EDQM Blood Conference
Innovation in Blood Establishment Processes

14-15 January 2025
Strasbourg, France

Session B1 (part 1):
Innovative & novel blood components
(13:30 – 15:00)

Moderators: **Ryan Evans**, Scottish National Blood Transfusion Service, Scotland
Richard Forde, CD-P-TS Secretary, EDQM

Speakers: **Peter O'Leary**, European Blood Alliance, Belgium
Stephen Vardy, NHS Blood and Transplant, England
Mike Wiltshire, NHS Blood and Transplant, England
Melanie Robbins, NHS Blood and Transplant, England
Luciana Teofili, Fondazione Policlinico Universitario A. Gemelli IRCCS, Italy

Please note:
- *Food and drink are not permitted in the conference rooms*
- *Photography & filming during the presentations are strictly forbidden*
- *Photos and videos may only be taken by Council of Europe staff members*
- *The session will be recorded for internal purposes only*

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European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

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Dried plasma: current considerations in Europe

Peter O'Leary

Executive Director, European Blood Alliance

EUROPEAN BLOOD ALLIANCE

Representing public and non-profit blood establishments across Europe

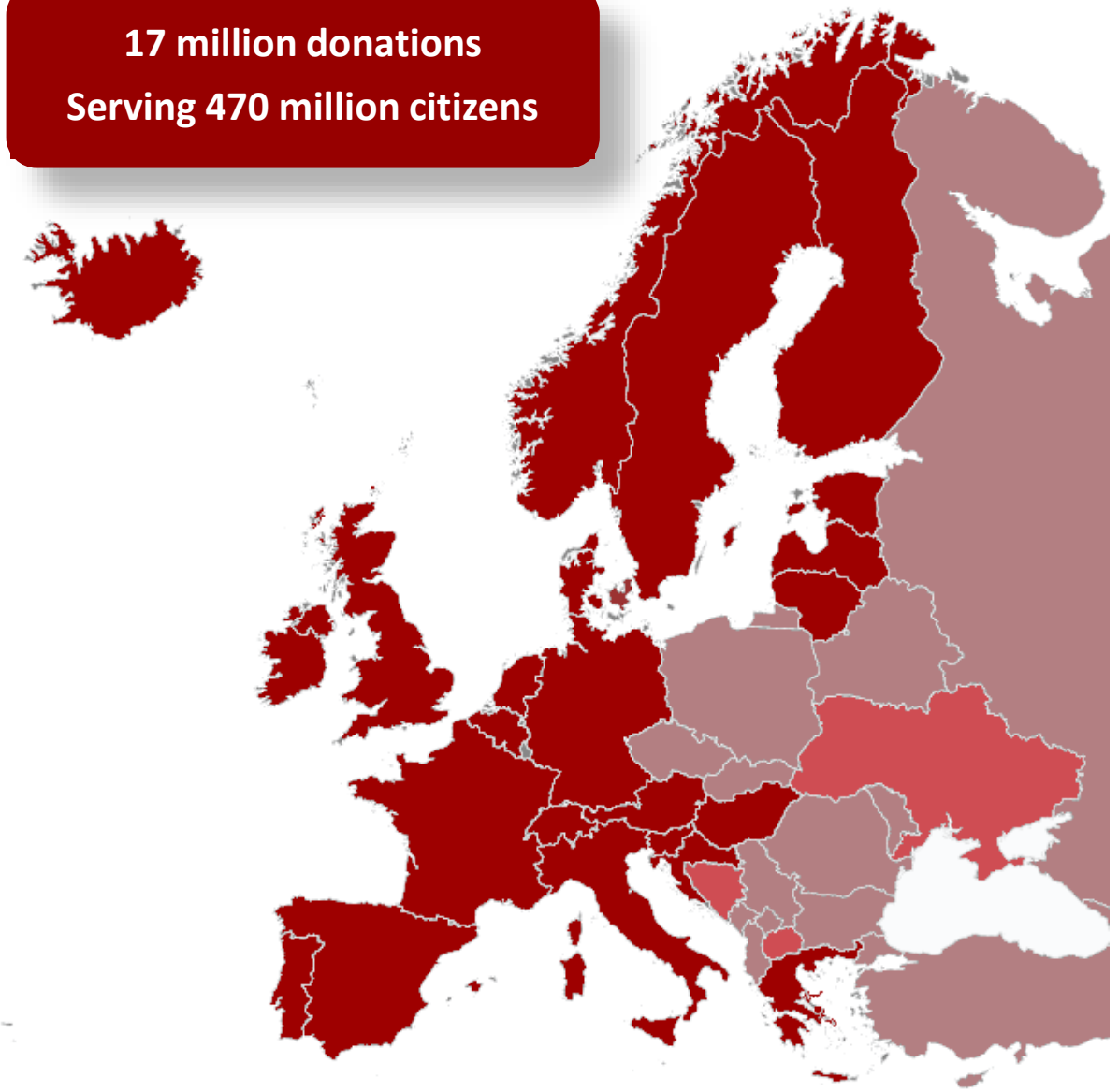
25 member countries, 4 candidate member countries, 1 observer

A Safe and Sustainable Blood Supply for Europe

Austria	Iceland	Portugal
Belgium	Ireland	Spain
Croatia	Italy	Sweden
Denmark	Latvia	Switzerland
Estonia	Lithuania	United Kingdom
Finland	Luxembourg	Bosnia & Herzegovina
France	Malta	North Macedonia
Germany	Netherlands	Ukraine
Greece	Norway	Albania
Hungary	Slovenia	

America's Blood Centers® It's About *Life.*

17 million donations
Serving 470 million citizens



Dried Plasma - Innovative and Novel?

World War 2:
Out of every one-hundred US soldiers wounded, it is estimated that ninety-six survived.

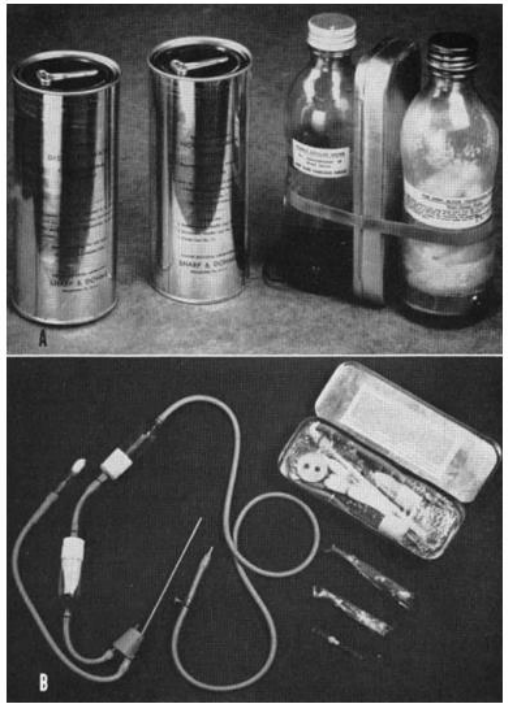


Fig. 1. (A) British (right) and US Army dried plasma units. (B) British dispensing set for plasma. Available from: https://upload.wikimedia.org/wikipedia/en/thumb/9/95/Britain_and_us_plasma_packages_wwii.jpg/162px-Britain_and_us_plasma_packages_wwii.jpg, accessed 30 Sept 2015.

"The foremost lifesaver is dried plasma.

Plasma saved shock and bleeding. Second in lifesaving was surgery"

Maj. Gen. Norman T. Kirk, surgeon general of the Army, address to the American Medical Association [AMA] June 7, 1943.

Dried plasma alternatives in Europe today

Lyoplas N-w (German Red Cross)
Freeze-dried single donor, blood group specific

FLYP: French **Ly**ophilized **P**lasma, (French Military Blood Institute, Centre de Transfusion Sanguine des Armées (CTSA).
Freeze-dried, pools of 11, pathogen reduced, Universal

Octaplas LG Powder (Octapharma)
Freeze-dried, pools of 630-1520, SD treated, blood group specific

****

FrontlineODP (Velico Medical).
Spray dried, single donor: local production in blood establishments via installation of an instrument/system
(*under evaluation in Europe and in USA)

Other development projects

EBA Consultation S2411_Dried Plasma Activities

Background:
An increasing interest in dried plasma (also referred to as freeze-dried plasma and/or lyophilised plasma) was identified by many EBA members who are facing queries about and/or requests for the product. These increases in demand are being driven by both civilian and military situations, for a number of reasons including:

• Shift in policy when it comes to treatment of patients with severe bleeding from a clear fluid-based to a blood-based resuscitation strategy

• Civilian and military guidelines recommend early blood transfusion for treatment of patients with life-threatening bleeding to improve survival

As a result of discussions, our EBA Innovation and New Products Working Group initiated a subgroup on EBA Dried Plasma. The purpose of this survey is to assist the EBA Dried Plasma subgroup better understand the Dried Plasma-related challenges and demands faced by Blood Establishments, and also prepare for the inclusion of a monograph on dried plasma in the EDQM Blood Guide, as recently agreed provisionally with CD-P-TS.

Please respond by 28 June 2024

* Required

1. Country *

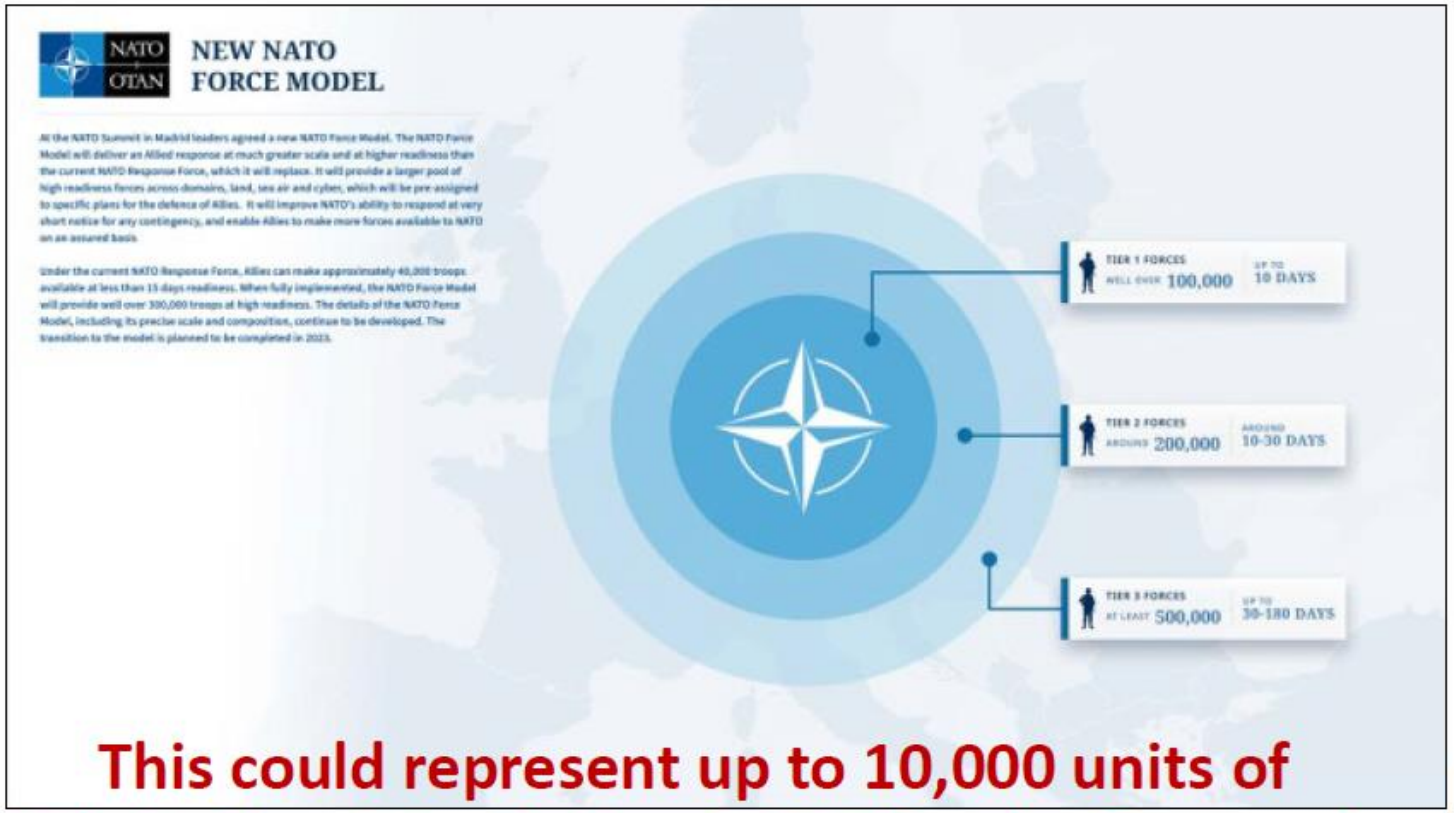
Enter your answer

Reasons for the survey

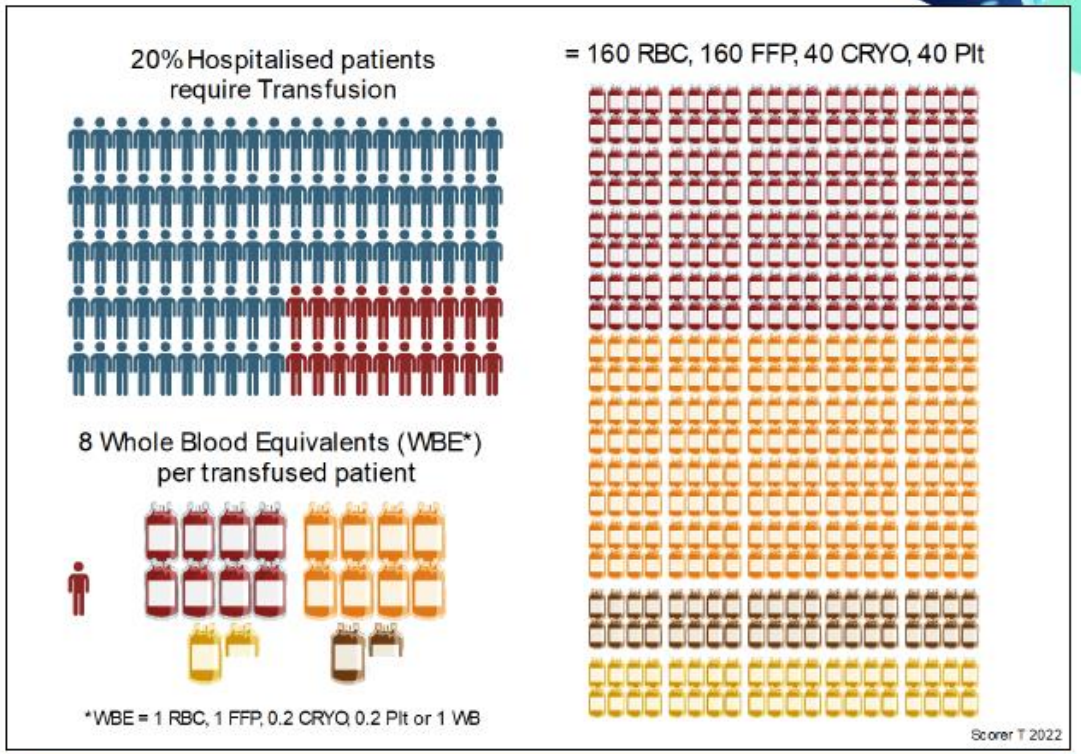
- Increasing interest in dried plasma
  - noted by many EBA members
  - To EBA, from regional, national, and European institutions
- Shift in treatment policy for patients with severe bleeding - from a clear fluid-based to a blood-based resuscitation strategy
- Civilian and military guidelines recommend early transfusion for treatment of patients with life-threatening bleeding to improve survival
- Increased focus on Contingency and Emergency Planning

Managing SoHO in emergency situations

Major General Tim Hodgetts, Chair COMEDS



This could represent up to 10,000 units of Whole Blood Equivalent (WBE) in the first week



Planning for contingency options prior to full combat operations

- Dried plasma
- Emergency donor panel (EDP)
- Walking Blood Bank (WBB)

The 5 C's of blood preparedness planning

(Adapted from: Finnish Red Cross Blood Service)

- **Capacity** (Donor pool, communication, accessibility)
- **Contingency** (reserve materials, instruments, facilities, mobility, personnel, logistics)
- **Cybersecurity** (multiplying, shielding, distribution, outsourcing, architecture, provider
- **Contacts** (NCA, situation analysis, peer network for support, customer stock levels)
- **Crisis specific products:** Dried Plasma, Whole Blood, FFP

NHS issues urgent call for O-type blood donors following London cyber attack

CYBER SECURITY, NEWS

10 June 2024

NHS Blood and Transplant - Blood donor centre sign (based on Cambridge Centre image)

Tammy Lovell

NHS Blood and Transplant (NHSBT) has urgently called for donations of O Positive and O Negative blood to boost stocks following a ransomware attack which has disrupted pathology services in London.

