Norwich University Hospital
North Bristol NHS Trust
North Cheshire Hospitals NHS Trust
North Devon District Hospital
North Manchester General Hospital
North Middlesex University Hospital
North Tyneside General Hospital
Northampton General Hospital
Northern General Hospital
Northwick Park Hospital
Nuffield Hospital Leeds
Nuffield Orthopaedic Centre
Oxford Radcliffe Hospitals NHS Trust
Papworth Hospital
Peterborough District Hospital
Pilgrim Hospital
Poole Hospital
Portsmouth Hospitals NHS Trust
Prince Charles Hospital
Prince Philip Hospital

Princess Alexandra Hospital
Princess of Wales Hospital Bridgend
Princess Royal University Hospital Orpington
Queen Elizabeth Hospital Birmingham
Queen Elizabeth Hospital Gateshead
Queen Elizabeth Hospital Woolwich
Queen Elizabeth Hospital, King's Lynn
Queen Elizabeth II Hospital Welwyn
Queen Elizabeth the Queen Mother Hospital
Queen Mary's Sidcup NHS Trust
Queen's Hospital Burton
Queens Hospital Romford
Queen's Medical Centre Nottingham
Ramsay Mount Stuart Hospital Torquay
Robert Jones & Agnes Hunt
Rotherham General Hospital
Royal Berkshire Hospital
Royal Bolton Hospital
Royal Brompton Hospital
Royal Cornwall Hospital
Royal Devon and Exeter Hospital (Wonford)
Royal Free Hospital
Royal Glamorgan Hospital
Royal Gwent Hospital
Royal Hallamshire Hospital
Royal Liverpool Children's Hospital
Royal Liverpool University Hospital
Royal Manchester Children's Hospital
Royal Marsden Hospital Fulham
Royal Marsden Hospital Sutton
Royal National Orthopaedic Hospital
Royal Oldham Hospital
Royal Preston Hospital
Royal Surrey County Hospital
Royal United Hospital
Royal Victoria Infirmary
Russells Hall Hospital
Salford Royal University Hospital
Salisbury District Hospital
Sandwell & West Birmingham Hospitals NHS Trust
Scunthorpe General Hospital
Sheffield Children's Hospital
Singleton Hospital
South Tyneside District Hospital
Southampton University Hospital
Southend Hospital
Southport and Ormskirk Hospital NHS Trust
Spire Cardiff Hospital
Spire Leeds Hospital
St. George's Hospital
St. Helier Hospital
St. Mary's Hospital Paddington
St. Peter's Hospital
St. Richard's Hospital Chichester
Stafford General Hospital
Stoke Mandeville Hospital
Sunderland Royal Infirmary
Tameside General Hospital
Taunton and Somerset Hospital
The Cardiothoracic Centre
The Great Western Hospital
The Hillingdon Hospital
The James Cook University Hospital
The Leeds Teaching Hospitals NHS Trust
The London Clinic
The Luton & Dunstable Hospital
The Mid-Yorkshire Hospitals NHS Trust
The Royal Bournemouth Hospital
The Shrewsbury and Telford Hospital NHS Trust
The Whittington Hospital
Torbay General Hospital
Trafford General Hospital
University College Hospital London
University Hospital Aintree
University Hospital of North Durham
University Hospital of North Staffordshire
University Hospital of North Tees
University Hospitals of Leicester NHS Trust
University Hospitals of Morecambe Bay NHS Trust
Wansbeck General Hospital
Watford General Hospital
West Middlesex University Hospital
West Suffolk Hospital
West Wales General Hospital
Weston General Hospital
Wexham Park Hospital
Whiston Hospital
William Harvey Hospital
Withybush General Hospital
Worthing Hospital
Wrexham Maelor Hospital
Wrightington,Wigan and Leigh NHS Trust
Yeovil District Hospital
York District Hospital
Ysbyty Gwynedd