

# 12<sup>th</sup> Annual Canadian Blood Services International Symposium

*Plasma: Transfuse it, Fractionate it or  
Forget it?*

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**Canadian Blood Services**  
*it's in you to give*

Ottawa Health Research Institute



Institut de recherche en santé d'Ottawa

A collage of images related to medical research and healthcare. It includes a scientist in a lab coat looking through a microscope, a person in a surgical cap, and a group of people in a meeting. The background is a light blue with white circular patterns.

# ***Frozen Plasma Use in Canada: Update from recent Canadian studies***

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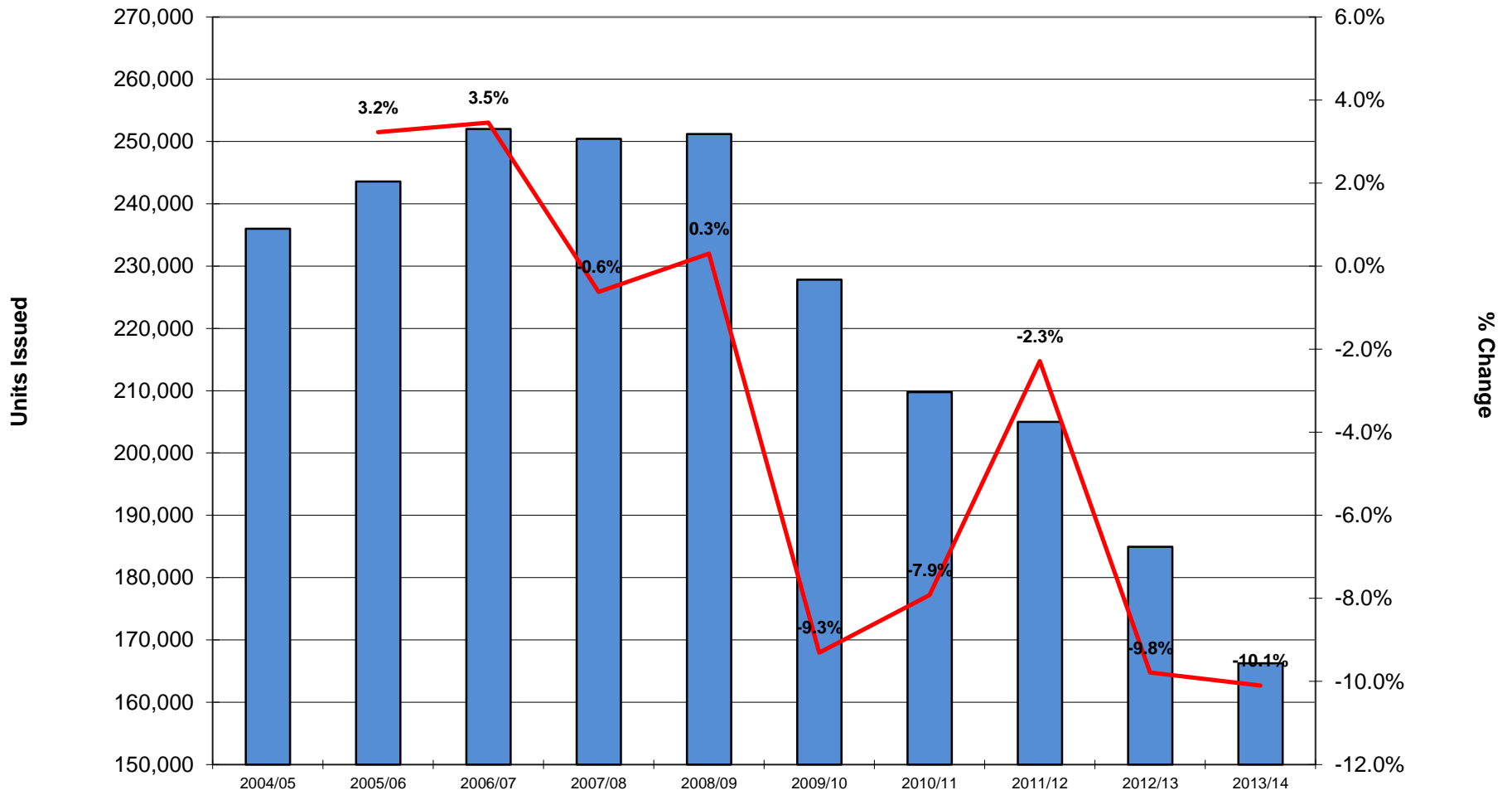
# Disclosure

- Medical consultant - Canadian Blood Services
- Grants – Canadian Institutes Health Research, Canadian Blood Services
- Honorarium – Amgen, GlaxoSmithKline, Novartis
- Unrestricted Educational Grant - Novartis

# Outline

- Overview of current FP utilization in Canada
- Assessing appropriateness of FP use

# Plasma Units Issued & Fiscal Period Growth Rates



Courtesy of Rick Trifunov, CBS

# Appropriateness of Frozen Plasma Use in Canada (2009)



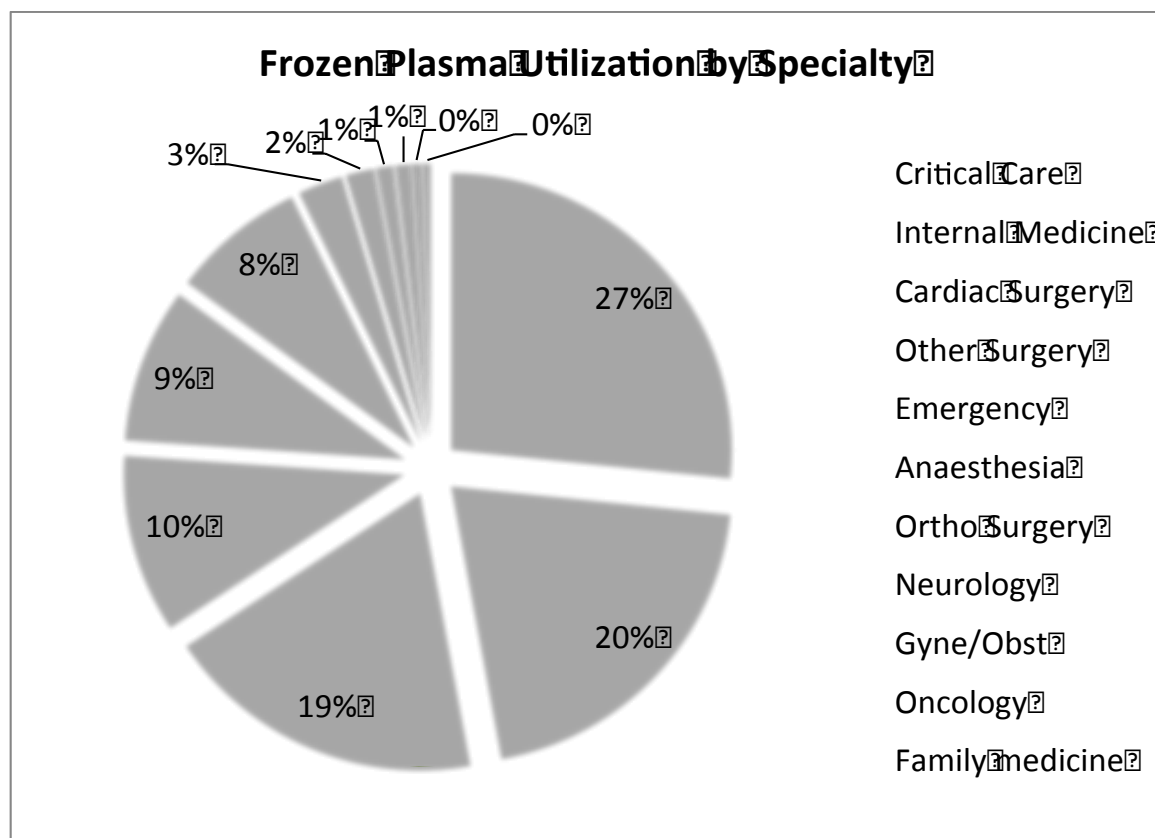
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Prospective 2-month cohort study of all Frozen Plasma transfusions at 10 Canadian centres

Appropriateness of Frozen Plasma transfusions across centres.