The Guardian

Four killed in Russian strikes on Ukraine that destroyed blood transfusion centre

Multi-wave overnight attack said to be in retaliation for successful strikes against Russian naval vessels

Russia-Ukraine war: latest updates

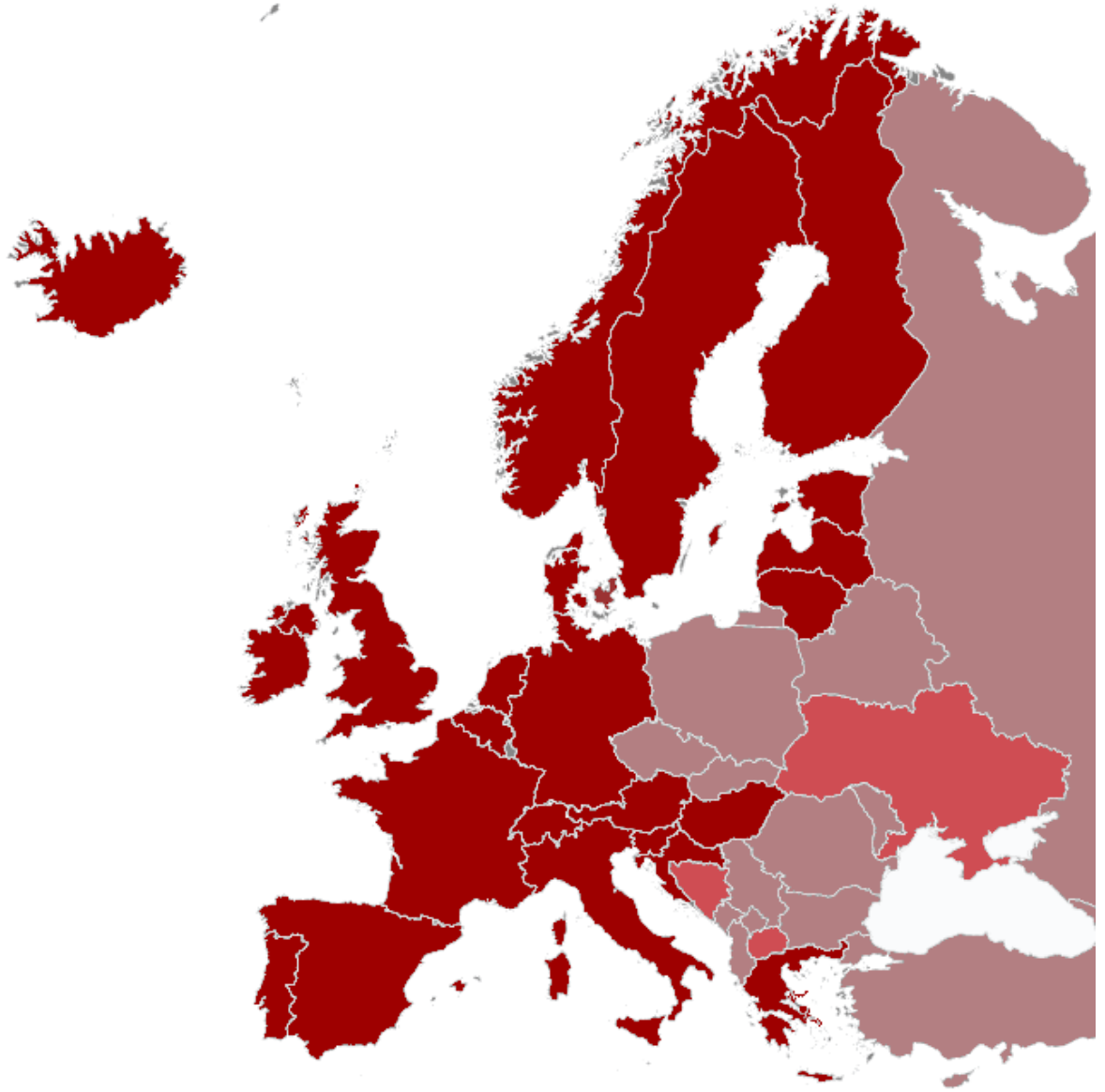
EUROPEAN BLOOD ALLIANCE

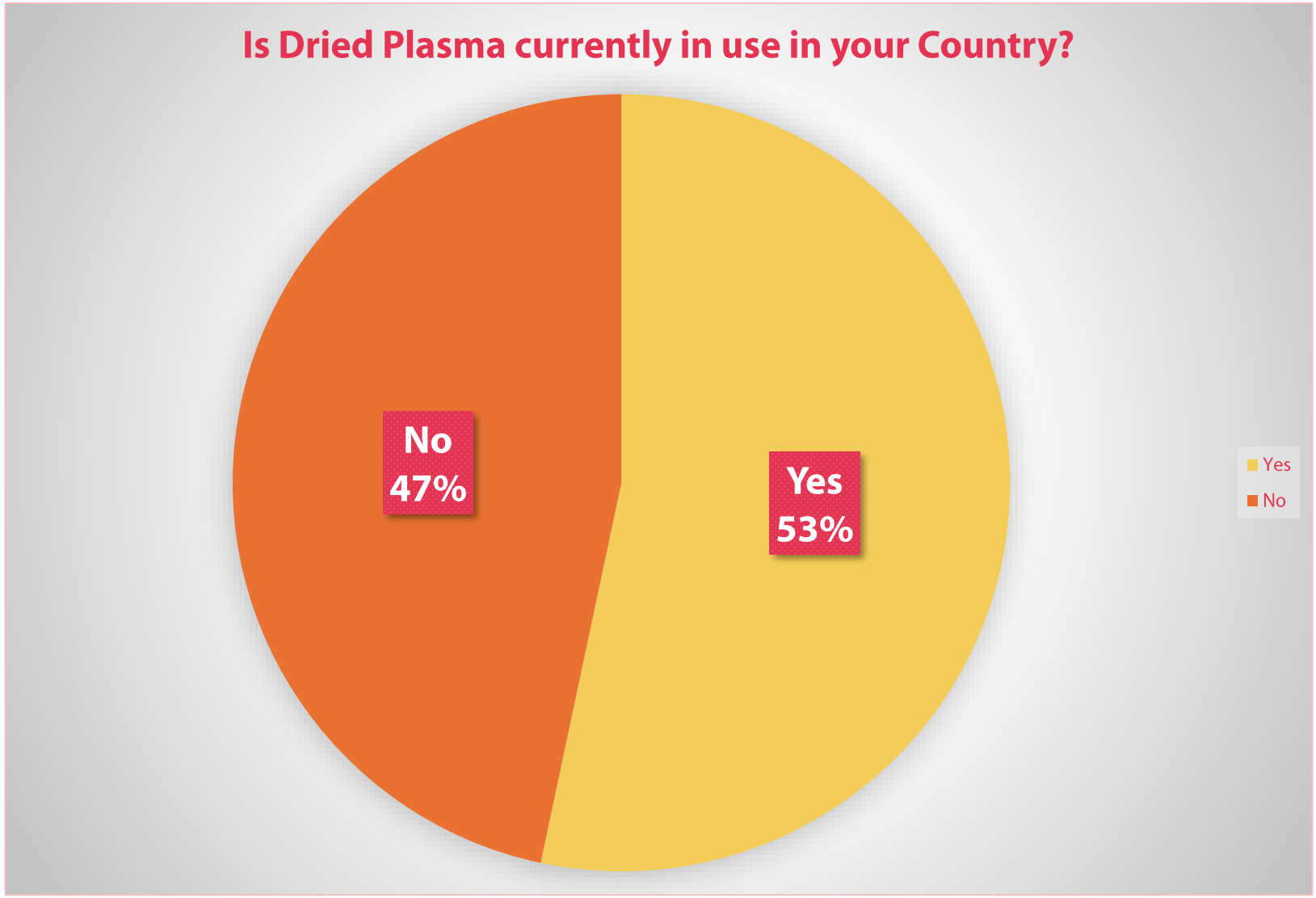
Survey response rate was **60%**

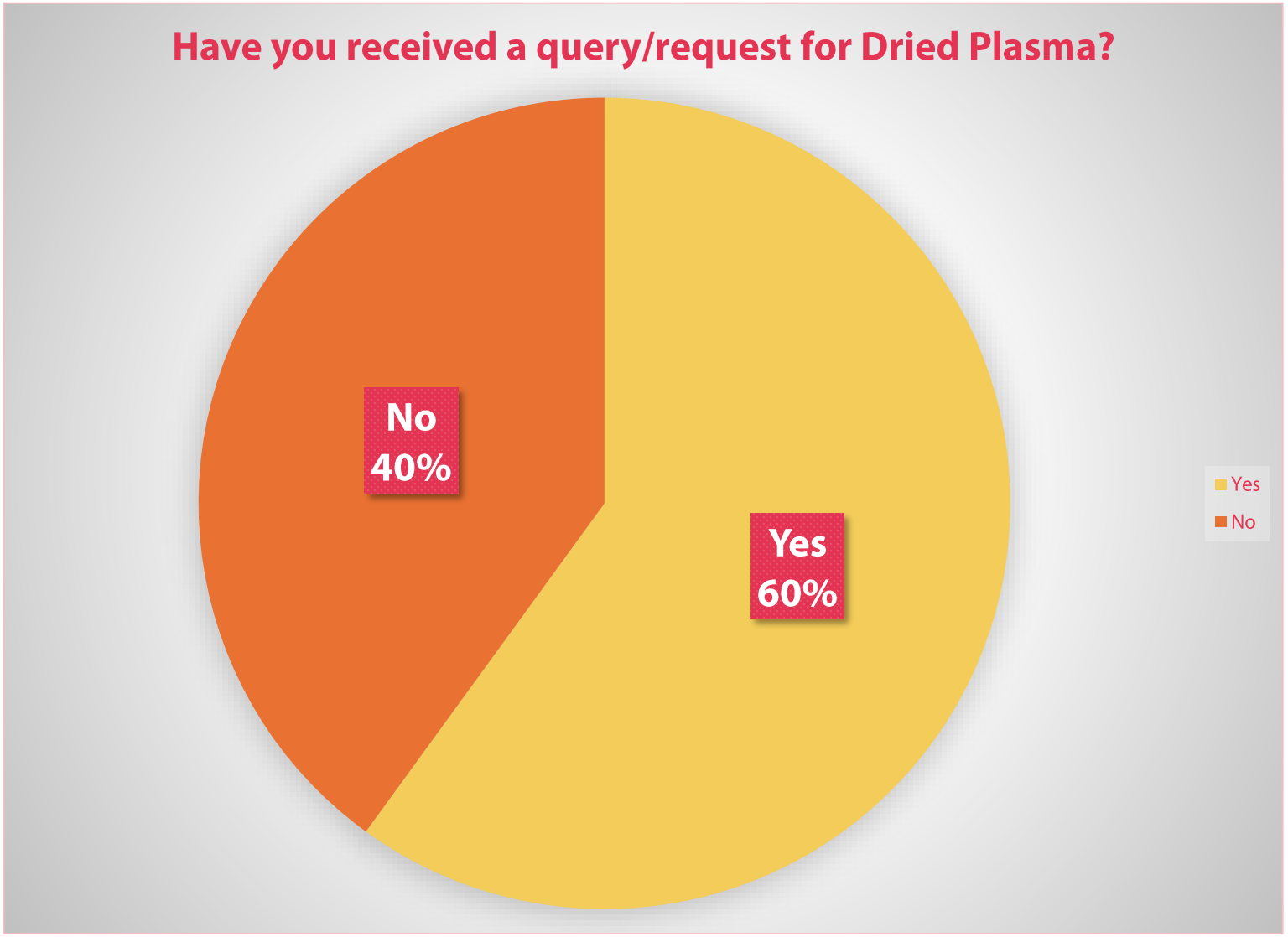
(15 responses from (then) 25 EBA member states).

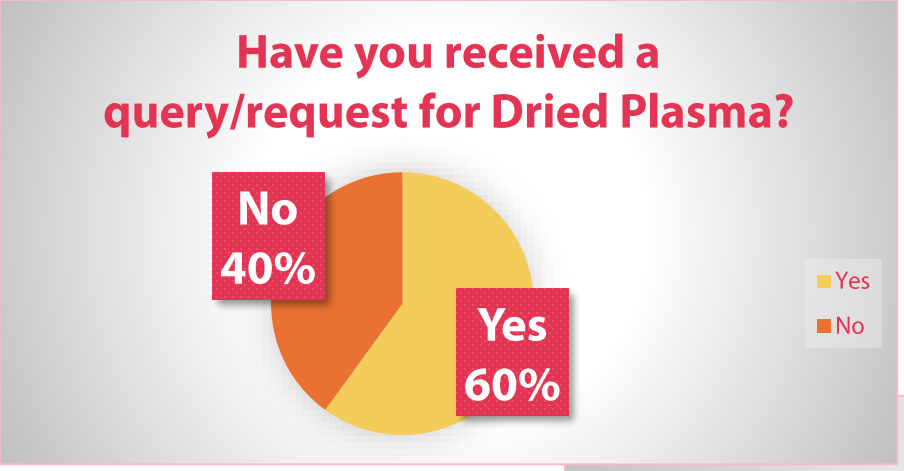
- Austria
- Belgium
- Croatia
- Denmark
- Estonia
- Finland
- France
- Germany
- Greece
- Hungary
- Iceland
- Ireland
- Italy
- Latvia
- Lithuania
- Luxembourg
- Malta
- Netherlands
- Norway
- Slovenia
- Portugal
- Spain
- Sweden
- Switzerland
- United Kingdom
- Bosnia & Herzegovina
- North Macedonia
- Ukraine
- Albania

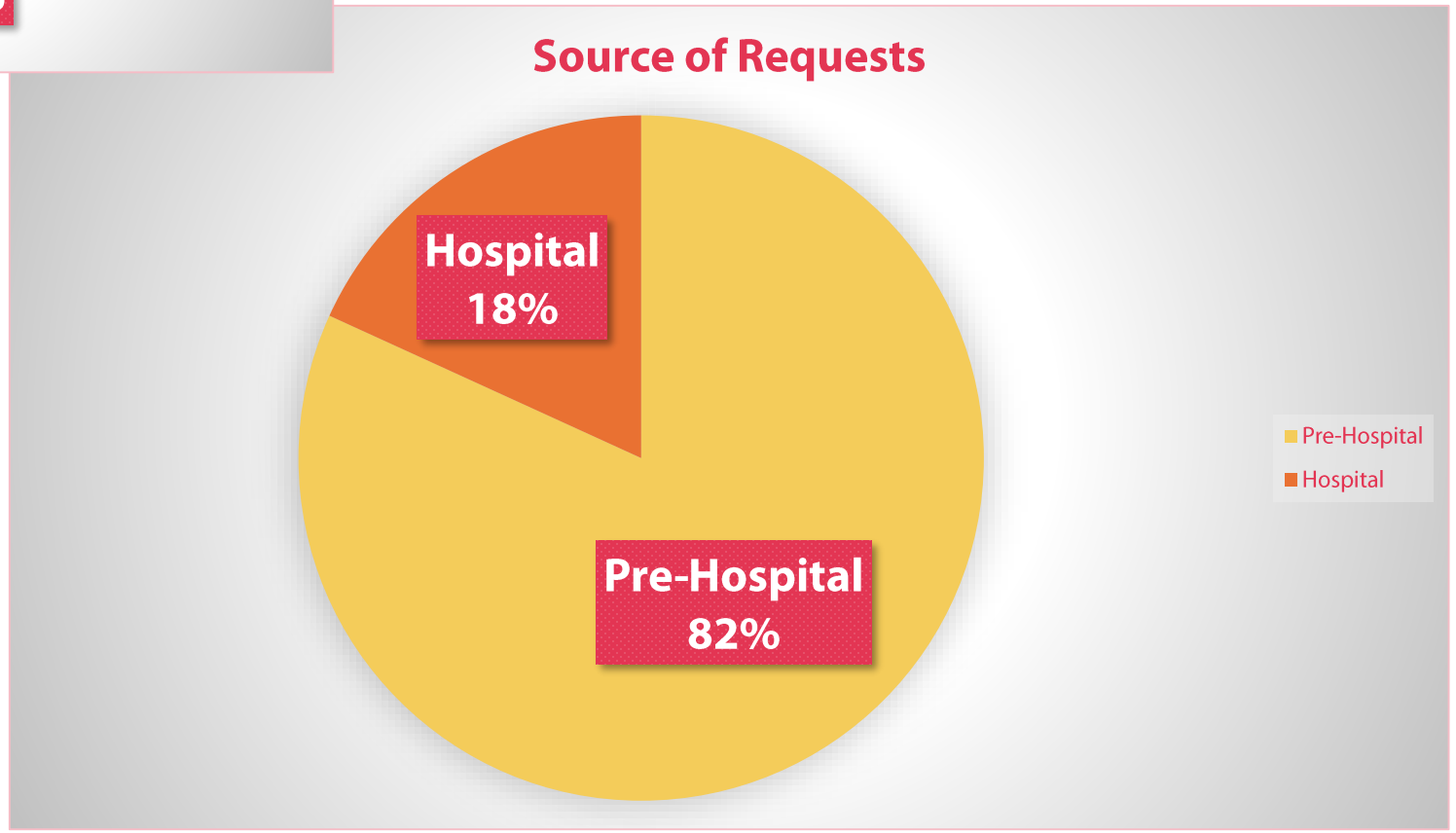
America's Blood Centers® It's About Life.