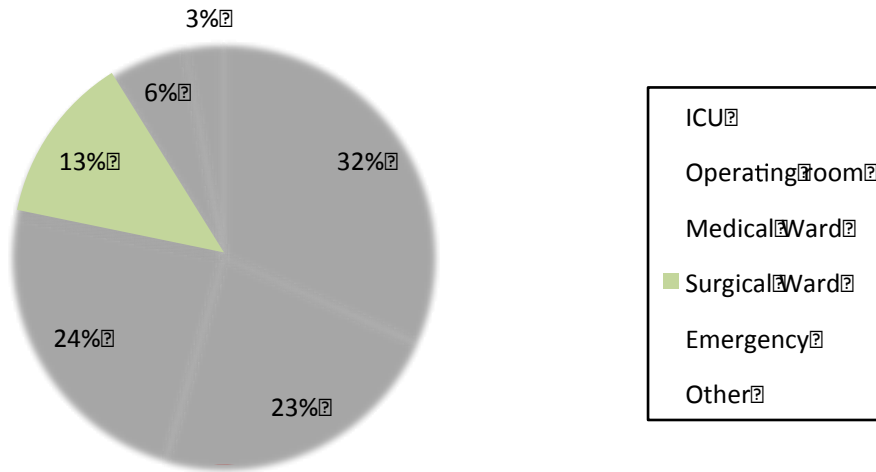
# Frozen Plasma Use in Canada - 2009

FP transfusions	2309
Mean INR (IQR)	2.09 (1.4-2.2)
Mean aPTT	27 sec

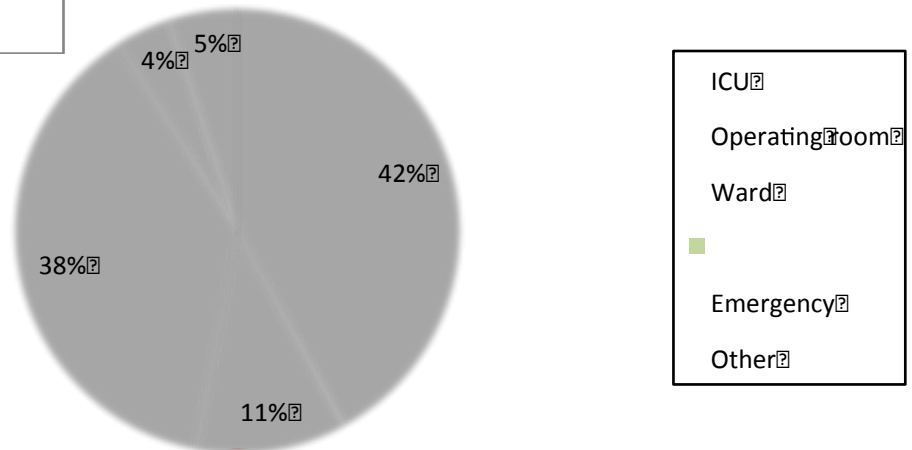


# FP Use in U.K. and U.S.A

England 2008

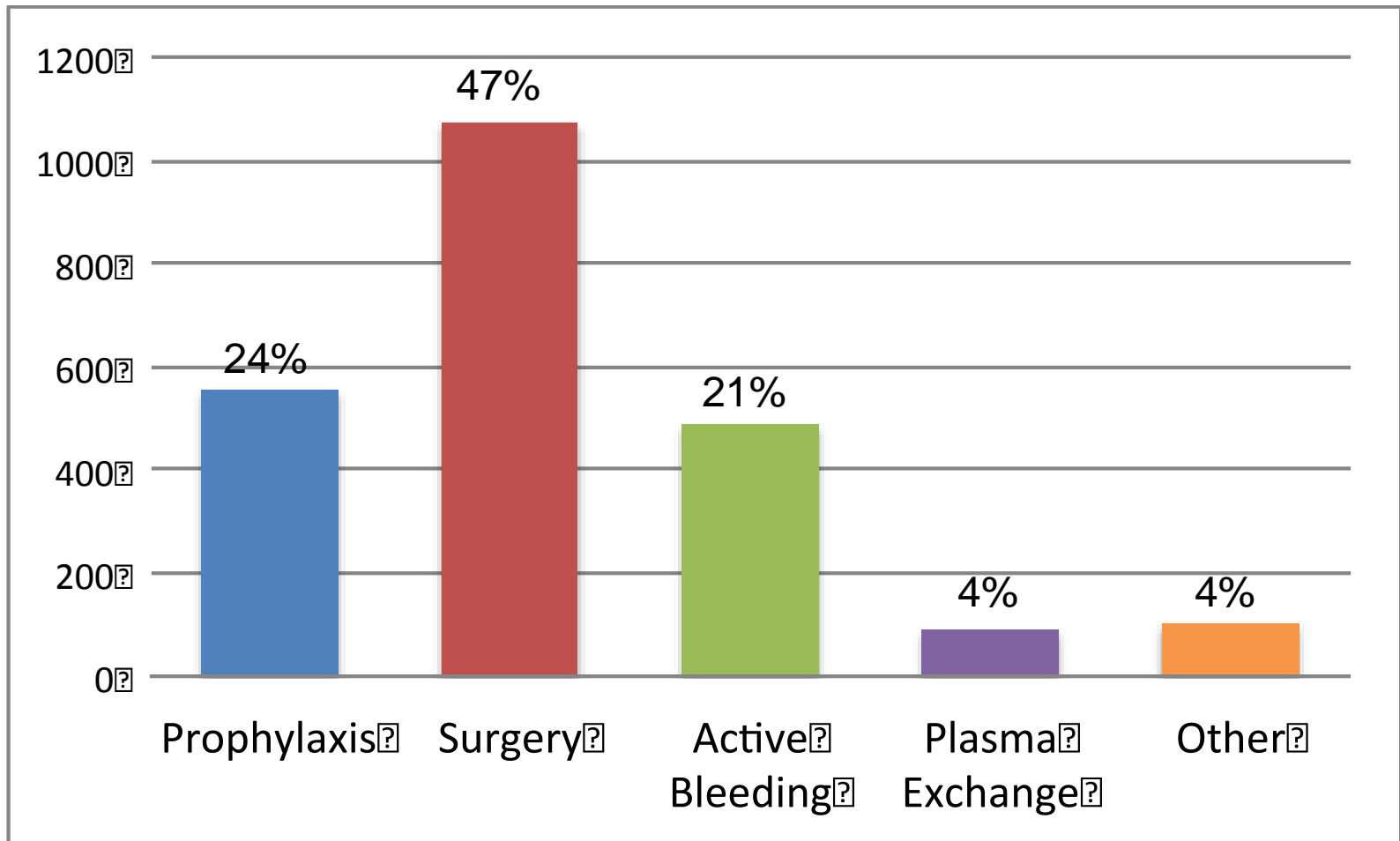


U.S.A. 2011-2012

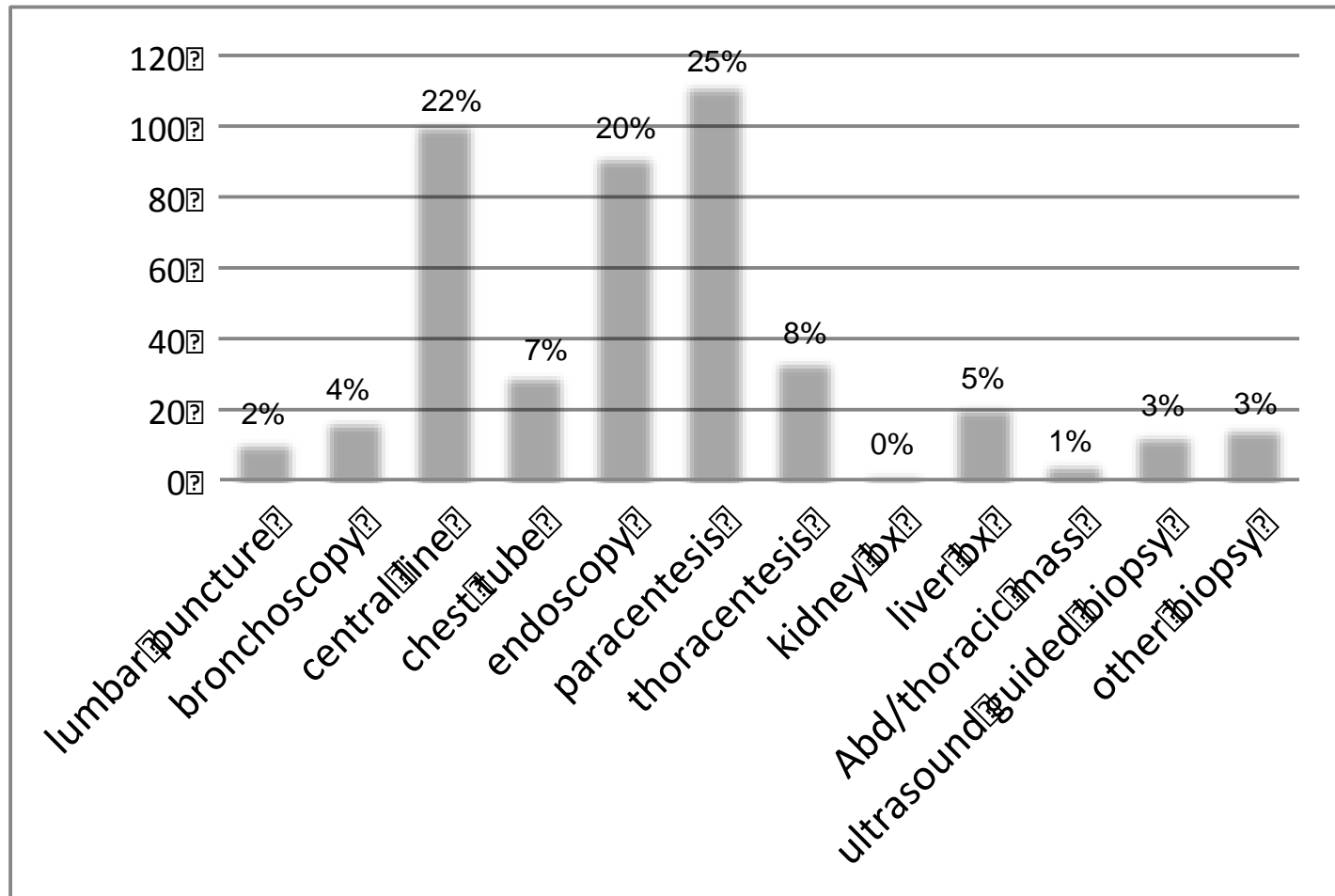




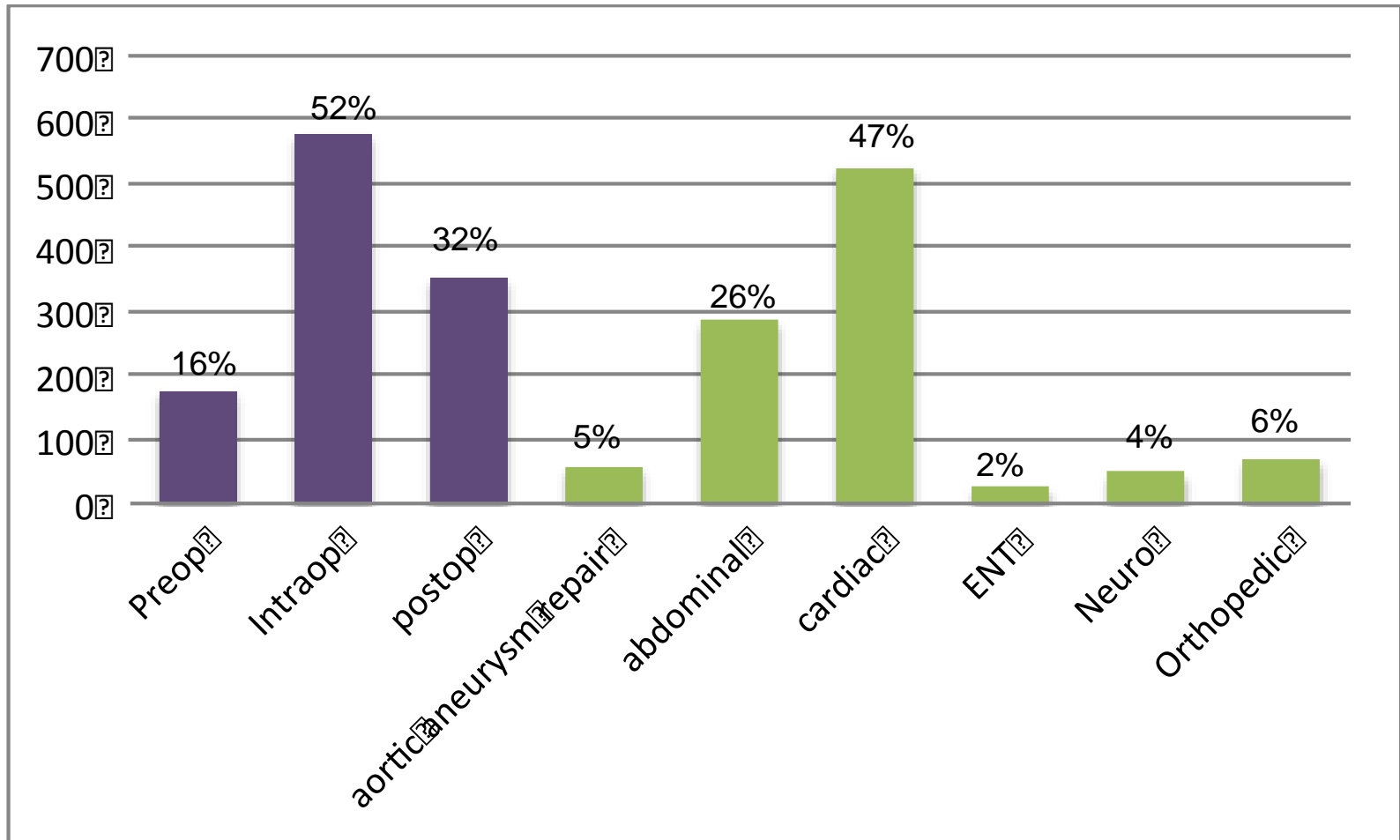
# Why is FP transfusion given?



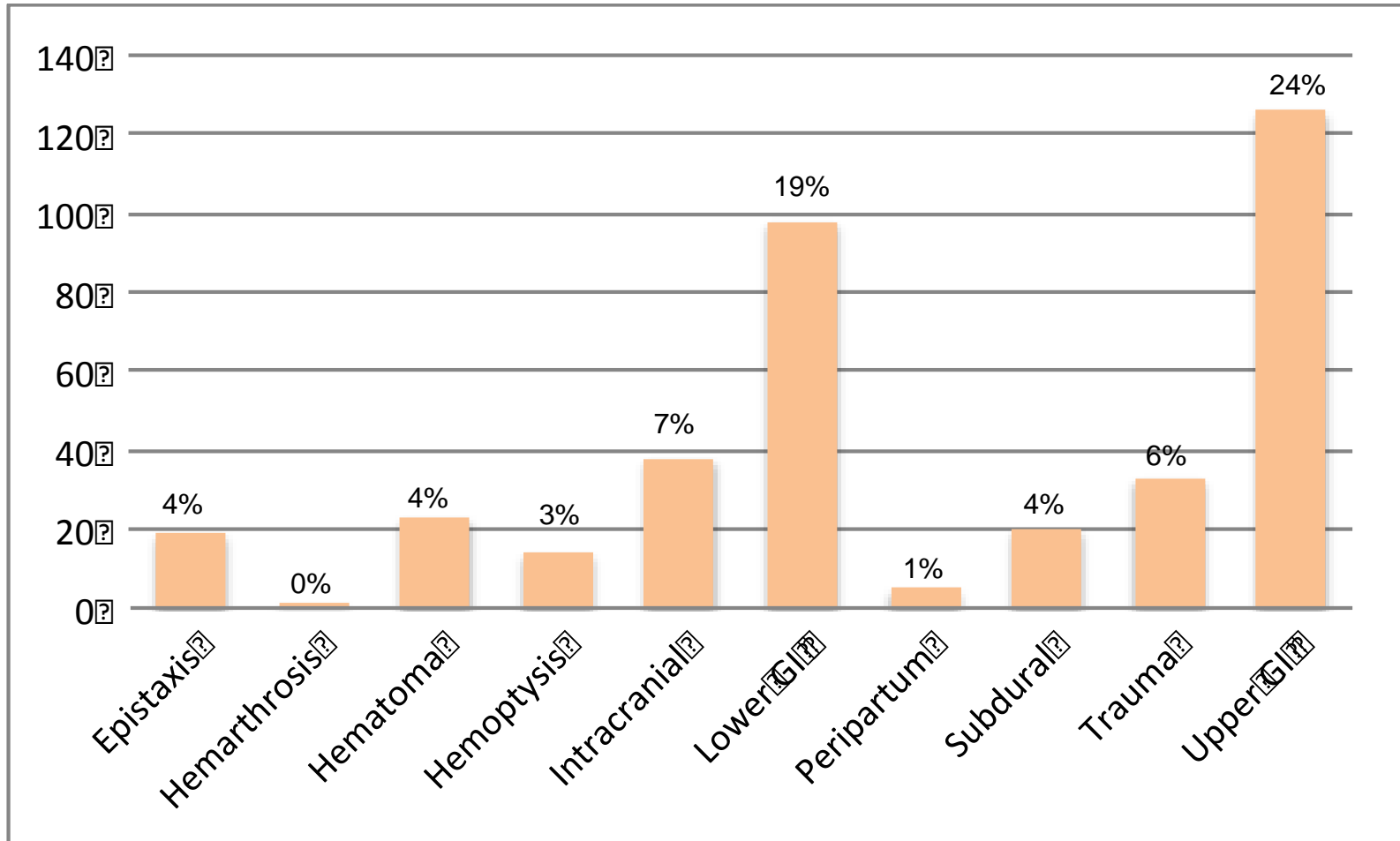
# Prophylaxis – prior to invasive procedures