Is Dried Plasma currently in use in your Country?
No
47%
Yes
53%
Yes
No

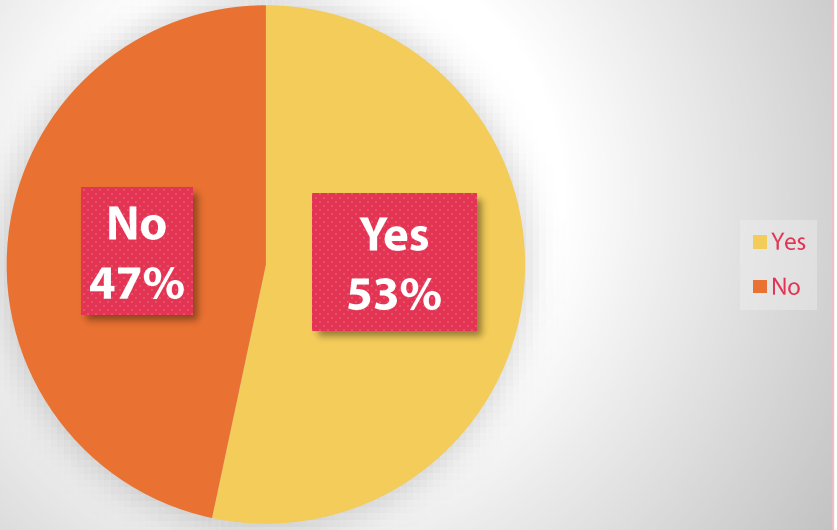

Have you received a query/request for Dried Plasma?
No
40%
Yes
60%
Yes
No



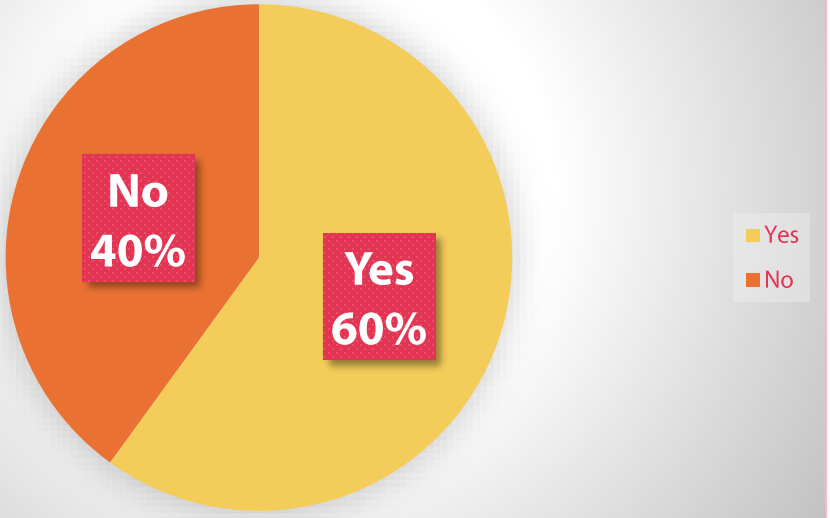


Both Civilian and Military sources

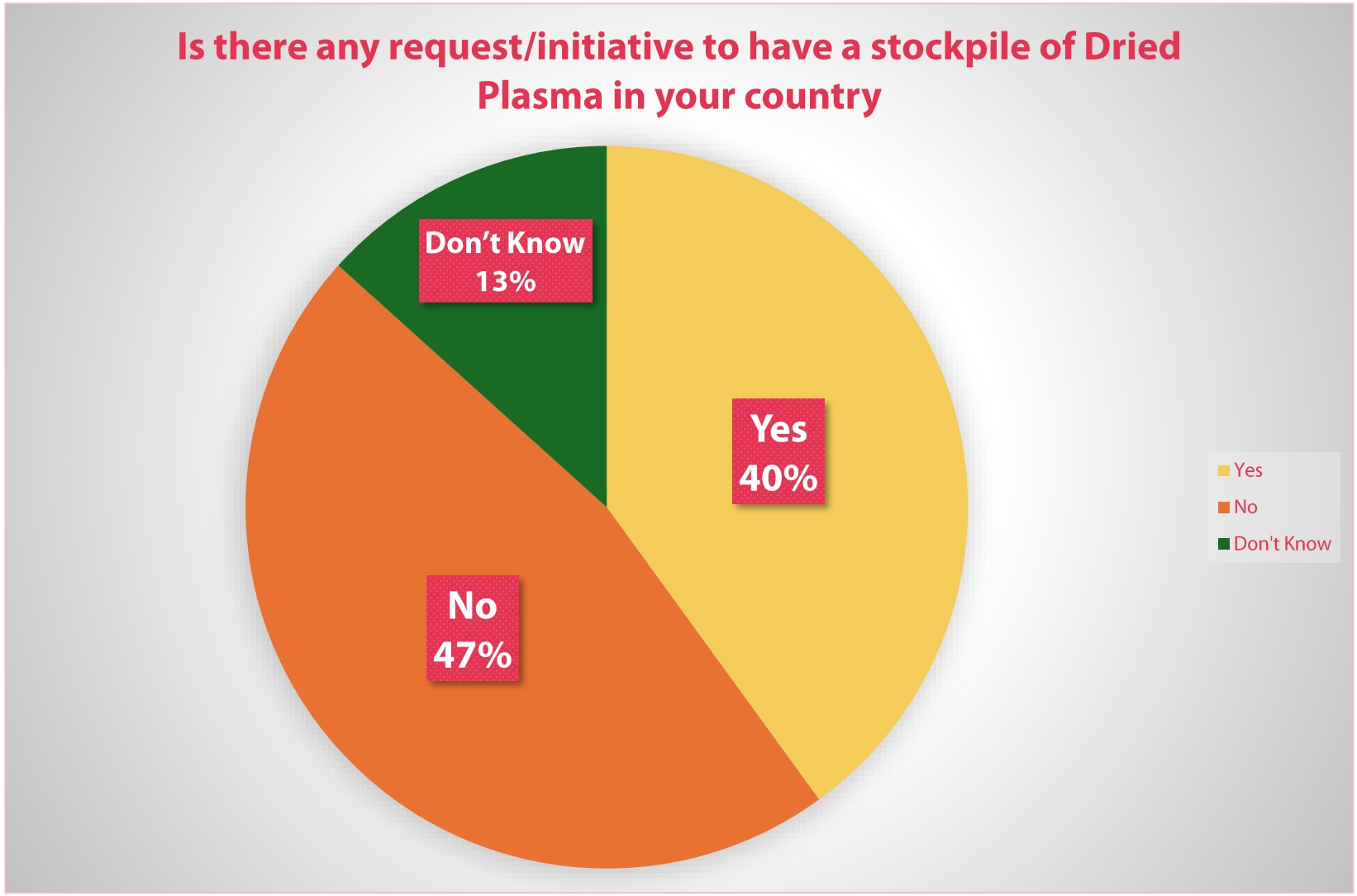
Is Dried Plasma currently in use in your Country?

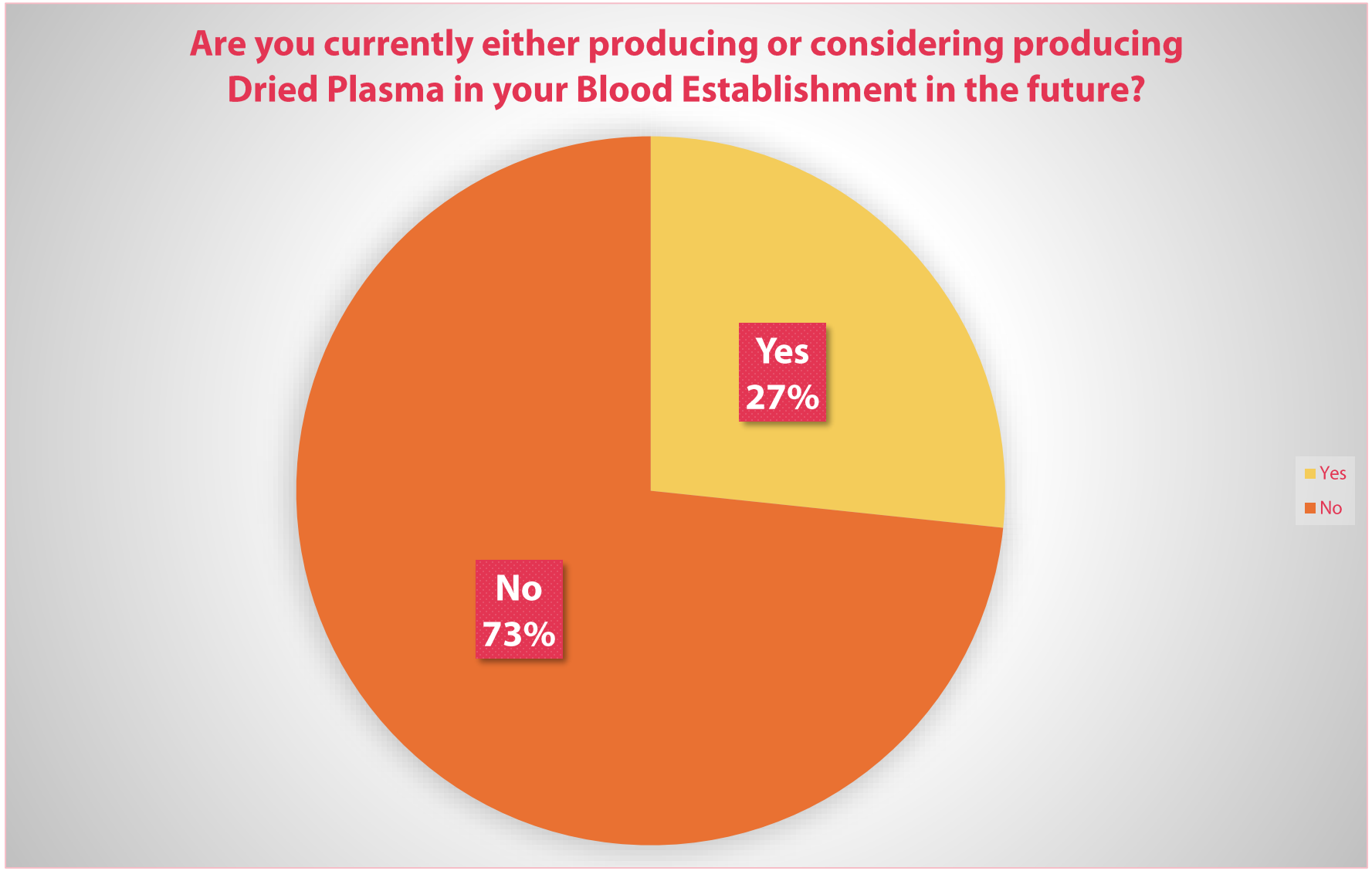


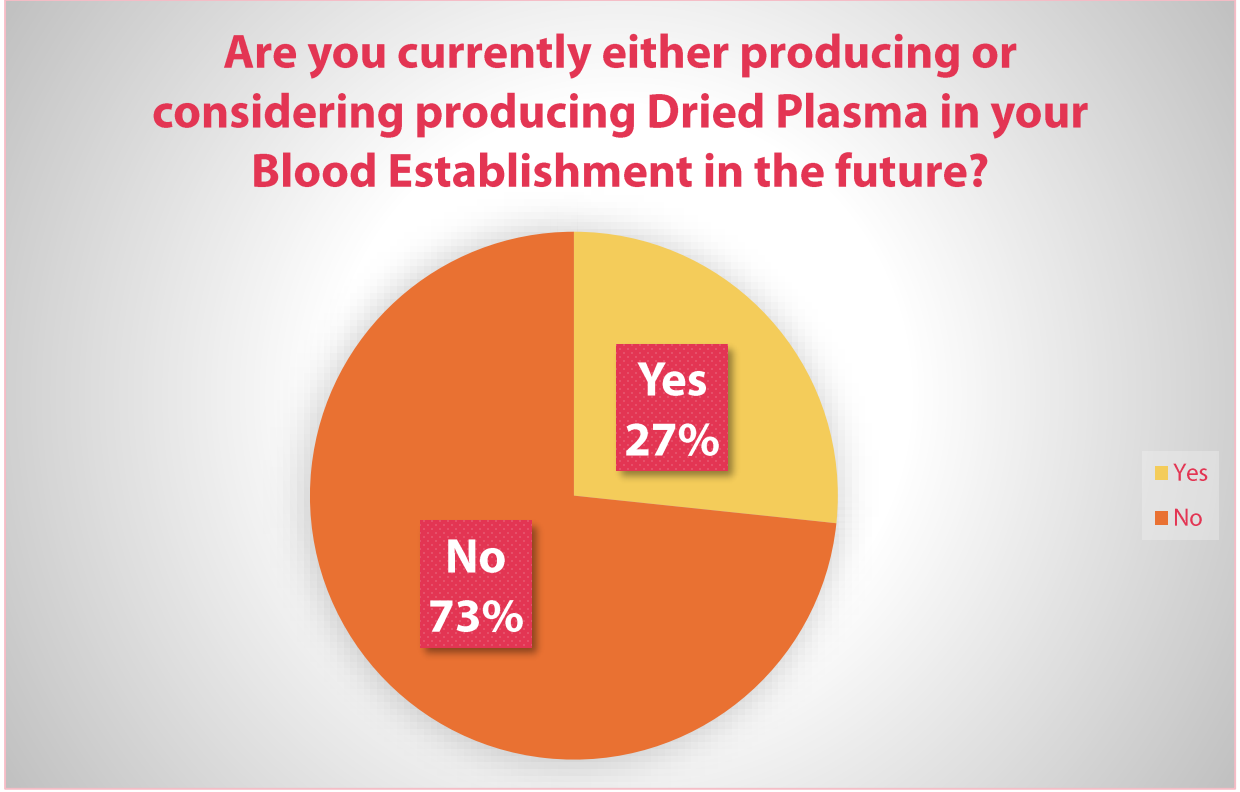
Have you received a query/request for Dried Plasma?



- All using commercially available products
- Where?
  - ❑ Air ambulance/Search & Rescue helicopters
  - ❑ Military services
  - ❑ Ground ambulance and municipal emergency
  - ❑ Oil industry
- Why?
  - ❑ traumatic bleeding in austere remote areas
  - ❑ treatment of massive haemorrhage in life-threatening /immediate emergencies


Is there any request/initiative to have a stockpile of Dried Plasma in your country
Don't Know 13%
Yes 40%
No 47%
Yes
No
Don't Know

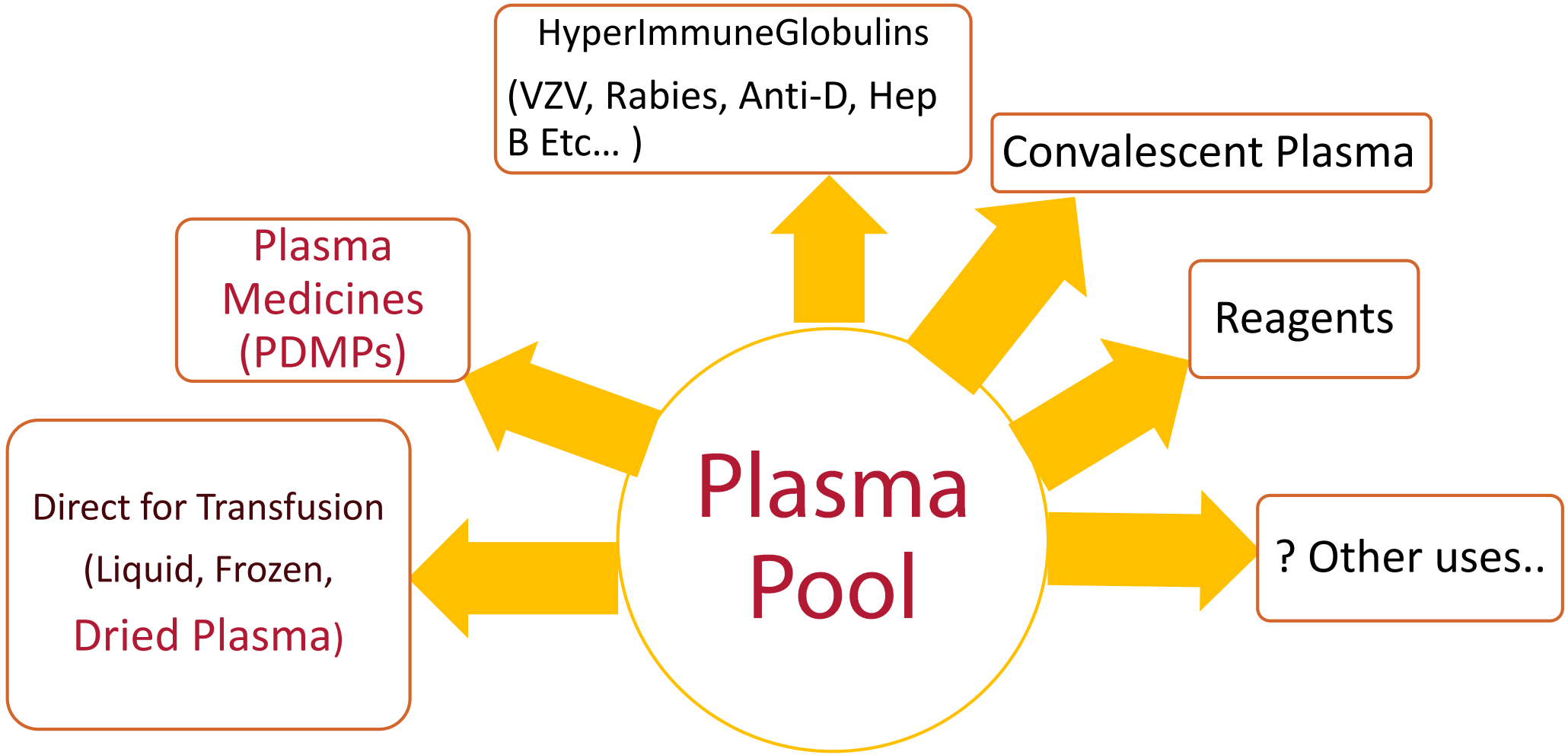

Are you currently either producing or considering producing Dried Plasma in your Blood Establishment in the future?
Yes 27%
No 73%
Yes
No



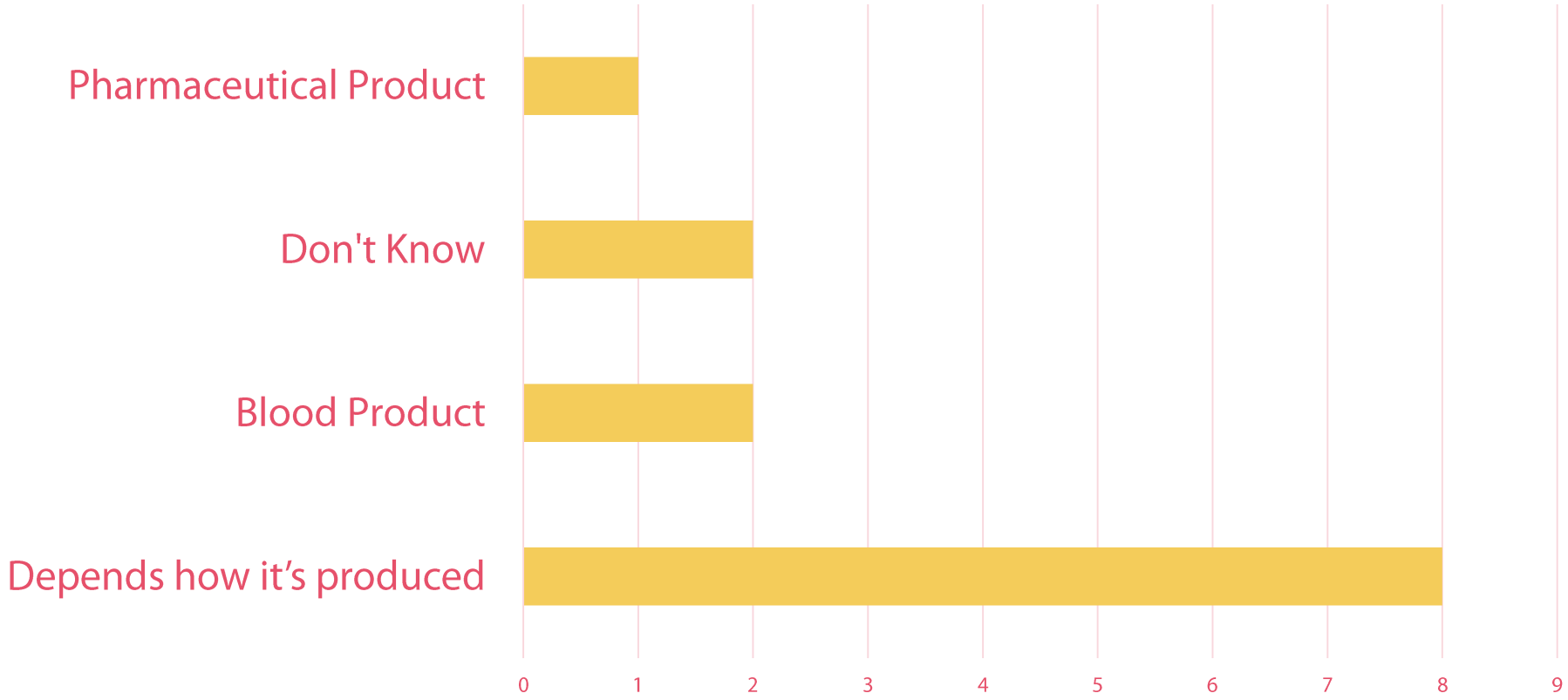
If not, why not?

5	Source limitations (insufficient plasma/plasma prioritised for other uses – fractionation, FFP..)
5	Technology not available for local production
4	No demand
4	Too expensive to produce
3	Regulatory Concerns

One Plasma Pool – Multiple roles for plasma..



Regulatory Aspects: in your Country, is Dried Plasma considered..



Recommendations

- National and international plasma strategies should
  - take account of all current and anticipated plasma requirements, including potential dried plasma stockpiles
  - Include both civilian and military stakeholders*
  - Include comprehensive risk-based return-on-investment considerations to ensure appropriate resourcing
- Include a monograph on dried plasma in the EDQM Blood Guide
- Clear technical guidelines for the production of dried plasma with a regulatory classification as a blood product would be helpful

*to ensure that sensitive data on possible and anticipated demand, for dried plasma and other blood products, is both included and appropriately treated.

Thank you

p.oleary@europeanbloodalliance.eu

Establishing spray dried plasma as a blood component in the UK - regulatory and scientific aspects

Mike Wiltshire - Component Development Laboratory Manager &
Stephen Vardy – Lead Quality Specialist

NHS Blood and Transplant

NHS
Blood and Transplant

Establishing spray dried plasma as a blood component in the UK - Scientific aspects

Mike Wiltshire PhD

Caring Expert Quality

Background – Why?

- MoD funded Project in England (NHSBT)
  - Feasibility study as part of the Blood Far Forward Programme
- Haemorrhage and Coagulopathy is a leading cause of preventable death for military personnel
- Early administration of plasma, along with red cells, reduces mortality

JAMA Surgery | Original Investigation

Association of Prehospital Plasma Transfusion With Survival in Trauma Patients With Hemorrhagic Shock When Transport Times Are Longer Than 20 Minutes

A Post Hoc Analysis of the PAMPer and COMBAT Clinical Trials

Anthony E. Pusateri, PhD; Ernest E. Moore, MD; Hunter B. Moore, MD, PhD; Tuan D. Le, MD, DrPH; Francis X. Guyette, MD, MPH; Michael P. Chapman, MD; Angela Sauaia, MD, PhD; Arsen Ghasabyan, MPH; James Chandler; Kevin McVaney, MD; Joshua B. Brown, MD; Brian J. Daley, MD; Richard S. Miller, MD; Brian G. Harbrecht, MD; Jeffrey A. Claridge, MD; Herb A. Phelan, MD, MSCS; William R. Witham, MD; A. Tyler Putnam, MD; Jason L. Sperry, MD, MPH

Options for Dried Plasma

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Finished products from outside UK

Germany	South Africa	France	Octapharma
			
Lyoplas-N	Bioplasma FDP	FlyP	OctoplasLG

+ Others in development

UK MoD require sovereign supply of 1000 units per annum to aid sufficiency and resilience. (UK dried plasma source)

Velico Medical
spray dried plasma

Terumo
Freeze-dried plasma

Project on hold

NHSBT have contracted with Velico to develop their system for manufacturing dried plasma for market in the UK/EU

Spray Dried Plasma

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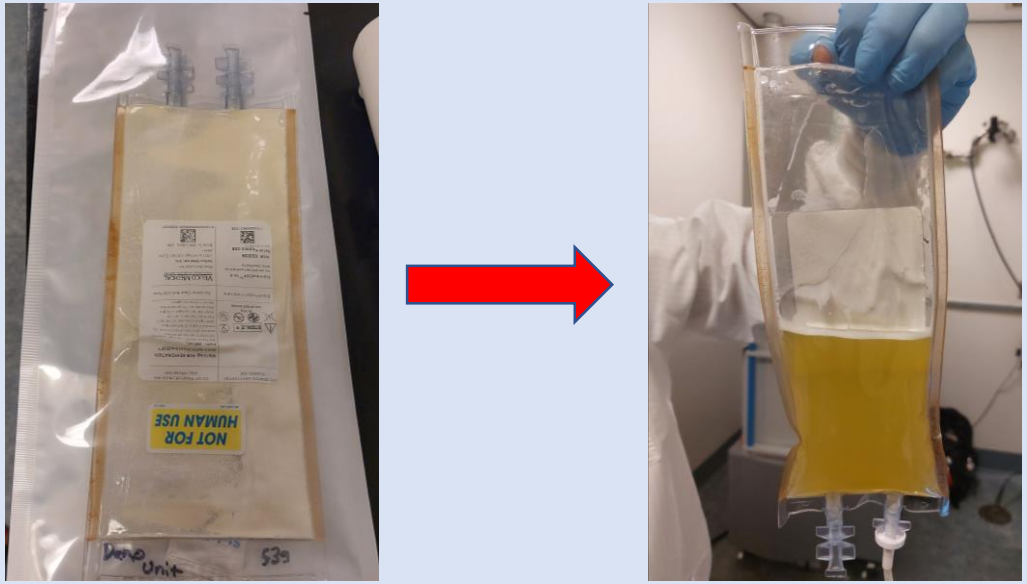
Fresh or frozen-thawed plasma (250ml) → + Pre-treatment solution → Spray dry (Velico system) 30 mins approx. → Reconstitute in 200mL sterile water <10min

Velico Frontline On Demand Plasma (ODP)

- ODP system designed for use in blood centres
- 1 dryer & 1 operator = 12 Units of dried plasma per 8h day
- 1 unit of dried plasma from 1 unit of plasma
- Final component in a plastic bag
- Expected shelf-life (dried):
  4°C >12 months
  Ambient several months

Example of final product component



Velico FrontlineODP™ System

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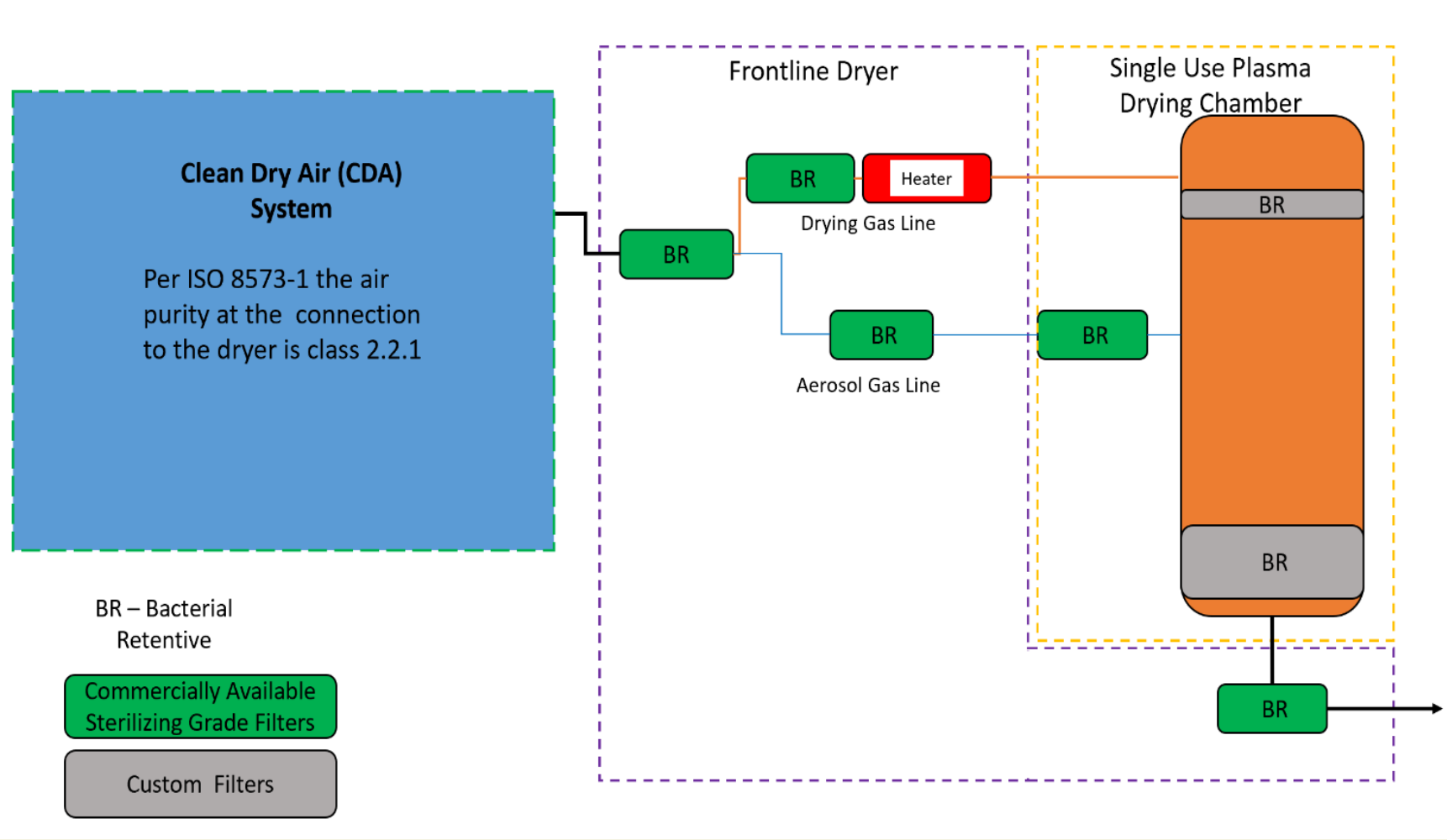

3 Year Feasibility Study

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Project Status

- GMP facility completed at NHSBT Cambridge
- Drying of plasma for laboratory validation commenced December 2024
- Clinical trial being planned

NHSBT Preliminary Study – UK plasma

- Small scale study
- WB derived plasma: Unpaired units
- Units frozen: 12h or 27h post VP
- Storage conditions: 4°C or 40°C
- Plasma tested for a range of coagulation factors

Preliminary Study – Results @ 4°C

Coagulation Parameter (Mean)	27h post VP (n=6)			12h post VP (n=12)		
	FFP	DP	% Loss	FFP	DP	% Loss
APTT	1.33	1.65	**-24.0**	1.27	1.44	**-13.2**
SD	*0.06*	*0.10*	*5.3*	*0.11*	*0.17*	*5.9*
PT	1.11	1.31	**-17.5**	1.08	1.21	**-12.5**
SD	*0.09*	*0.14*	*5.4*	*0.06*	*0.07*	*5.3*
Fibrinogen	2.47	2.18	**11.7**	2.35	1.95	**16.4**
SD	*0.22*	*0.19*	*3.8*	*0.58*	*0.45*	*3.9*
FV	0.67	0.55	**16.4**	0.84	0.78	**7.8**
SD	*0.14*	*0.11*	*2.9*	*0.07*	*0.09*	*6.7*
FVII	0.87	0.77	**11.4**	0.97	0.83	**13.7**
SD	*0.26*	*0.24*	*4.8*	*0.18*	*0.12*	*5.5*
FVIII	0.69	0.48	**31.0**	0.89	0.67	**24.4**
SD	*0.13*	*0.10*	*3.1*	0.21	0.18	*10.2*
Protein S Activity	82.0	71.5	**14.1**	102.3	81.8	**19.9**
SD	*20.3*	*24.7*	*8.8*	*17.1*	*13.8*	*7.3*
vWF Activity	76.9	46.3	**40.0**	92.0	54.8	**41.2**
SD	*21.0*	*13.6*	*2.7*	*27.7*	*19.7*	*6.7*
vWF Antigen	101.7	96.5	**5.1**	126.0	117.2	**6.4**
SD	*21.3*	*20.7*	*5.7*	*37.3*	*34.5*	*5.7*

Changes in Coagulation Parameters from Pre- to Post-Drying (Mean ± SD).

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Failed to meet desired value (20% pre to post)

- 12hr VP to freeze time showed improved labile coagulation parameters compared to 27h
- vWF Activity decreased by approximately 40% pre-to post-drying in both studies
- vWF Antigen showed a decrease of <10% pre- to post-drying in both studies

Preliminary Study – Results @ 40°C

Coagulation Parameters	% Loss	
	Month 1 (n=3)	Month 2 (n=3)
APTT	**-68.2**	**-93.9**
SD	*9.5*	*28.6*
PT	**-59.2**	**-68.1**
SD	*9.4*	*2.6*
Fibrinogen	**73.1**	**74.0**
SD	*2.2*	*9.6*
FV	**41.0**	**40.2**
SD	*2.8*	*2.7*
FVII	**33.4**	**33.5**
SD	*8.3*	*5.8*
FVIII	**58.0**	**63.4**
SD	*3.3*	*2.0*
FXI	**31.8**	**29.3**
SD	*4.5*	*2.1*
Protein S Activity	**28.8**	**15.6**
SD	*5.0*	*8.7*
vWF Activity	**52.4**	**53.6**
SD	*8.6*	*9.1*
vWF Antigen	**15.4**	**2.6**
SD	*7.0*	*5.4*

Failed to meet desired value

- Following storage at 40°C, decreases were observed in several coagulation parameters
- Fibrinogen decreased by approximately 70%
  - Fibrinogen is normally stable in plasma components, but similar decreases have been observed in Lyoplas

Percentage loss in Coagulation Parameters Post-Drying, following storage at 40°C for 1 and 2 Months (Mean ± SD).

Summary – Scientific Aspects

- Preliminary data indicates that spray dried UK plasma will be of acceptable quality
- Starting plasma has a significant impact on quality of Dried Plasma
    - Enhancing quality of source plasma, e.g. by reducing the time from donation to freezing should improve the quality of the dried plasma
- Storage temperature affects the quality and shelf-life of Dried Plasma
- Full laboratory validation of Dried Plasma due to complete Spring 2025

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Establishing spray dried plasma as a blood component in the UK - Regulatory aspects

Stephen Vardy

Caring Expert Quality

Regulatory Aspects

- Challenges
  - Classification of the Dried Plasma product – Blood Component v Medicine?
  - Route to approval of the Velico ODP System as a medical device – CE/UKCA?
  - New facility within the Cambridge Blood Centre to manufacture the Dried Plasma
  - Qualification of specialist plant (CDA) and novel equipment (dryer and sealer – 1st commercial model)
  - Brand new component without a finalised specification/monograph

Classification of NHSBT Dried Plasma

The Regulations:

The Human Medicines Regulations 2012 (as amended)
PART 1 General, 2. Medicinal Products
(2) These Regulations do not apply to –
(a) whole human blood; or(b) any human blood component, other than plasma prepared by a method involving an industrial process.

Blood Safety and Quality Regulations 2005 (as amended)
1.- (3) "blood component" means a therapeutic constituent of human blood (red cells, white cells, platelets and plasma) that can be prepared by various methods;
2. -(2) Subject to the following paragraphs, the requirements of these Regulations apply to the collection and testing of blood and blood components, whatever their intended purpose, and to their processing, storage, and distribution when they are intended to be **used for transfusion.**

Outcome: MHRA in agreement = BLOOD COMPONENT

NHSBT Dried Plasma to be classified as a Blood Component as:

- Manufactured from single units of plasma – NO pooling
- Manufactured using equipment designed for use in blood establishments
- Low scale production, 1 dryer = 12 Units of dried plasma per day (with 1 operator)
- FDA consider dried plasma a blood component
- Other components with greater manufacturing complexity are considered blood components in the UK e.g. pathogen inactivated pooled cryoprecipitate
- JPAC and SACBC appropriate safety and advisory groups to define specification

Route to Medical Device Approval

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Complicated by the fact that UK Medical Device Regulations are not currently aligned with the EU Medical Device Regulation.

Options appraisal performed August 2023. Agreement to gain CE marking under EU MDR (initially).