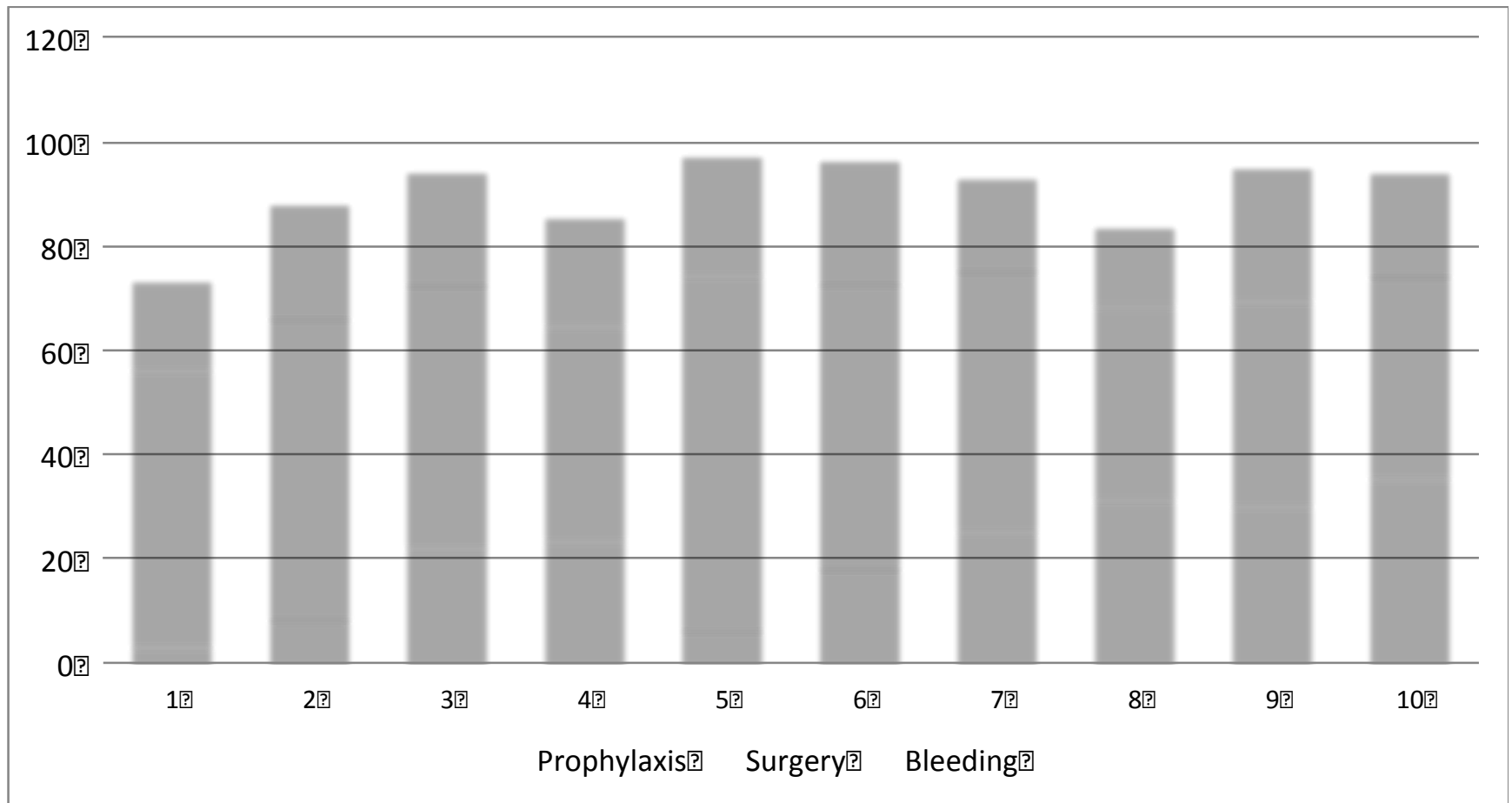
# Surgical use of FP



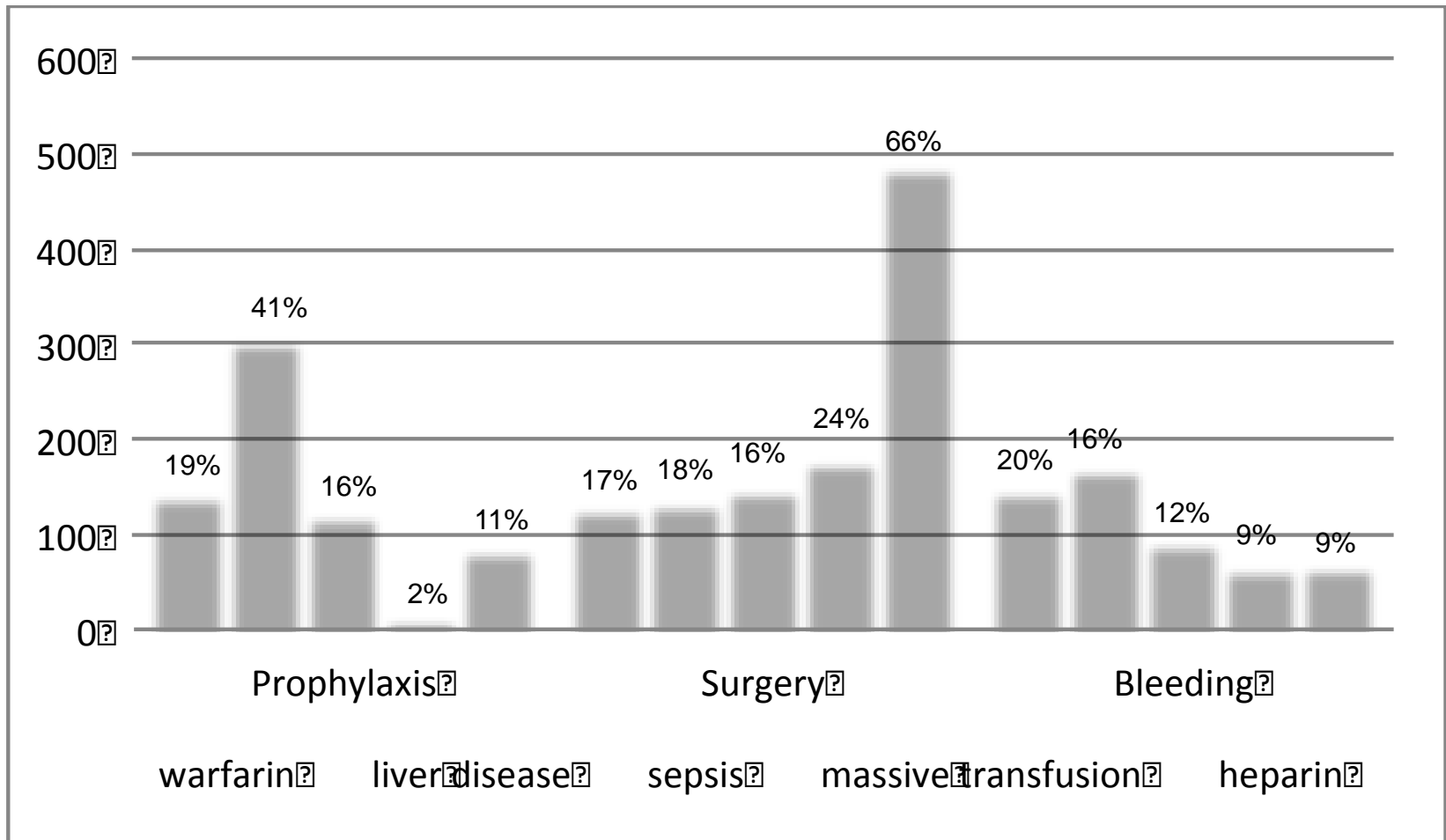
# FP for bleeding



# Variation in FP use by site



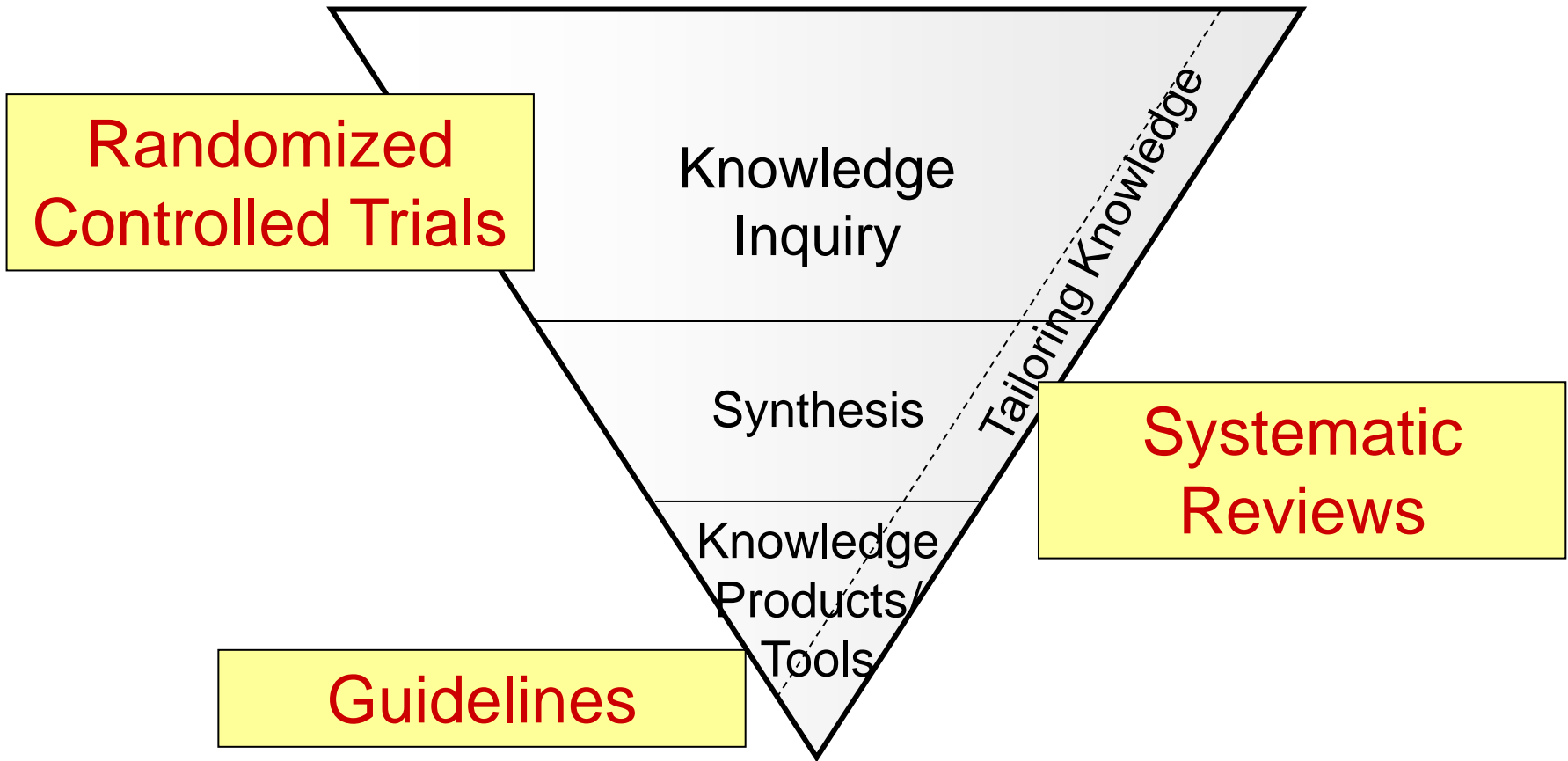
# Coagulopathy of patients receiving FP



# FP Use 3 Canadian Hospitals - 2012

Most Responsible Diagnosis (ICD10)	Total # of Plasma Products Transfused <sup>1</sup> (% of total units transfused)			
	Hospital A	Hospital B	Hospital C	Total (Overall)
Diseases of the circulatory system	1608 (16.2)	2159 (31.3)	2018 (29.5)	5785 (24.4)
Diseases of the musculoskeletal system and connective tissue	2216 (22.3)	1635 (23.7)	1334 (19.5)	5185 (21.9)
Diseases of the digestive system	1057 (10.6)	576 (8.3)	934 (16.7)	2567 (10.8)
Neoplasms	896 (9.0)	558 (8.1)	646 (9.4)	2100 (8.9)
Certain infectious and parasitic diseases	877 (8.8)	135 (2.0)	527 (7.7)	1539 (6.5)
Diseases of the blood and blood-forming organs	683 (6.9)	180 (2.6)	28 (0.4)	891 (3.8)

# Appropriateness of FP use



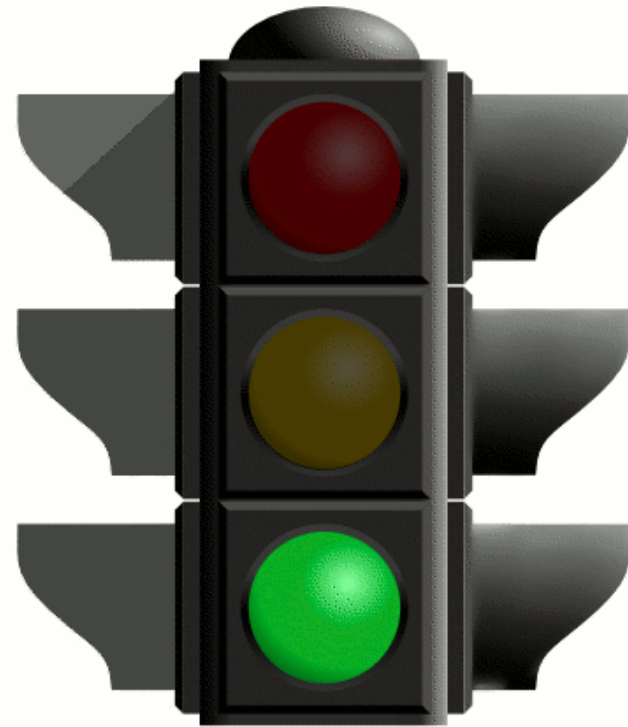


# What do the guidelines say?

Guideline	Single factor deficiency	Multiple factor deficiency	Reversal of warfarin effect	Liver disease	Surgical bleeding, massive transfusion	Volume replacement
British Committee for Standards in Haematology <sup>29, 30</sup>	No safe fractionated product available	Multiple factor deficiencies with severe bleeding +/- DIC	Only in presence of severe bleeding. Partial effect only	Doubtful value. Monitor coagulation for effectiveness	If, and amount, guided by timely tests of coagulation	Not indicated