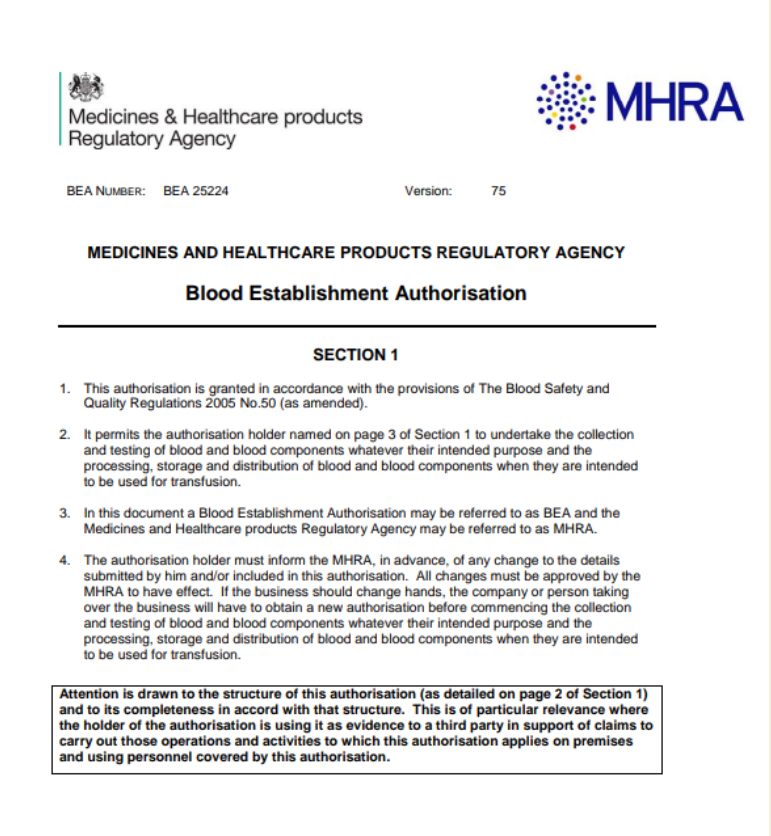
Similar process in parallel in US to gain Pre-Market Approval from FDA.

Requirement to notify MHRA on the use of a non-UKCA/CE marked device as part of clinical trial approval process.

	Option 1:	Option 2:	Option 3:
Solution	Gain approval under current UK MDR, yet to be updated in line with EU MDR.	Gain CE marking under EU MDR (already updated).	Gain UK CA marking under updated UK MDR - lasts indefinitely.
Approval validity	Approval would last 3 years post effective date of updated UK MDR to June 2028.	CE recognized for up to 7 years, longer than Option 1 UKCA under current MDR. Would require UKCA marking by Jun 2030 .	Valid indefinitely
Timeline	• Projected update to UK MDR effective July 1st 2025 per new UK regulatory timelines	• Recognized and accepted until June 2030	• Projected July 2025 per new UK regulatory timelines
Disadvantages	• Approval only lasts 3 years • Requires more work to update UK MDR in 3 years • Less likely to support CE marking under EU MDR	• More stringent requirements for EU MDR • Would require additional UKCA marking by Jun 2030 but less work than option 1	• Unknown timeline for harmonization between UKCA and CE marking • Would likely require separate CE mark
Advantages	• Updated timeline for UKCA before July 1 2025 may better align with PMA • Initially easier to achieve marking to current UK MDR • May be adequate to support initial approval for cardiac patient CT	• Would provide UKCA marking up until 2030 • Will more easily support updated UKCA MDR marking • CE would last indefinitely	• Lasts indefinitely • Won't require an updated UKCA submission • More likely to support CE mark
Conclusion	**DISCOUNTED**	**RECOMMENDED**	**DISCOUNTED**

Update Blood Establishment Authorisation

- Required prior to manufacture of Dried Plasma for clinical use (including for the clinical trial)
- New facility built and operating to required GMP/GPG specification
- Equipment qualified/process validated. (Has been challenging to date due to issues with the CDA and specialist equipment. Now in PQ for these items)
- Defined & approved specification for the component, to include ongoing Quality Monitoring requirements
- Evidence that manufactured component meets required specification (outputs from Lab studies)
- Inspection to confirm the above by UK Competent Authority (MHRA), before NHSBT's BEA licence updated to include manufacture of Dried Plasma for clinical use at the Cambridge Centre



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BEA Number: BEA 25224 Version: 75

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY

Blood Establishment Authorisation

SECTION 1

1. This authorisation is granted in accordance with the provisions of The Blood Safety and Quality Regulations 2005 No.50 (as amended).
2. It permits the authorisation holder named on page 3 of Section 1 to undertake the collection and testing of blood and blood components whatever their intended purpose and the processing, storage and distribution of blood and blood components when they are intended to be used for transfusion.
3. In this document a Blood Establishment Authorisation may be referred to as BEA and the Medicines and Healthcare products Regulatory Agency may be referred to as MHRA.
4. The authorisation holder must inform the MHRA, in advance, of any change to the details submitted by him and/or included in this authorisation. All changes must be approved by the MHRA to have effect. If the business should change hands, the company or person taking over the business will have to obtain a new authorisation before commencing the collection and testing of blood and blood components whatever their intended purpose and the processing, storage and distribution of blood and blood components when they are intended to be used for transfusion.

Attention is drawn to the structure of this authorisation (as detailed on page 2 of Section 1) and to its completeness in accord with that structure. This is of particular relevance where the holder of the authorisation is using it as evidence to a third party in support of claims to carry out those operations and activities to which this authorisation applies on premises and using personnel covered by this authorisation.

Other required approvals/licenses

- Sterile Water for Infusion classified as a medicine. Storage & distribution licence in place
- Clinical Trial approvals

Regulatory Aspects - Summary

- NHSBT's Dried Plasma has been classified as a Blood Component in the UK
- Agreement to gain CE marking under EU MDR for the Velico FrontlineODP™ system
- Blood Establishment Authorisation licence to be updated following inspection from the Competent Authority, for which:
  - Facility and Equipment must be qualified
  - The end-to-end process must be validated
  - There must be an agreed specification in place for the dried plasma
  - There must be evidence that this specification is met

Establishing spray dried plasma as a blood component in the UK

Ministry of Defence

velico

NHS Blood and Transplant

Dried Plasma Team

NHSBT

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MoD

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Paul Moor

Thank-you for listening…….

NHS
Blood and Transplant

Developing Universal plasma and platelets - What challenges do we need to consider?

Melanie Robbins – Translational Research Programme Lead, NHSBT

Caring Expert Quality

Some images created by BioRender

Clinical Risk – Plasma

NHS Blood and Transplant

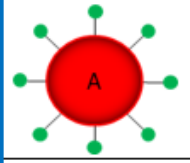
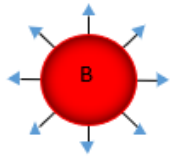
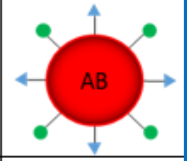
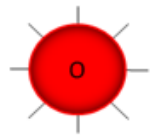
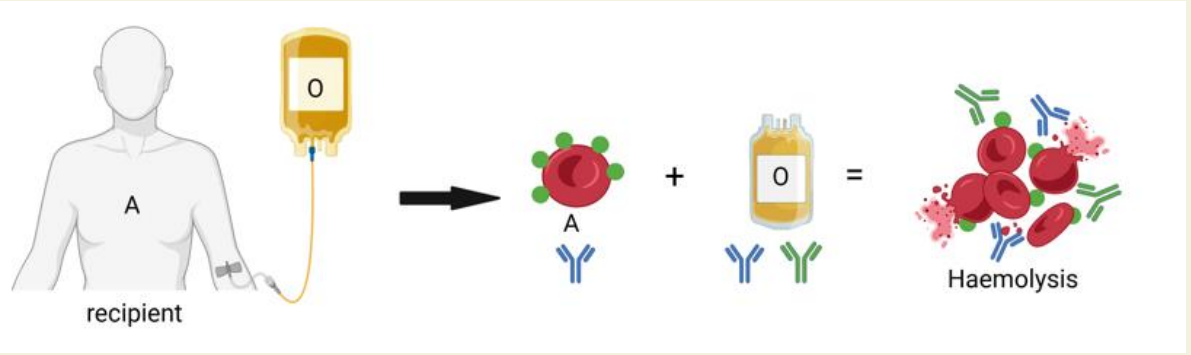
	A	B	AB	0
ABO Blood Group				
ABO Antigens present on red blood cells	 A antigen	B antigen	 A + B antigens	None
ABO Antibodies present in plasma	 Anti-B	 Anti-A	None	 Anti-A + Anti-B
ABO Antibodies and Antigens present in platelet preparations	 A antigen + Anti-B	 B antigen + Anti-A	 A + B antigens + no antibodies	 No antigens + Anti-A + Anti-B

Figure 1: The ABO Blood group system

Plasma Transfusion – e.g. Group O plasma to A recipient



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Clinical Risk – Platelets

NHS Blood and Transplant

ABO Blood Group	A	B	AB	O
ABO Antigens present on red blood cells	A antigen	B antigen	A + B antigens	None
ABO Antibodies present in plasma	Anti-B	Anti-A	None	Anti-A + Anti-B
ABO Antibodies and Antigens present in platelet preparations	A antigen + Anti-B	B antigen + Anti-A	A + B antigens + no antibodies	No antigens + Anti-A + Anti-B

Figure 1: The ABO Blood group system

ABO Blood Group	A	B	AB	O
ABO Antigens present on red blood cells	A antigen	B antigen	A + B antigens	None
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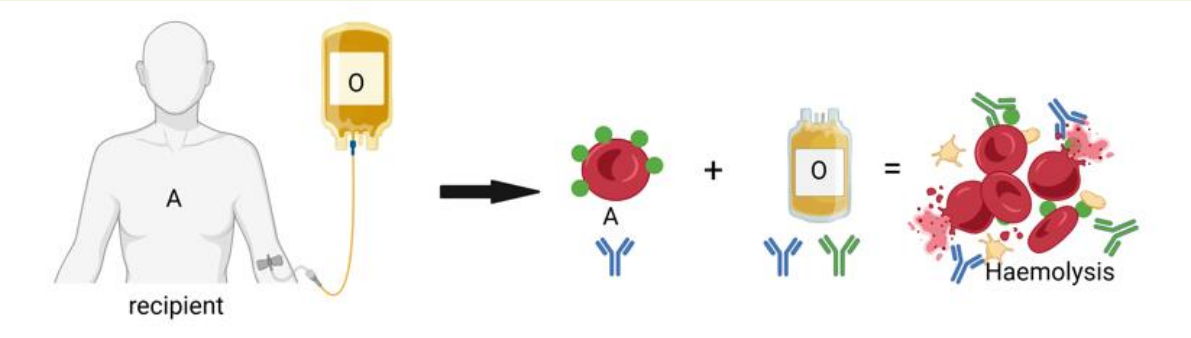
Figure 1: The ABO Blood group system

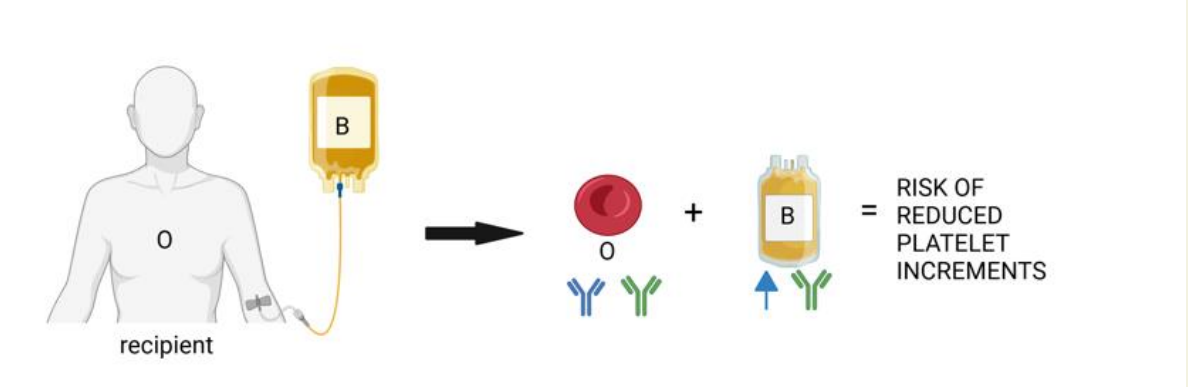
Platelet Transfusion – e.g. Group O platelets to A recipient

MINOR ABO INCOMPATIBILITY ➡ risk of HTR



Platelet Transfusion – e.g. Group B platelets to O recipient

MAJOR ABO INCOMPATIBILITY



Or **bidirectional incompatibility**, e.g. B donor, A recipient

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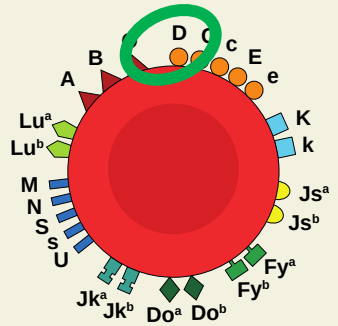
Understanding clinical risk of HTR

NHS Blood and Transplant

Safest transfusion is no transfusion

➢ A recipient's residual risk of a HTR depends on:-



1. ABO matching policy
   - ➢ Different for plasma and platelets

2. Extent of ABO non-identical transfusion

3. HT screening

4. Dilution/pooling of product

5. Patient related factors

Most patients - match for ABO & Rh D (contaminating red cells)

- ➢ If not possible, transfuse HTneg for anti A/B

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Current Clinical Practice (UK)

NHS Blood and Transplant

Platelets

BJHaem BRITISH JOURNAL OF HAEMATOLOGY | British Society for Haematology

Guideline | Free Access

Guidelines for the use of platelet transfusions

Recommendations

- **Hospitals should establish a strategy to maximise the transfusion of ABO compatible platelets especially to patients who require regular platelet support (2B).**
- **It is acceptable to use ABO incompatible platelets to reduce wastage. Units tested and negative for high titre haemagglutinins and non-group O platelets are associated with a lower risk of haemolysis. Pooled platelets suspended in PAS would also be expected to reduce this risk. (1B).**

Plasma

BJHaem BRITISH JOURNAL OF HAEMATOLOGY | British Society for Haematology

Guideline | Free Access

British Society of Haematology Guidelines on the spectrum of fresh frozen plasma and cryoprecipitate products: their handling and use in various patient groups in the absence of major bleeding

Recipients	O	A	B	AB
a)High titre (HT) positive, or HT untested units [a]				
1st choice	O	A	B	AB
2nd choice	A	AB	AB	A [b]
3rd choice	B	B [b]	A [b]	B [b]
4th choice	AB	–	–	–
b)HT negative [b]				
1st choice	O	A	B	AB
2nd choice	A	B	A	A
3rd choice	B	AB	AB	B
4th choice	AB	–	–	–

[a] Group O must only be given to group O recipients

[b] Only suitable for emergency use in adults

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International Practice

NHS Blood and Transplant

TABLE 2 Policy and practice for platelet ABO matching

Country	National or local policies?	% ABO non-identical transfusions	Priority given to minor or major compatibility	Risk mitigation for minor mismatch	Frequency of HTR due to ABO incompatible transfusion
Australia	National	Not known	Minor	Storage in PAS. Low-titre for anti-A/B.	No cases since the introduction of anti-A/B testing of donations.
Brazil	National	36%	NR	Low-titre for anti-A/B.	None seen in years but are reportable to HV scheme.
Canada	National	20%	Minor	Low-titre for anti-A/B. Volume reduction.	2 reports since 2017.
England	National	10%–15% likely higher for neonates.	Minor	Low titre for anti-A/B. Pooled platelets in PAS. Avoid group O for non-O patients.	1:625000. None since 2016 - PAS introduced for pooled platelets. No fatalities since testing standardized in 2008.
France	No policy	16% major.	Major	Low-titre for anti-A/B.	Reportable but very rare over past 8 years.
Germany	National	–	Major	Storage in PAS.	13 fatal cases 2000–2017 nationally, 1:600000 platelets.
India	Local	5%	Minor. Avoid group O for latter.	Apheresis platelets, volume reduced if there is time.	None observed at centre last year, but reportable to national HV.
Japan	National	0% apart from HLA matched - 30%.	For HLA matched, minor.	Low-titre for anti-A/B. Washing for HT units or for children. Hospitals can volume reduce.	1:2million PC overall, 1:19108 for HLA matched platelets.
Netherlands	National	5%	Major. Group O RhD neg used in trauma packs	All PC in PAS. Low-titre for anti-A/B anti-A/B for neonates, infrequently volume reduction.	None in 2018.
New Zealand	National	23%	Major	Storage in PAS.	6 reports between 2005–2012 all due to group O PC. None since 2012, PAS introduced 2010–11.
Russia	National	21%	Not stated	Storage in PAS.	NR
Saudi Arabia	Local	20%	Not stated	Volume reduction to 30% for some patients - especially for neonates.	None reported but there is a system to report to national body.
Spain	None	NK	Major - risk of minor reduced by suspension in PAS	Storage in PAS. No testing for anti-A/B.	Not observed in past 30 years, reportable to national HV scheme.
Sweden	Local	22%	Minor but sometimes major.	Storage in PAS for BC PC, apheresis donors tested for anti-A/B. May also wash apheresis PC if from an HLA matched donor with HT antibodies.	Not observed in centre in last 15 years. One case reported to national HV scheme in past 10 years.
USA	Local	42%	Minor	Storage in PAS –OR- volume reduced to 50 ml.	Observed, so considering testing for anti-A/B.

INTERNATIONAL FORUM

Vox Sanguinis ISBT

International Forum on Policies and Practice for Transfusion of ABO and RhD Non-Identical Platelets: Summary

Cardigan et al 2022

- Significant variability between countries
- ABO-matched if possible

- Preference given to reducing risk of minor incompatibility

➢Various ways of mitigating risk

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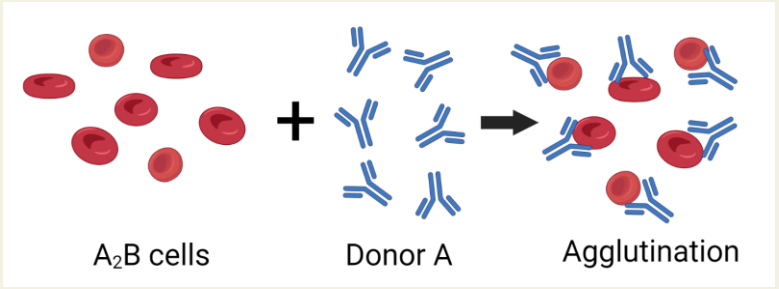
Current methods to reduce Clinical Risk

NHS Blood and Transplant

A. Transfuse ABO identical (*if possible*) or select ABO group with lowest level of antibodies

B. Screening

- Test anti-A/B levels in donations and label high titre positive or negative. Avoid HT units if transfusing ABO incompatible plasma/platelets.