College of American Pathologists <sup>31</sup>	No safe fractionated or single factor product available	Active bleeding. PT 1.5x mid-point normal range, PTT 1.5x top of normal range	Active bleeding or urgent surgery	No specific recommendation	Active bleeding or before invasive procedure + laboratory evidence of coagulopathy	Contra-indicated
Canadian Medical Association <sup>32</sup>	Concentrates preferred	Active bleeding or urgent surgery with significant increase in PT, INR or PTT	Severe bleeding or urgent surgery. Pro-thrombin complex preferred.	Actual bleeding. PT, INR, PTT elevated. Not indicated for pre-procedure prophylaxis if INR= $\leq$ 2.0	Severe bleeding in presence if possible of laboratory evidence of coagulopathy	Not indicated
Australian Natl. Health and Med. Res. Council <sup>33</sup>	Specific factors if available	Active bleeding	Life-threatening bleeding	May be appropriate with active bleeding and evidence of coagulopathy.	Bleeding with coagulopathy	Not indicated
American Society of Anesthesiologists <sup>34</sup>	Only if specific concentrates are not available	Microvascular bleeding. PT or PTT >1.5x normal	Urgent reversal	No comment	Active bleeding when timely laboratory tests are not available	Contra-indicated

# Indications for Frozen Plasma

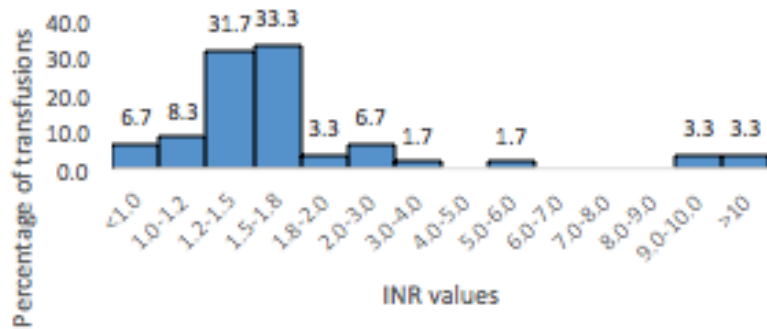
1. INR or PT > 1.5
2. Bleeding or prior to invasive procedure
3. No specific treatment to reverse coagulopathy
  - Warfarin = PCC
  - Congenital deficiencies



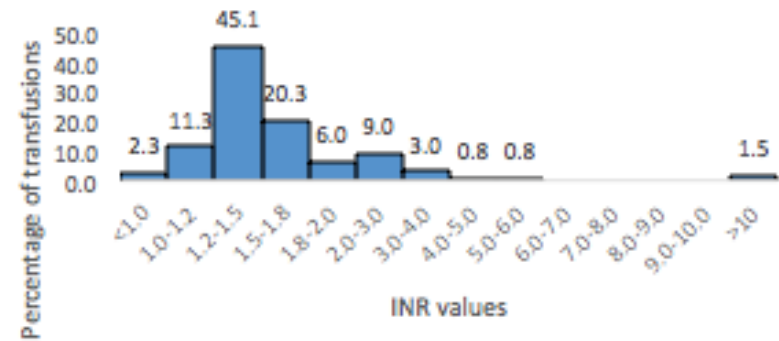
# FP Use 3 Canadian Hospitals – 2012

## Cardiac Surgery

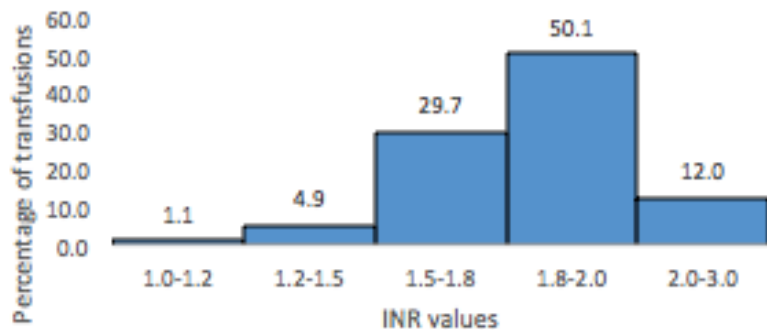
Proportion of plasma transfusions by INR values for CABG (Hospital A)



Proportion of plasma transfusions by INR values for CABG (Hospital B)



Proportion of plasma transfusions by INR values for CABG (Hospital C)