HTpos

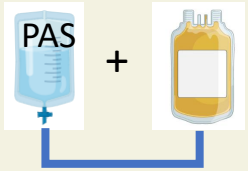
In the UK we test every donation every time,
If titre >128 we label the product HT pos

C. Reduction in plasma volume in component

- Pooled components

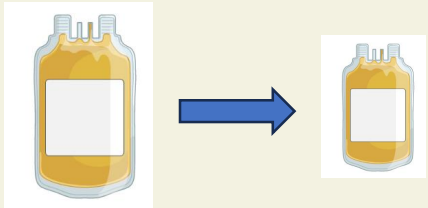
In the UK we pool 4 platelet units. If all 4 are HT neg we label the final pooled product HT neg

- Dilute in platelet additive solution



- Washed components

- Volume reduced components



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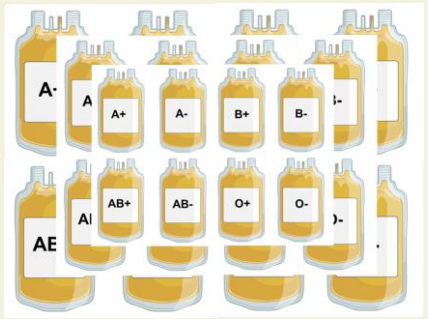
The need for Universal

NHS Blood and Transplant



>128 platelet types stocked at NHSBT

Platelet shelf-life 3-4 days after issue

Aneg platelets are the best choice if group specific unavailable

A- donors 8% population
A- platelets 16% demand
Imbalances in supply and demand

UK National news

First ever amber alert for NHS blood supplies could mean cancelled surgery

Hospitals level ami

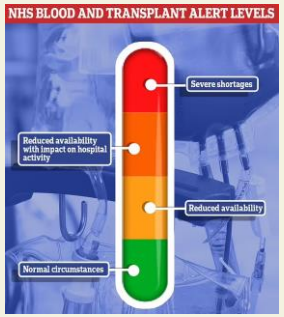
Urgent NHS call for blood donors after cyber attack delays transfusions

Donation centres need 13,(cancel operations

O-type blood donors needed after London cyber-attack

Shortage of blood supplies prompts amber warning

10 pre-amber alerts on Aneg plts (2016-22)



Could Universal components balance out supply and demand?

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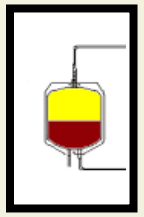
Current options to remove anti-A/B

NHS Blood and Transplant



Mixing of RBCs and plasma or buffy coats to neutralise antibodies

UNIVERSITÄT GREIFSWALD
Wissen lockt. Seit 1456

Pre-clinical dev

Buffy coats

cellulose particles

macopharma
DESIGNED FOR LIFE

Pre-clinical dev

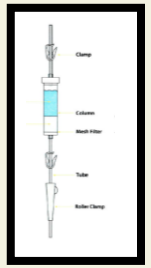
Cellulose particles grafted with ABO antigens

Technical Options

column matrix

Glycorex
Transplantation

MDD CE mark



Column based tech with ABO antigens attached

Filter

CytoSorbents™

Pre-clinical dev

Column based tech with ABO antigens attached

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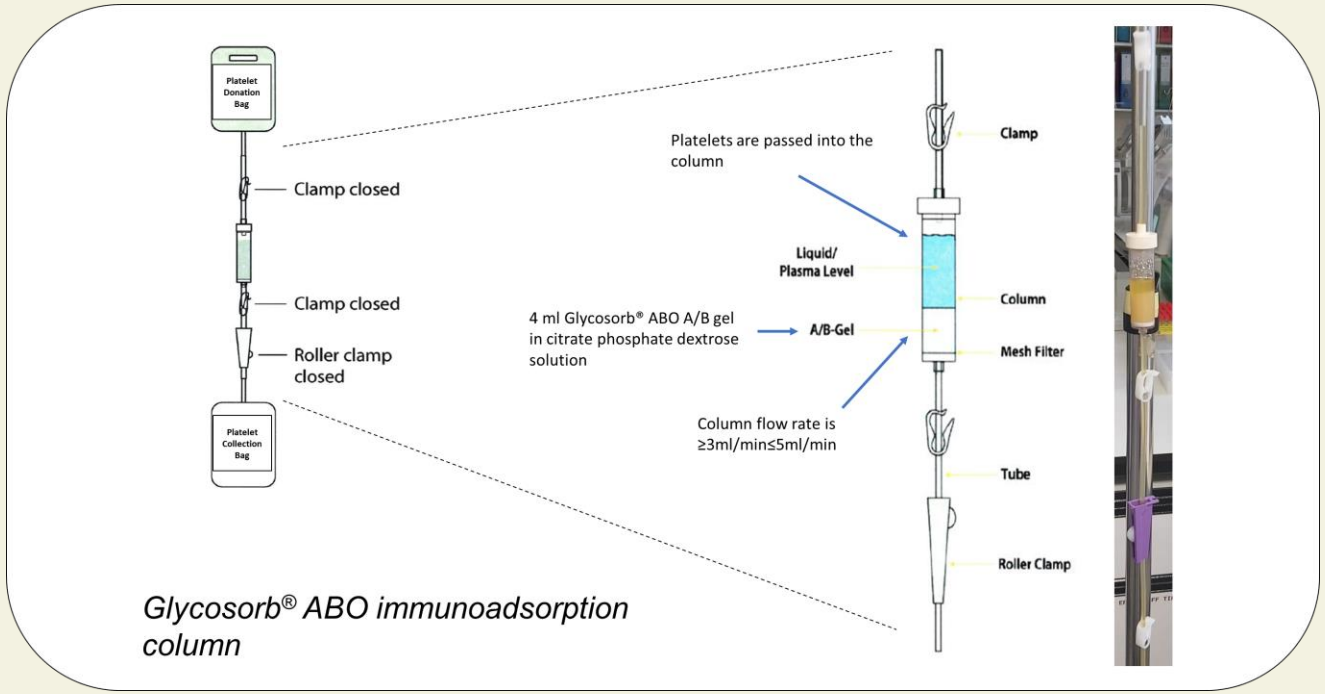
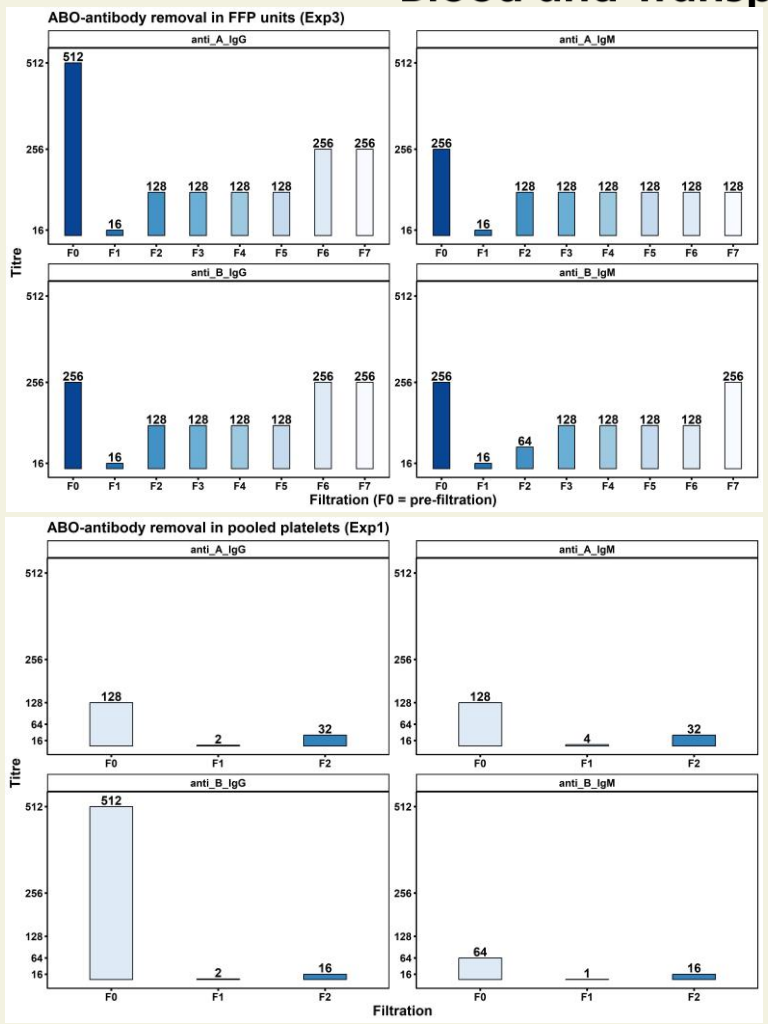
Evaluation of the Glycorex Column

NHS Blood and Transplant

NHSBT have evaluated the CE marked GlycoRex device as one possible medical device to produce Universal plasma and Universal platelets



Glycosorb® ABO immunoadsorption column



- The Glycosorb® ABO column has potential for use as a titre reduction method for both plasma and platelet units.

- No significant changes in platelet count, platelet concentrate volume, platelet pH, platelet activation markers, coagulation factors, CD62P, platelet microparticles or red cell microparticles post filtration

Robbins et al, Reduction of Anti-A and Anti-B Isoagglutinin Titres of Group O Platelet Units with an ABO Antibody Immune Adsorption Column. 2023. Abstract. P-CB.22, Transfusion 160A.

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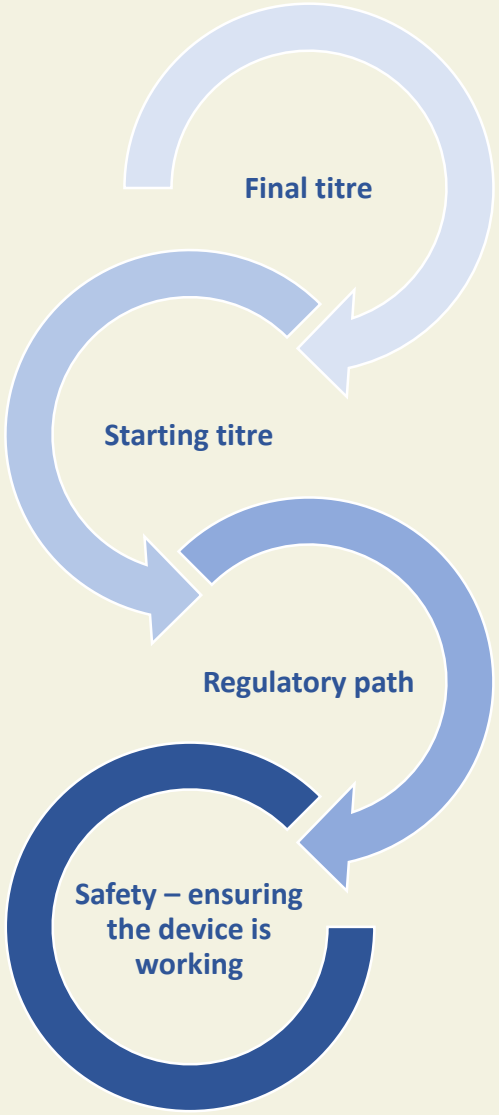
Issues to overcome on the path to ABO Universal

NHS Blood and Transplant



What titre do we consider “Universal”?

Varying levels of anti A/B in donor population, What capacity does the device need?

What level of data is required to gain regulatory approvals?
Does the medical device have any leachables or particulate matter?

How often do we need to confirm removal of antibodies – every unit?
Reproducibility of removal?

What is Universal?

NHS Blood and Transplant

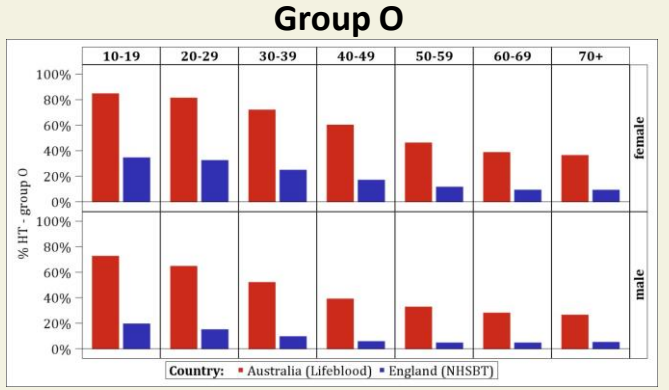
How do we define Universal plasma/platelets when we cross groups?

- In the majority of cases, reports of HTRs are usually with transfusions of group O plasma/platelets to non-group O recipients
- Both IgM and IgG antibodies have been implicated in HTRs but not always clear which (as not everyone measures both)
- Titres as low as 1:32 have been reported to cause haemolysis (anti-A), although generally titres for IgM are >1:128 and for IgG are >1:256
- Defining a cut off for Universal is challenging as there is no absolute relationship between titre and risk of HTR with other factors playing a role
  - Volume – generally HTR after a low volume of ABO non identical plasma is transfused are rare
  - ABO zygosity
  - Complement regulatory deficiencies

Levels of Anti-A and Anti-B vary in the donor population

NHS Blood and Transplant

- Potential in variation in tests across different blood establishments
  - Use of manual versus automated platforms
  - Different red cell reagents
  - Different dilutions
  - Different test methods
  - Testing for IgM versus IgG



Australia

England

Differences in HT positivity rates with respect to sex, age and ABO group

Differences in HT positivity – likely due to different red cell reagents*

- In NHSBT we use a set of controls (positive and negative standards) to attempt to ensure comparability of data with different testing methods

➢ To increase reproducibility ideally there should be an external quality assessment scheme with a standardised assay

* Robbins et al, Influence of donor age, sex and ethnicity on high-titre anti-A and -B: Review of 6 million donations from two national blood providers Vox.Sang. (2024) 119(9):987-995.

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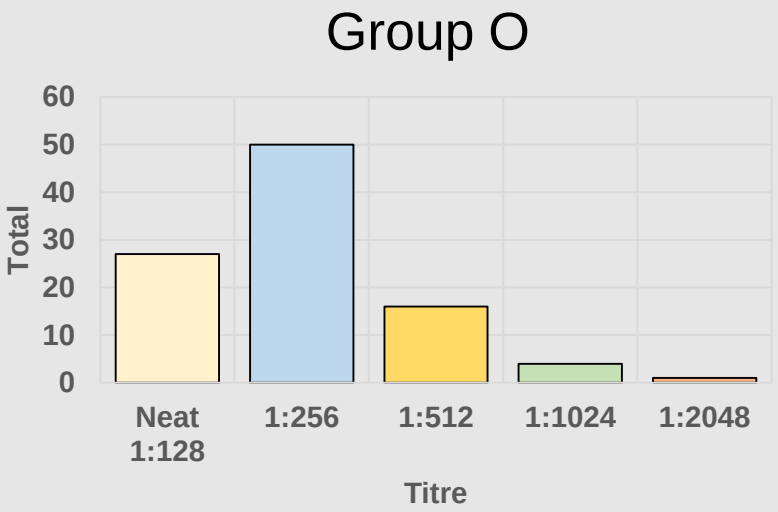
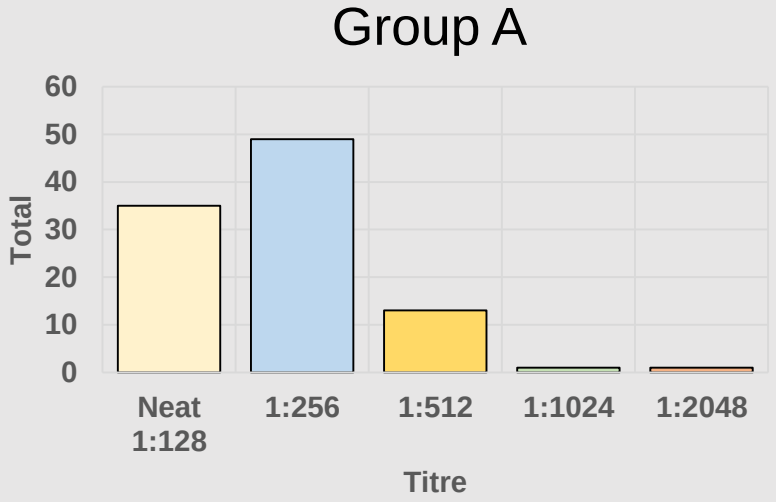
Device Capacity - High Titres

NHS Blood and Transplant

Different countries manage donor's high titre antibody levels in different ways
But how high is high?





Data from UK donor population – 100 samples group O and 100 samples group A – using PK7300

Adapted from Alice Wardle talk "How high is high? An assessment of anti-A/B titres in the UK donor population", 2024 (ISBT)

- Evidence for the need to remove donations testing > 1:128
- Or build extra capacity into the device

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Regulatory Approval

NHS Blood and Transplant

There is currently no specification for Universal plasma or platelet components.

Despite this there is a device (MDD CE mark) on the market for this purpose

In order to establish such a specification, you need to take account of :-

1. Classification of the device – unclear what this would be.
    1. Depends on how the Ag is grafted, chemicals used in the manufacture etc
2. Potential leachables from the device
3. Potential particulate matter remaining in final Universal component
4. Testing methods used to assure safety every time.
5. Level of clinical data required for approvals - unclear

No UK or EU component monograph for universal components

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Considerations around leachables and particulate matter

NHS Blood and Transplant

- Devices may contain leachables – e.g. antigens, particles (depend on tech), DEHP
- Devices may leave residual particulate matter

Leachables

DEHP phthalates – sunset date 2030
Future of other phthalates – e.g. PVC
Medical device preferably DEHP-free

Other toxic chemicals in the medical device or in the production of the medical device (e.g. grafting of antigens process)?

Particles may leach

Particulate matter

- Standard – Eur. Pharmacopeia 2.9.19

Test 2.A – Solutions for infusion or solutions for injection supplied in containers with a nominal content of more than 100 ml

The preparation complies with the test if the average number of particles present in the units tested does not exceed 12 per millilitre equal to or greater than 10 µm and does not exceed 2 per millilitre equal to or greater than 25 µm.

Q – Is this appropriate for a transfusion?

What may help with the path to ABO Universal

NHS Blood and Transplant

1. Standardisation of titration assay and EQA
   a) False positives, false negatives means current assay analysis is tricky and titres can be +/-1 titre
   b) Differences in assay in different blood establishments

2. Defining a Universal level
   a) What residual level of anti-A/B is “Universal”
   b) Set the specification for Universal plasma and platelet components

3. Define how we monitor process capability
   a) How often do we need to test for residual antibody levels in Universal components?