### Percentage of Total FP Use

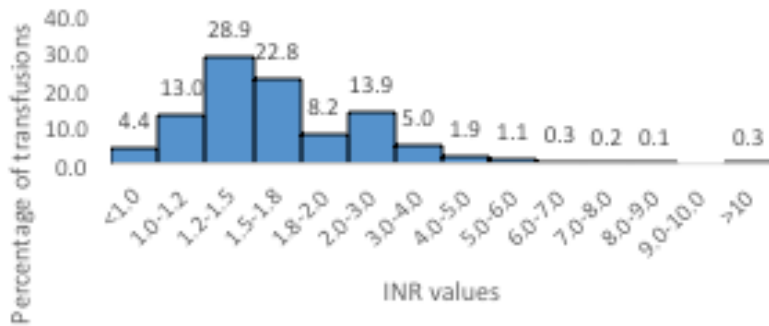
Hospital A – 2.0%

Hospital B – 17.0%

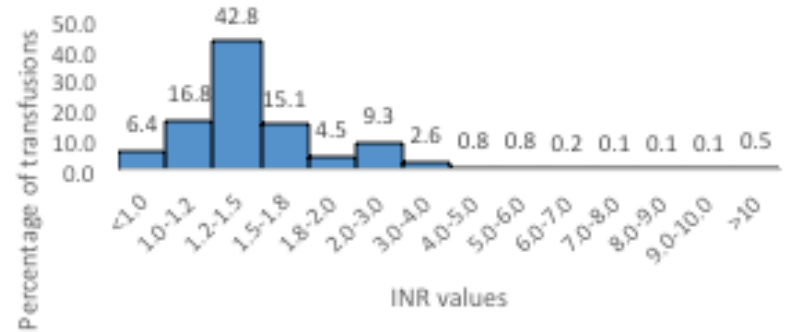
Hospital C – 10.4%

# FP Use 3 Canadian Hospitals – 2012 Critical Care Patients

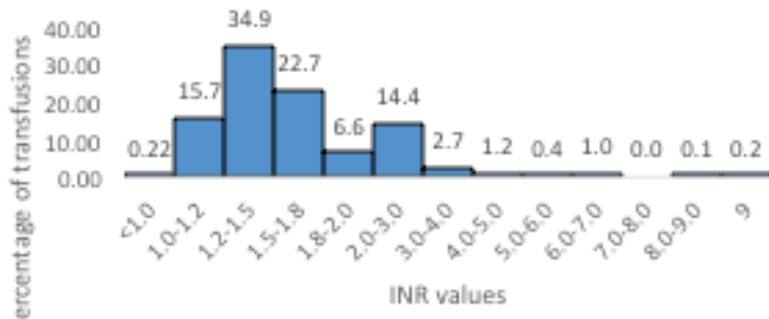
Proportion of plasma transfusions by INR values for ICU patients (Hospital A)



Proportion of plasma transfusions by INR values for ICU patients (Hospital B)



Proportion of plasma transfusions by INR values for ICU patients (Hospital C)



## Percentage of Total FP Use

Hospital A – 34.6%

Hospital B – 53.5%

Hospital C – 45.3%

# Appropriate use of FP in the ICU

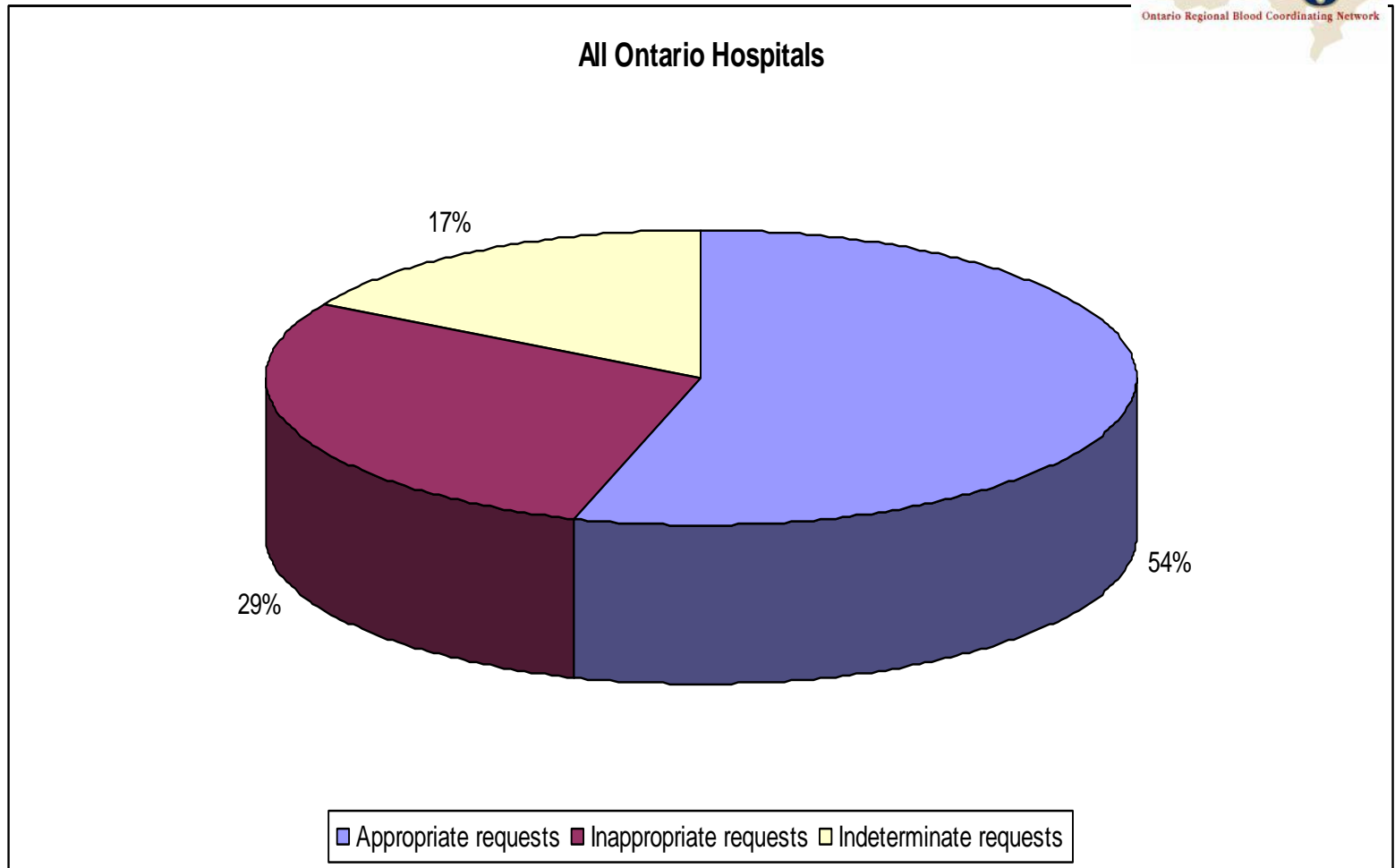
**Table 1** Criteria for the evaluation of FP transfusions in the ICU

Adjudication category	Criteria
Consistent with guidelines <sup>a</sup>	Significantly prolonged INR ( $\geq 1.5$ ) due to vitamin K deficiency, warfarin therapy, liver disease, massive transfusion, or DIC Active, major bleeding Planned urgent major invasive procedure
Inconsistent with guidelines yet appropriate for ICU	Significantly prolonged INR ( $\geq 1.5$ ) due to vitamin K deficiency, warfarin therapy, liver disease, massive transfusion, or DIC Recent (but not active) major bleeding Recent major surgical procedure Bleeding of unclear severity Urgent large-bore central venous catheter insertion
Inappropriate	INR $< 1.5$ Minor/no bleeding Nonurgent procedures

**Table 3** Adjudication of FP transfusion requests in phase III (after deployment of the multifaceted educational intervention) compared with phase I (before the intervention)

	Phase I (n = 66)	Phase III (n = 120)	<i>P</i>
Inappropriate	60%	46%	.09
Consistent with guidelines	23%	22%	.86
Inconsistent with guidelines yet appropriate for the ICU	17%	32%	.04

# Appropriateness of Frozen Plasma Use in Ontario in 2008



# Appropriate use of FP



<b>Total no of appropriate Frozen Plasma requests</b>	<b>314 (54.8%)</b>
Coagulopathy (not warfarin / vit K deficiency) Bleeding <i>and</i> INR >1.5 and/or PTT >1x normal .	96 (16.8)
Peri-surgical bleeding INR>1.5 and/or PTT>1x normal.	80 (14.0)
Coagulopathy (not warfarin / vit K deficiency) Urgent intervention or surgery INR >1.5 and/or PTT>1x upper limit of normal.	43 (7.5)
Reversal of warfarin or vitamin K deficiency. Bleeding INR >1.5 and/or PTT >1x normal.	37 (6.4)
“Massive transfusion” INR>1.5 and/or PTT >1x normal.	35 (6.1)

# Inappropriate use of FP



<b>Total no of inappropriate Frozen Plasma requests</b>	<b>164 (28.6%)</b>
INR < 1.5 and normal PTT Irrespective of bleeding status or procedure status	97 (16.9 %)
Reversal of warfarin or vitamin K deficiency Absence of bleeding	41 (7.2 %)
Reversal of other coagulation defect INR >1.5 and PTT>1x upper limit of normal. No bleeding or surgery/procedure planned	15 (2.6 %)
Heparin reversal (regardless of INR)	10 (1.7 %)
INR ≤ 1.0 and normal PTT Irrespective of bleeding status or procedure status	7 (1.2 %)



# Indeterminate use of FP



<b>Total no. of Frozen Plasma Indeterminate requests</b>	<b>95 (16.6%)</b>
Abnormal coagulation pre- or post- transfusion Bleeding unknown	31 (5.4%)
No laboratory coagulation data pre- or post-transfusion	27 (4.7%)
No laboratory coagulation data pre- transfusion (with normal coagulation results post-procedure)	17 (3.0%)
Abnormal coagulation – diagnosis unknown, Not bleeding and procedure unknown	12 (2.1%)
“Massive transfusion” INR<1.5 and/or PTT <1x normal or no laboratory coagulation data available	8 (1.4%)