4. Define the level of laboratory and clinical data required to demonstrate safety and efficacy for regulatory approvals

Acknowledgements

NHS Blood and Transplant

Universal Team at NHSBT

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Dr Melanie Robbins (Munro)

Principal Investigator:
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Lead Quality Specialist and regulatory lead
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Alice Wardle
Gillian Grafton
Richard Knowles
Tinu Odunsi
Shradha Amatya

Component Development at NHSBT

Funders

NHS National Institute for Health Research

NHS Blood and Transplant

Collaborations

macopharma DESIGNED FOR LIFE

NIRI

Glycorex Transplantation

CytoSorbents™

UNIVERSITÄT GREIFSWALD
Wissen lockt. Seit 1456

Caring Expert Quality

EDQM Blood Conference
Innovation in Blood Establishment Processes
14-15 January 2025 | Strasbourg, France

Fetal hemoglobin-enriched red blood cell concentrates: an “investigational blood product” for preterm neonate transfusion

Luciana Teofili
on behalf of the «BORN study group»

Policlinico Universitario A. Gemelli IRCCS
Università Cattolica del Sacro Cuore
Rome

Gemelli 60 1964 2024

Financial disclosures

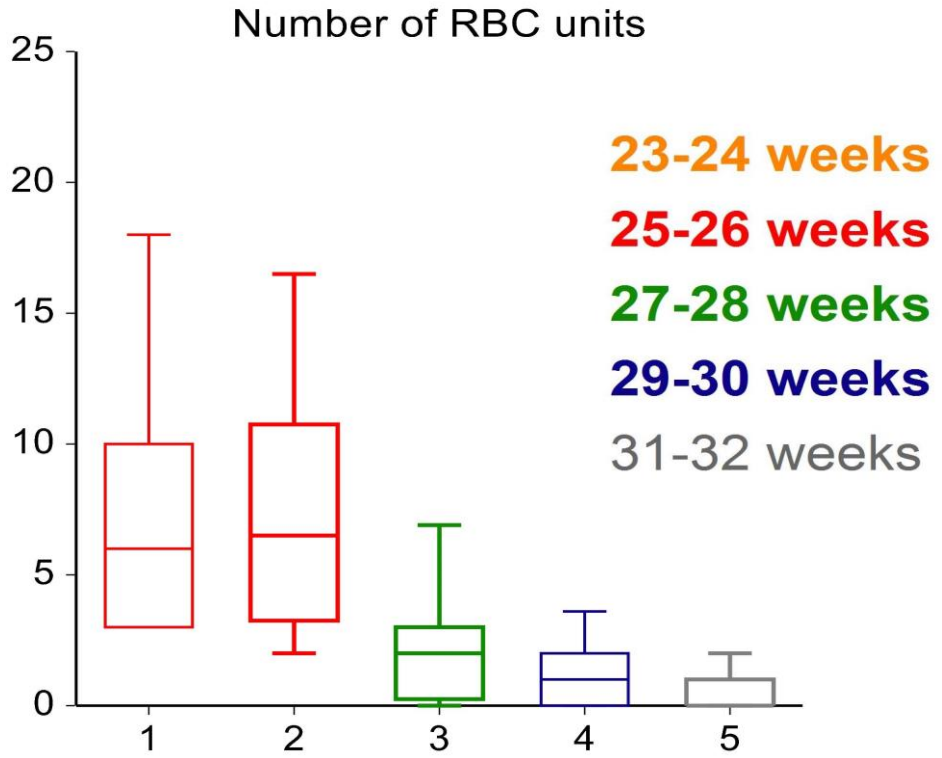
- Research support: Fresenius Kabi
- Co-inventor of BioNest (patented by Meditalia SRLA, Fondazione Policlinico A Gemelli IRCCS, Università Cattolica).

Anemia of prematurity

Anemia in preterm neonates

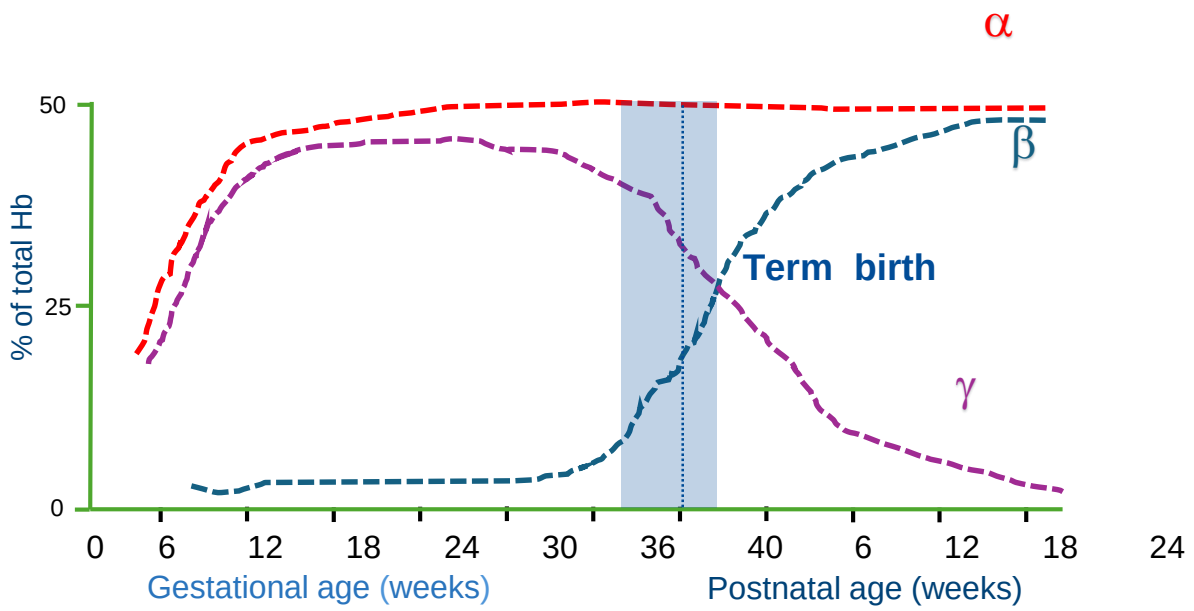
- Multifactorial
  - Impaired erythropoiesis
  - **Concomitant morbidities**
  - **Phlebotomy for laboratory testing**

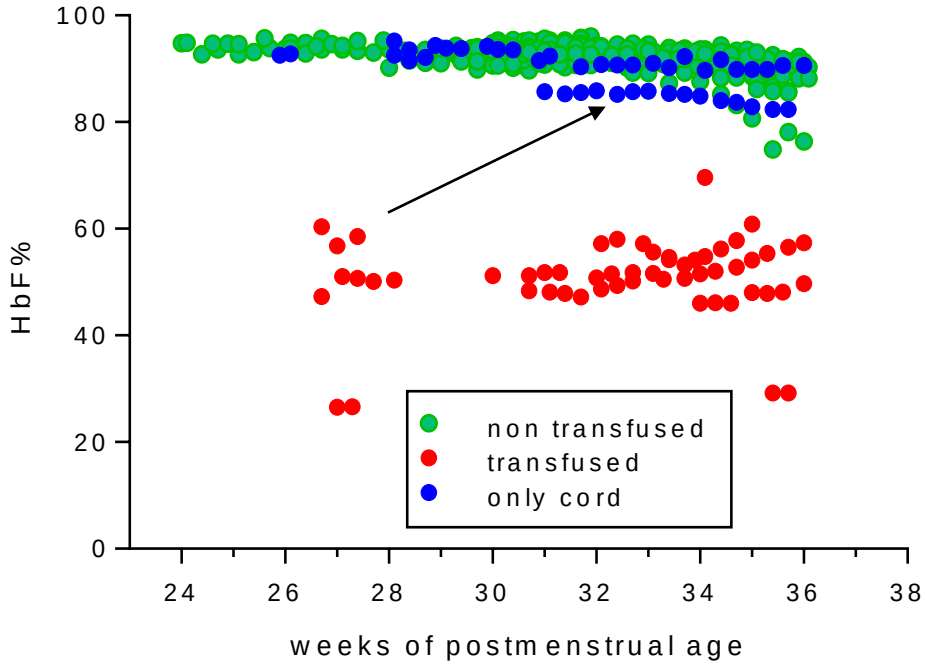
- Poorly responsive to medical therapies



Gemelli 1964 2024

Hb switch is constitutional





** Data from the «CB-Trip study» Teofili L. et al. Br J Haematol 2020*

Diseases or prematurity and oxidative stress: the role of HbF

Immature antioxidant defense

Infections
Anemia
Inflammation

oxidative stress

Oxidative stress related diseases

- Retinopathy of prematurity
- Bronchopulmonary dysplasia
- Intraventricular hemorrhage/periventricular leukomalacia
- Necrotizing enterocolitis

Biochemical characteristics of HbF

→ Higher oxygen affinity
→ Higher tetrameric stability
→ Greater pseudo-peroxidase activity
→ Higher unbound NO generation

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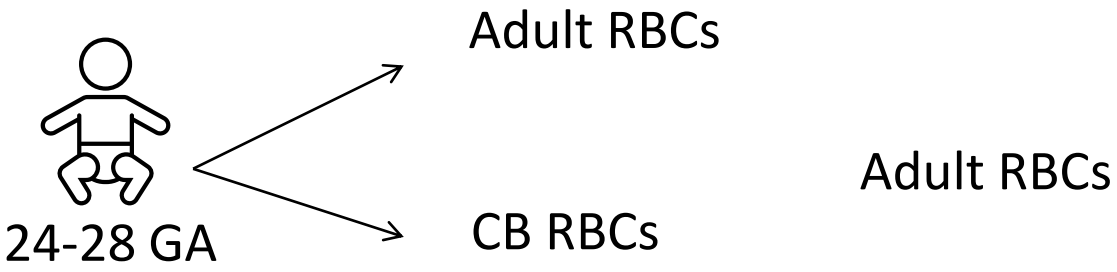
BORN: Allogeneic HbF-enriched RBC concentrates and ROP

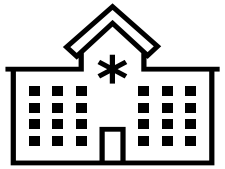
Teofili *et al. Trials* (2022) 23:1010
https://doi.org/10.1186/s13063-022-06949-8

Trials

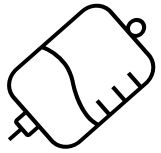
STUDY PROTOCOL Open Access

BORN study: a multicenter randomized trial investigating cord blood red blood cell transfusions to reduce the severity of retinopathy of prematurity in extremely low gestational age neonates





8 NICUs



8 Cord blood banks

Cord blood RBC concentrates

- Whole blood filtration (BioR Flex filter Fresenius)
- Fractionated at CompoMat G5® (Fresenius)
- Suspended in SAG-mannitol (2:1)
- γ irradiated at distribution

Main outcome
Severe ROP at 40 weeks or discharge

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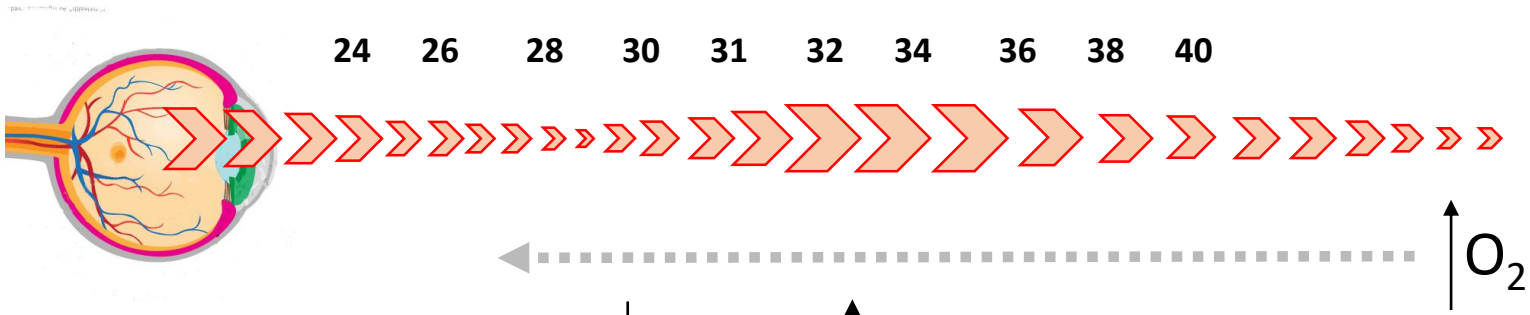
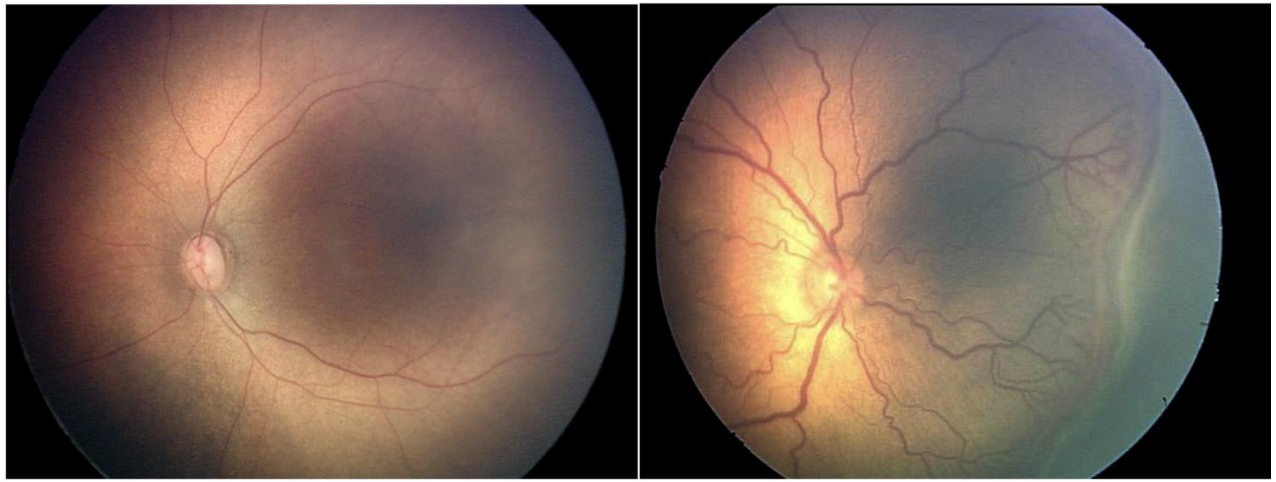
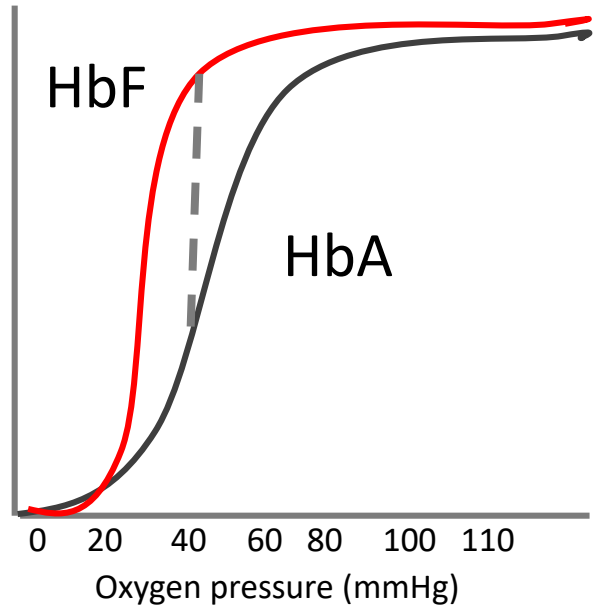
Retinal vasculogenesis and angiogenesis





from Coyner AS et al JAMA Ophthalmol. 2024;142(4):327-335.