# Ontario FP Guidelines

## Situations in which the transfusion of FP is reasonable:

Clinical Indication	Reason
Bleeding	Liver disease or DIC with INR above 1.5
	Massive transfusion (expect more than 10 RBC units transfused in 24 hours) with INR above 1.5 (or rapidity of bleeding does not allow for MD to wait for results)
	Reversal of warfarin or vitamin K deficiency only where intravenous vitamin K would not suffice <b>and</b> prothrombin complex concentrate (Octaplex®) is unavailable
	Inherited or acquired single factor deficiencies where specific factor concentrate is unavailable
Emergency surgery or major procedure (within 6 hours)	Reversal of warfarin or vitamin K deficiency only where intravenous vitamin K would not suffice <b>and</b> prothrombin complex concentrate (Octaplex®) is unavailable
Surgery or major procedure	Liver disease or DIC with INR above 1.5
	Inherited or acquired single factor deficiencies where specific factor concentrate is unavailable
Plasma exchange	Thrombotic thrombocytopenic purpura (TTP)

## Situations in which transfusion of FP is NOT useful:

- INR 1.5 or less (including major or minor procedure/surgery)\*
- Use of 1:1 (FP:RBC) replacement when patient is unlikely to require massive transfusion
- Coagulopathy in the absence of bleeding or need for emergency surgery
- Elective reversal of warfarin where time allows for warfarin cessation and/or use of vitamin K
- Reversal of anticoagulants other than warfarin (eg: heparin/LMWH, rivaroxaban)
- Volume expansion or "nutrition support"

# Appropriateness of Frozen Plasma Use in Canada

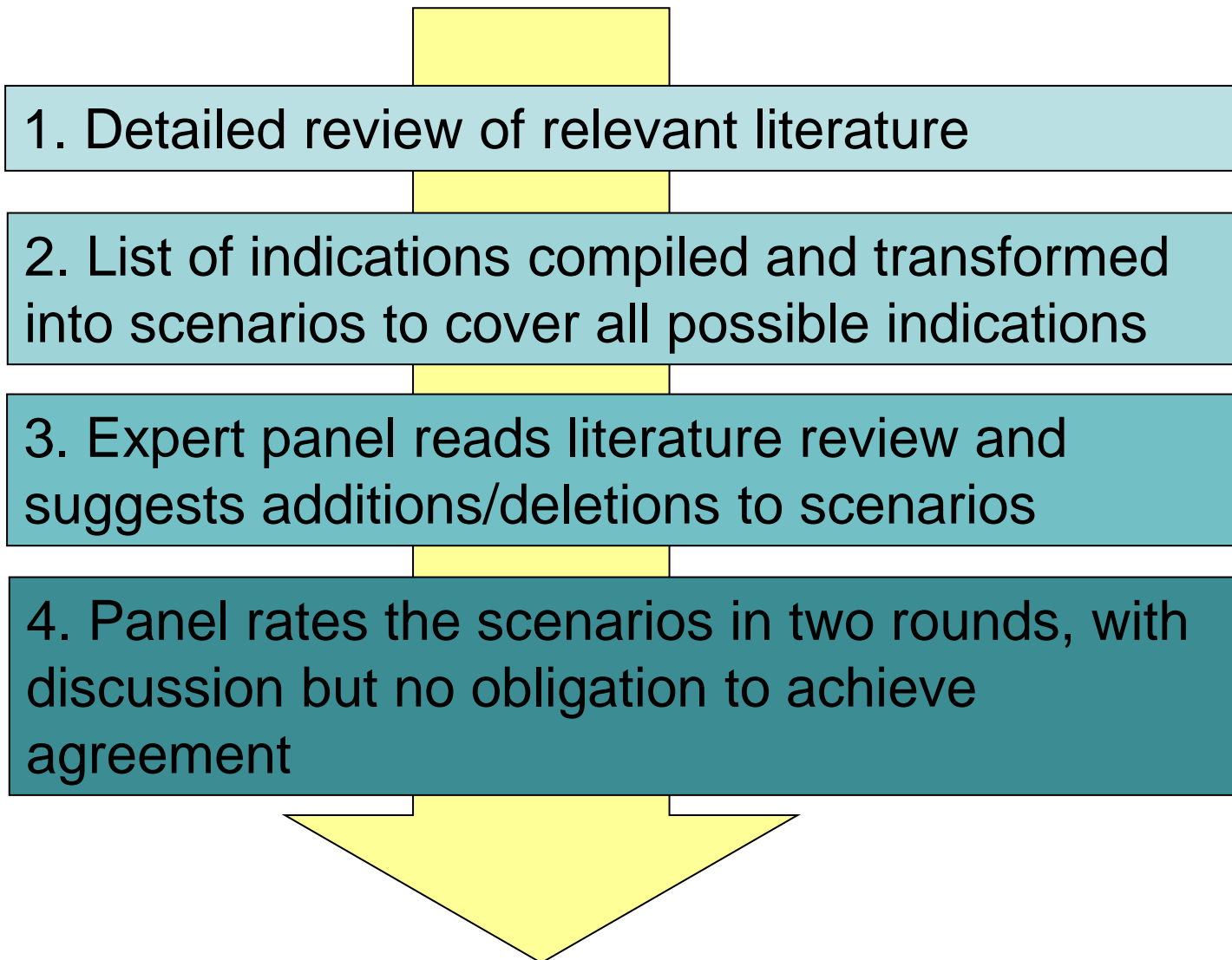


Multidisciplinary expert panel determined appropriateness ratings for clinical scenarios

Prospective 2-month cohort study of all Frozen Plasma transfusions at 10 Canadian centres

Appropriateness of Frozen Plasma transfusions across centres.

# RAND (modified delphi) Consensus Process



# Expert Panel

- Internal Medicine / Obstetrics
- Internal Medicine / Laboratory
- Critical Care
- Hematology
- Transfusion Medicine
- Radiology
- Cardiac surgery
- Cardiac anesthesia
- General surgery / trauma
- Anesthesia

# Assessing appropriateness of FP use: clinical scenarios

- Scenarios produced for prophylaxis, bleeding and surgery
  - 33 base scenarios
- Key clinical factors varied for each base scenario
  - Hgb and platelet for most scenarios + other scenario specific factors
  - Total number of scenarios – 239 scenarios
- For each scenario varied coagulopathy (liver disease, warfarin) and level of INR.
  - Over 2500 variations with individual ratings

# Clinical scenarios

<b>Prophylaxis</b>	<b>Surgery</b>	<b>Bleeding</b>
1. Renal biopsy	1. Abdominal Aneurysm	1. Epistaxis
2. Liver biopsy	2. Abdominal/Thoracic	2. Hemarthrosis
3. Lumbar puncture	3. Cardiac	3. Hematoma
4. Lymph node excision	4. ENT	4. Hematuria
5. U/S biopsy of mass	5. Intraop major bleed	5. Hemoptysis
6. Bone Marrow	6. Intraop microvascular	6. Intracranial bleed
7. Bronchoscopy	7. Post op bleed	7. Subdural bleed
8. Central line insertion	8. Liver transplant	8. Lower GI bleed
9. Chest tube insertion	9. Neurosurgery	9. Upper GI bleed
10. Endoscopy	10. Orthopoedic	10. Peripartum bleed
11. Paracentesis		11. Trauma
12. Thoracentesis		

# Assessing appropriateness of FP use: clinical scenarios

- Scenarios produced for prophylaxis, bleeding and surgery
  - 33 base scenarios
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# Clinical scenario: bronchoscopy

Panelist Name:

Topic: Prophylaxis – Bronchoscopy (a)

**Clinical Scenario:** A 67 year male smoker is admitted to ICU with respiratory distress. Chest x-ray shows bilateral diffuse infiltrates. He requires an FiO<sub>2</sub> of 70% by mask. His vital signs are stable. A bronchoscopy is to be performed for tracheal toilet and to obtain diagnostic samples. The Hgb is 125 g/L and platelet count is 183 x 10<sup>9</sup> /L. Based on the available literature and your expert medical opinion, please use the following scale to rate the appropriateness of transfusion with frozen plasma given the following known medical conditions and INR results.

INR (sec)	Liver disease			Warfarin (Octaplex available)			Warfarin (Octaplex not available)		
	Inappropriate	Uncertain	Appropriate	Inappropriate	Uncertain	Appropriate	Inappropriate	Uncertain	Appropriate
<1.2	1 2 3 4 5 6 7 8 9			1 2 3 4 5 6 7 8 9			1 2 3 4 5 6 7 8 9		
1.2 -1.5	1 2 3 4 5 6 7 8 9			1 2 3 4 5 6 7 8 9			1 2 3 4 5 6 7 8 9		
1.51 – 1.8	1 2 3 4 5 6 7 8 9			1 2 3 4 5 6 7 8 9			1 2 3 4 5 6 7 8 9		
1.81 – 2.1	1 2 3 4 5 6 7 8 9			1 2 3 4 5 6 7 8 9			1 2 3 4 5 6 7 8 9		
2.11 – 3.5	1 2 3 4 5 6 7 8 9			1 2 3 4 5 6 7 8 9			1 2 3 4 5 6 7 8 9		
>3.51	1 2 3 4 5 6 7 8 9			1 2 3 4 5 6 7 8 9			1 2 3 4 5 6 7 8 9		

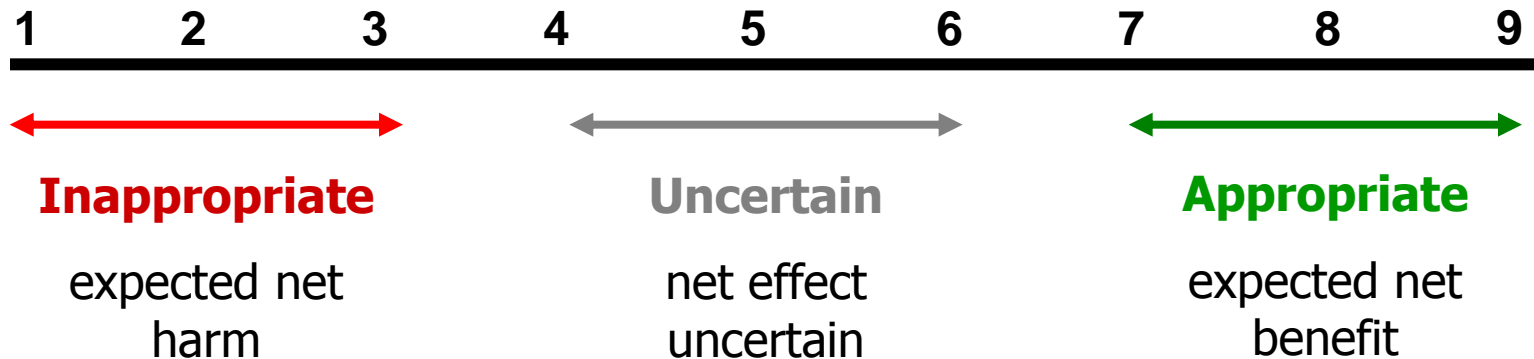
**Score:** 1 – 2 – 3 → Inappropriate indication for Frozen Plasma. Transfusion is not generally acceptable and is unlikely to improve outcome.

4 – 5 – 6 → Uncertain indication for Frozen Plasma. Transfusion may improve or worsen outcome; more information is needed.

7 – 8 – 9 → Appropriate indication for Frozen Plasma. Transfusion is generally acceptable and is likely to improve outcome.

# Appropriateness Scale

- Ordinal nine point scale
- Median ratings are used



# Appropriateness ratings: Prophylaxis

Coagulopathy	Rating	INR	Comments
Warfarin	Inappropriate	All	PCC available (if not then similar to liver disease)
Liver Disease	Inappropriate	$\leq 1.8$	$\leq 1.5$ if higher risk (e.g. low platelets)
			$\leq 2.1$ if lower risk (e.g. IJ line or paracentesis)
	Indeterminate	1.8 - 2.1	$> 2.1$ if lower risk
	Appropriate	$> 2.1$	No appropriate INR level for lower risk

# Appropriateness ratings: Surgery pre-op

Coagulopathy	Rating	INR	Comments
Warfarin	Inappropriate	All	Assumes PCC available.
Liver Disease	Inappropriate	$\leq 1.5$	Assumes urgent Sx. All cardiac Sx inappropriate.
	Indeterminate	1.5 – 1.8/2.1	Assumes urgent Sx.
	Appropriate	$> 1.8 / 2.1$	Assumes urgent Sx.

# Appropriateness ratings: Surgery intra-op

Coagulopathy	Rating	INR	Comments
Microvascular	Inappropriate	$\leq 1.2$	No inappropriate if multiple RBCs.
	Indeterminate	1.2 – 1.8	$\leq 1.5$ if multiple RBCs and/or cardiac Sx.
	Appropriate	$> 1.8$	Lower threshold if multiple RBCs and/or cardiac Sx.
Major bleed	Indeterminate	$\leq 1.5$	$\leq 1.8$ if liver disease.
	Appropriate	$> 1.5$	$> 1.8$ if liver disease

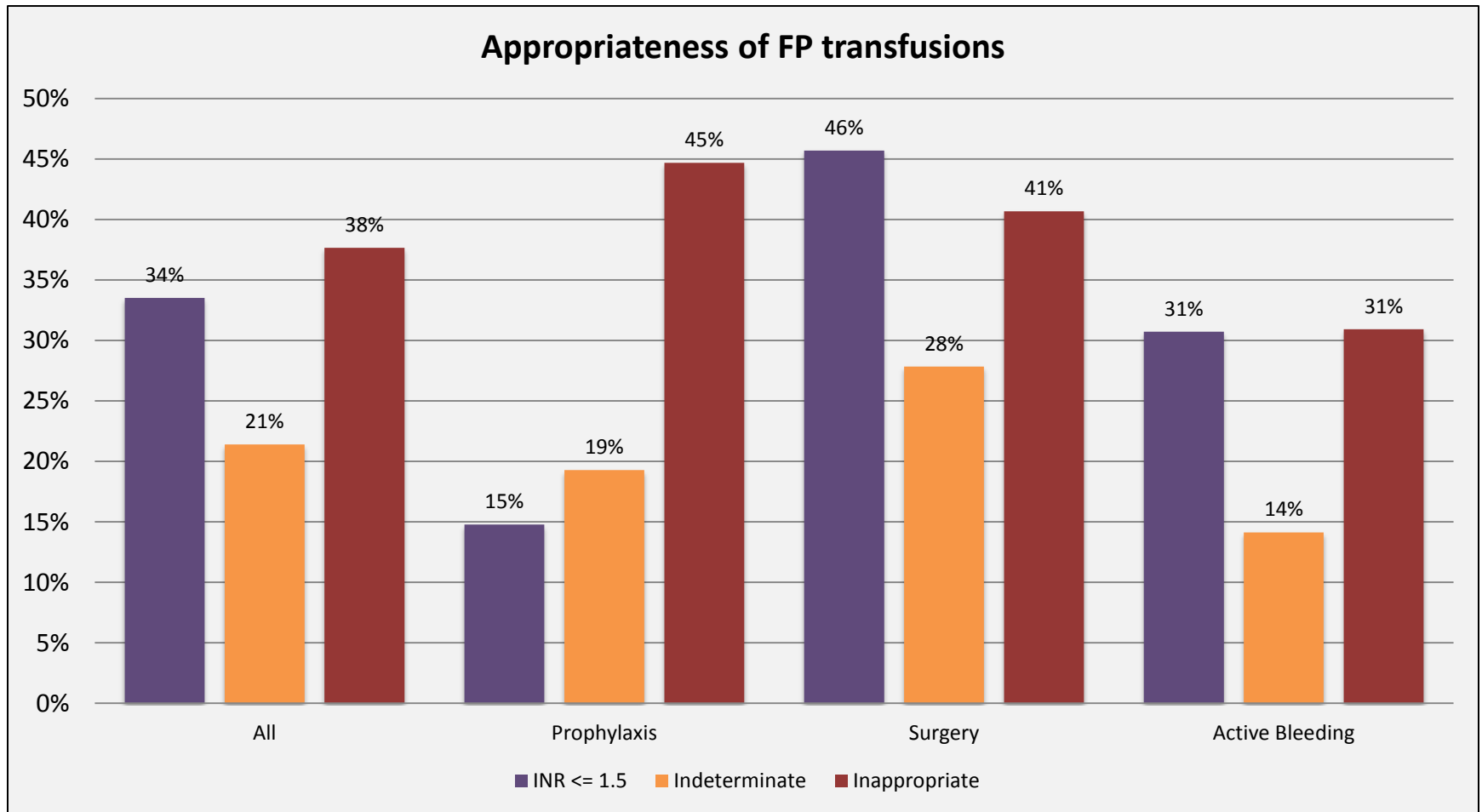
# Appropriateness ratings: Surgery post-op

Coagulopathy	Rating	INR	Comments
No Bleeding (immediate)	Inappropriate	$\leq 1.5$	For CABG $\leq 1.8 - 2.1$
	Indeterminate	1.5 - 3.5	For CABG $> 2.1$
	Appropriate	3.5	
Bleeding (immediate)	Indeterminate	$\leq 1.8$	For CABG 1.5 – 1.8
	Appropriate	$> 1.8$	
No bleeding (24 h)	Inappropriate	$\leq 1.8$	
	Indeterminate	$> 1.8$	
Bleeding (24 h)	Inappropriate	$\leq 1.5$	Lower if low platelets or liver disease.
	Indeterminate	1.5 – 2.1	
	Appropriate	$> 2.1$	

# Appropriateness rating: Bleeding

Coagulopathy	Rating	INR	Comments
Warfarin	Inappropriate	All	PCC available
Liver disease	Inappropriate	$\leq 1.5$	$\leq 1.8$ for less severe
			$\leq 1.2$ for intracranial bleed
	Indeterminate	1.5 – 2.1/3.5	1.2 – 1.8 for intracranial bleed
	Appropriate	$> 2.1$	$> 1.8$ for more severe/CNS bleeding
			$> 3.5$ for less severe bleeding

# Appropriateness of FP transfusions





# Conclusions

- Specific groups largest users of FP
  - Intensive Care Unit
  - Cardiac Surgery
  - Gastrointestinal
- Large amount of inappropriate use
  - Based on current guidelines / recommendations
- Additional studies to determine “true” appropriateness

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