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BORN: Study population

	All patients n = 142	A-RBCs n = 73	CB-RBCs n = 69	P
Gestational age, weeks	26.1 (25.0-27.0)	26.0 (24.9-27.0)	26.4 (25.0-27.3)	0.634
Weight, gr	750 (650-911)	720 (597-870)	775 (691-942)	0.064
Time to randomization, days	1 (0-3)	1 (0-3)	2 (0-5)	0.079
Male / Female, n (%)	76(53.5) /66 (46.5)	43 (58.9) /30 (41.1)	33 (47.8) /36(52.2)	0.238
Twins, n (%)	28 (19.7)	14 (19.1)	14 (20.2)	0.778
Apgar score 1 min	5 (4-7)	5 (4-6)	6 (3-7)	0.865
Apgar score 5 min	8 (7-8)	8 (7-8)	8 (7-8)	0.699
CRIB II score	11 (10-13)	12 (10-13)	11 (9-13)	0.185
Probability of mortality (%)	17.8 (12.2-34.8)	25.4 (12.2-34.8)	17.8 (8.1-34.8)	0.185
Documented chorioamniotitis	13 (9.2)	6 (8.3)	7 (10)	0.942
Hb at birth, g/dL	15.1 (13.8-16.5)	15.5 (13.8-16.5)	15.0 (13.8-16.6)	0.730
Hct (p) at birth (%)	48.0 (42.0-54)	48.0 (44.0-56.0)	47.0 (41.5-53.5)	0.439
Death, n (%)	30 (21.1)	17 (23.3)	13 (18.8)	0.543
Follow up, days	98 (67-124)	98 (68-123)	107 (68-1128)	0.582

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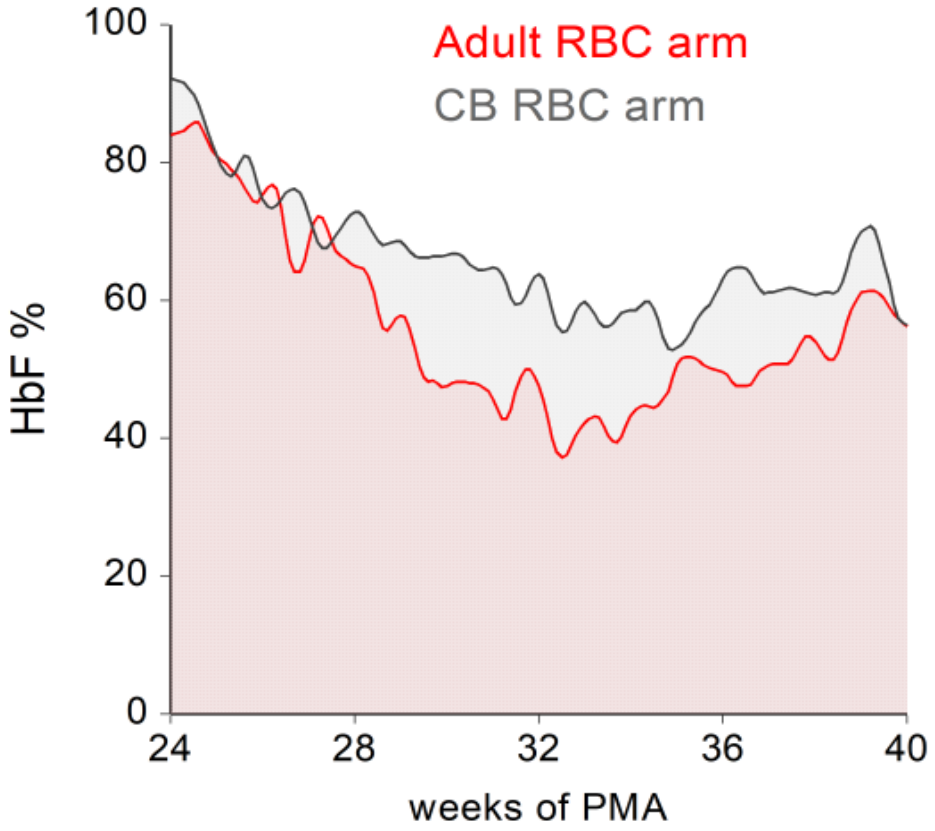
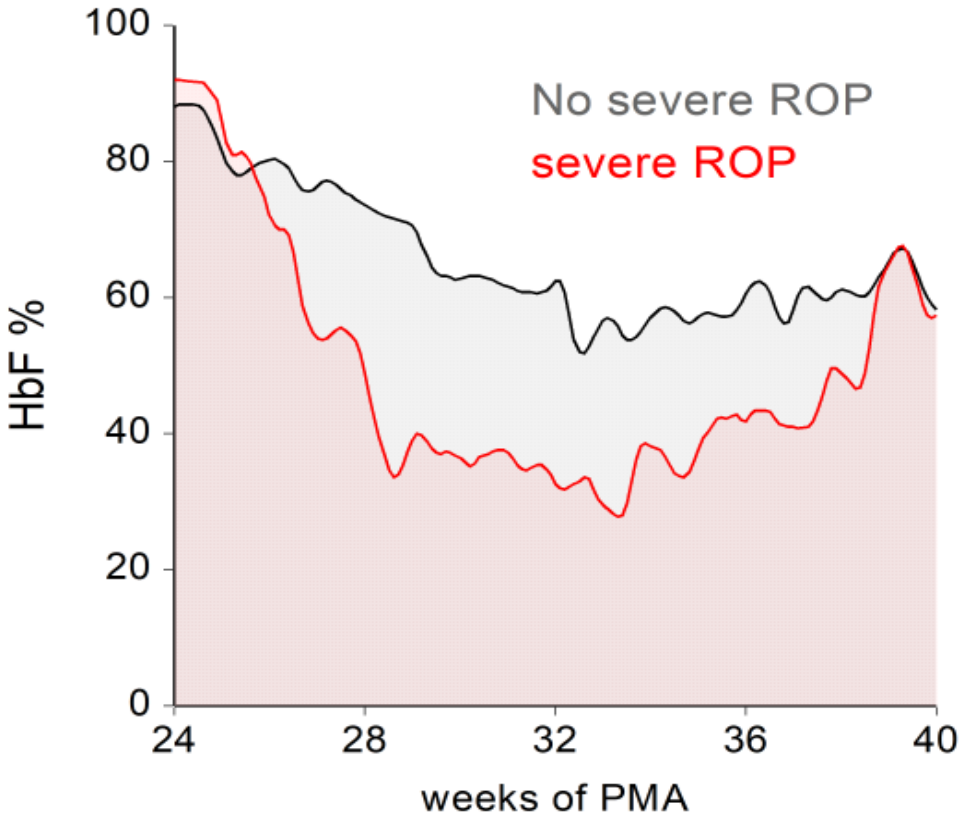
BORN: 458 RBC transfusions

	All patients (n = 142)	A-RBCs (n = 73)	CB-RBCs (n = 69)	p
Transfused patients	118 (83.1)	60 (82.2)	58 (8.1)	0.825
RBCs (total)	458	241	217	0.389
A-RBCs (total)	342	241	111	0.389
CB-RBCs (total)		0	106	
RBCs <30 PMA (total)	**312 (68)**	**165 (68)**	**147 (68)**	**0.424**
A-RBCs < 30 PMA	232	165	67	
CB-RBCs < 30 PMA	80	0	80	
Protocol deviations	**29 (20.4)**	**0**	**29 (41.4)**	
A-RBCs	13 (9.1)	0	13 (18.6)	
A-RBCs and CB-RBCs	16 (11.3)	0	16 (22.8)	

BORN: study results from another perspective





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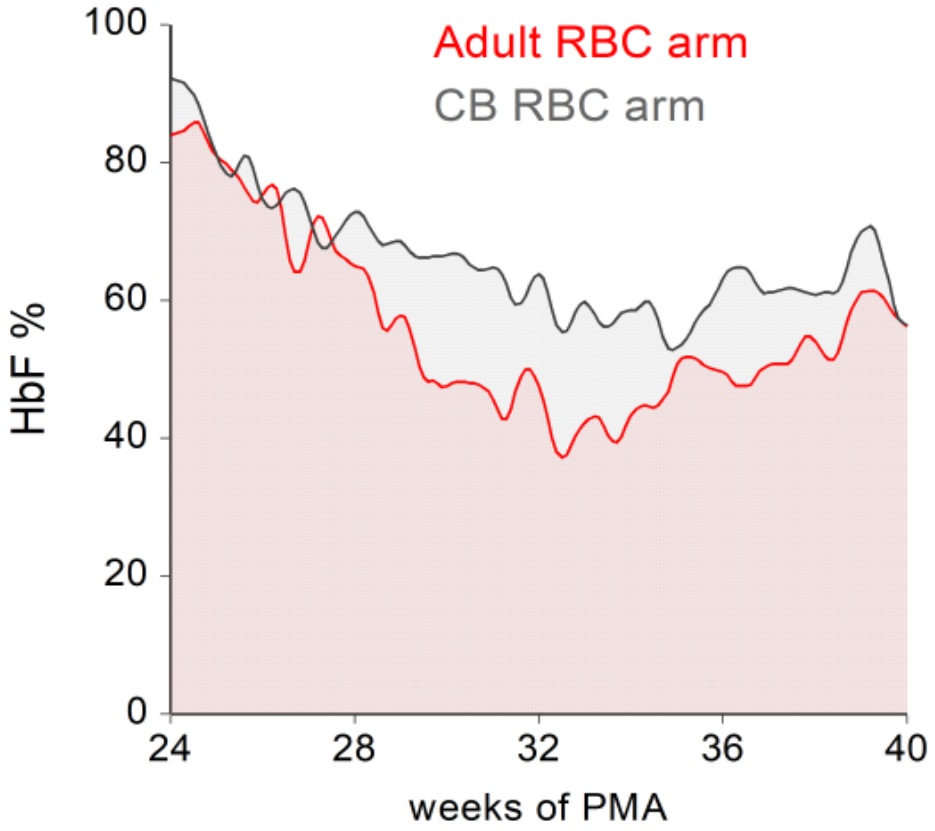
BORN: study results from another perspective



	Arm A n = 56	Arm B n = 56	P
Severe ROP	16 (28.6)	14 (25.0)	0.831
ROP treatment	12 (21.4)	11 (19.6)	0.815

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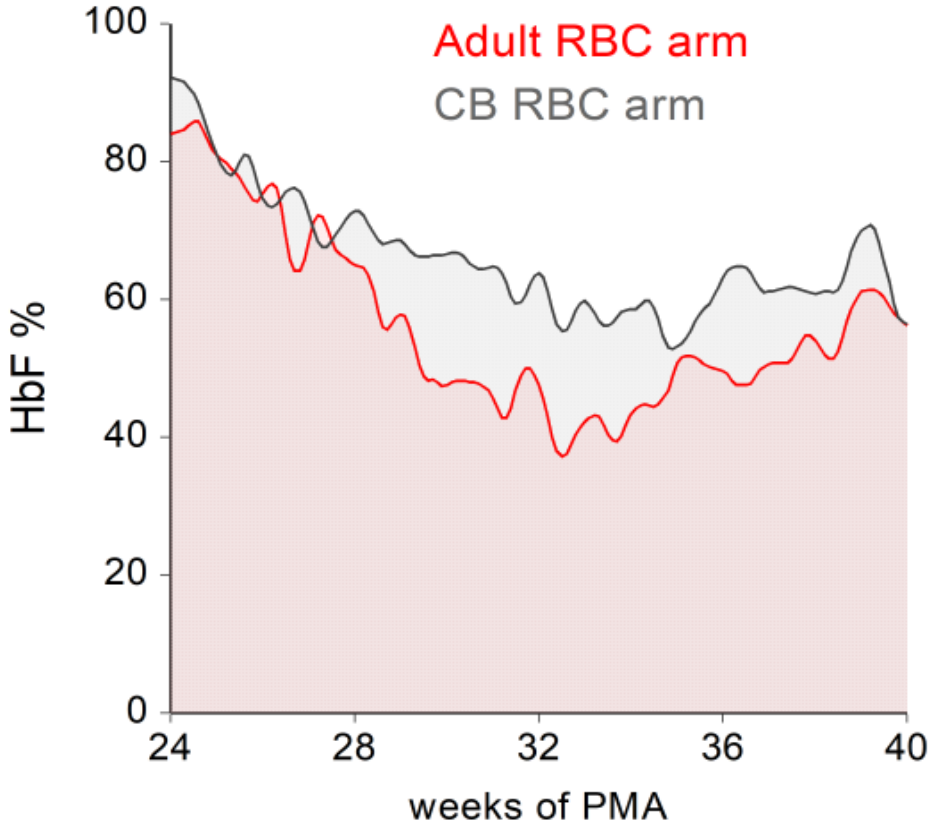
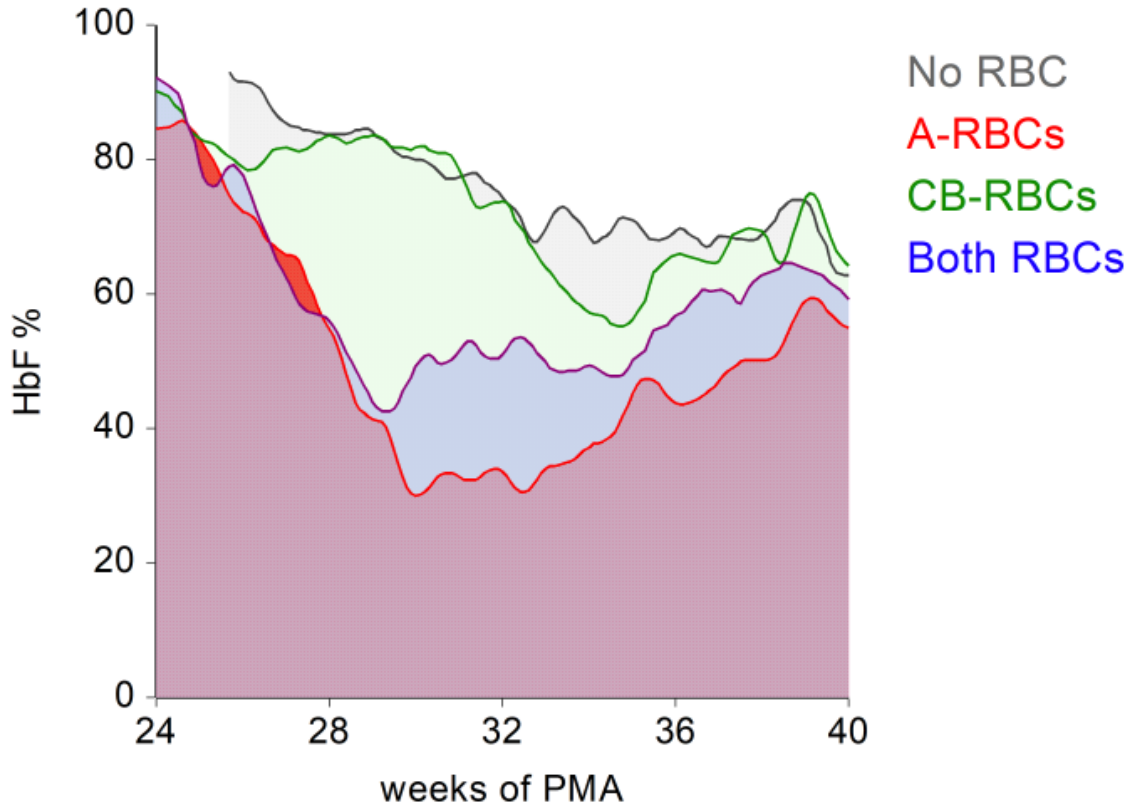
BORN: study results from another perspective





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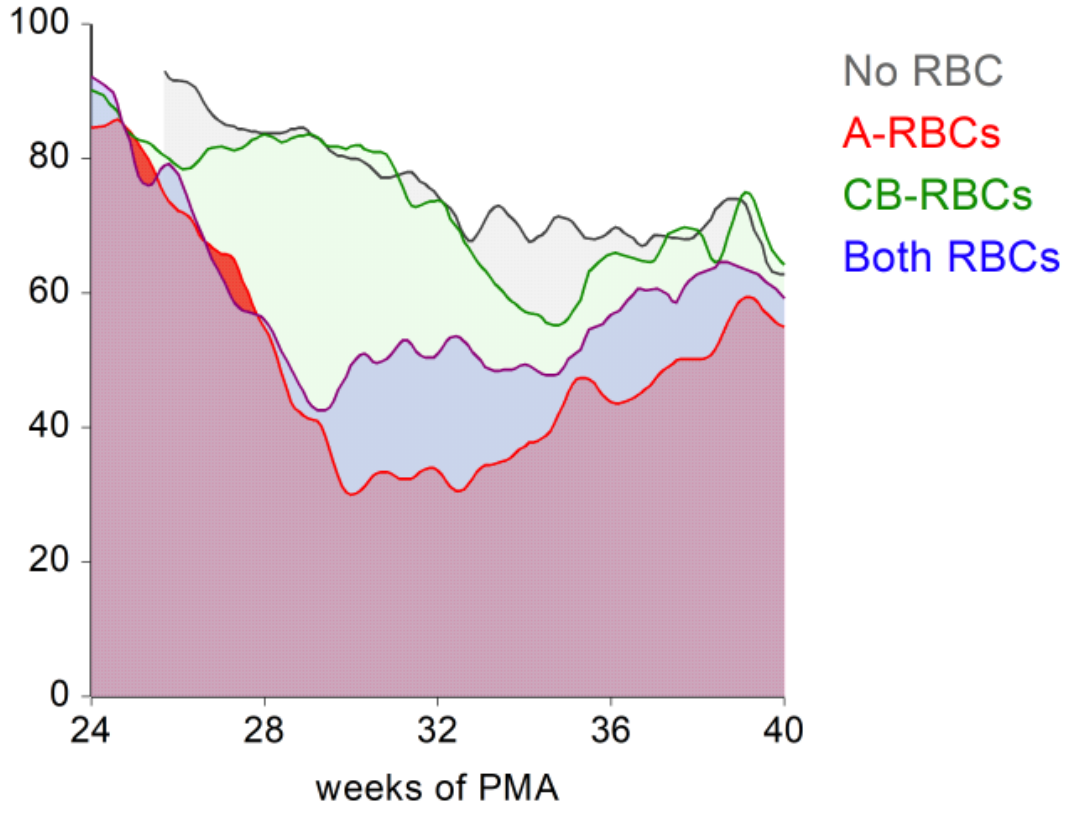
BORN: study results from another perspective

	Patients n = 112	Severe ROP n = 30	P
No RBC	31	4 (12.9)	<0.001
A-RBCs	49	18 (36.7)	
CB-RBCs	17	0 (0)	
Both RBCs	15	8 (53.3)	



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BORN: CB-RBC transfusion safety and efficacy

	A-RBC (n = 351)	CB-RBC (n = 107)	P
Acute anemia	143 (40.9)	54 (50.5)	0.147
Chronic anemia	147 (40.9)	42 (39.3)	
Surgery	14 (4)	4 (3.7)	
RBC unit Hct, %	60 (57-69)	57 (54-60)	<0.001
Dose (ml/Kg)	15,6 (14,8-20,0)	18,3 (15.0- 20,1)	0.016
Pre-transfusion Hct, %	26.5 (24.0-30.0)	28.0 (25.1-30.1)	0.049
Post-transfusion Hct, %	38.3 (35.0-43.0)	38.7 (34.1-42.1)	0.706
Δ Hct, %	11.5 (8.0-15.6)	10.0 (8.0-13.6)	0.129
Post-transfusion pH	7.33 (7.27-7.38)	7.32 (7.28-7.38)	0.680
Post-transfusion lactate, mmol/L	1.2 (0.9-1.9)	1.2 (0.9-1.6)	0.169
Post-transfusion potassium, mEq/L	4.4 (3.8-4.7)	4.3 (3.8-4.8)	0.924

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Insights for reflection (1)

Fetal hemoglobin-enriched red blood cell unit transfusions in premature neonates

- Are safe
- Raise Hb levels without depleting fetal Hb
- In contrast to A-RBCs, they do not increase the risk for severe ROP, by multivariate logistic regression analysis

CB availability

442 CB-RBC units were fractionated, 107 transfused, with 67 missed requests (!!)

- RhD neg
- Microbial contamination (4.3%)
- Short shelflife (2 weeks)

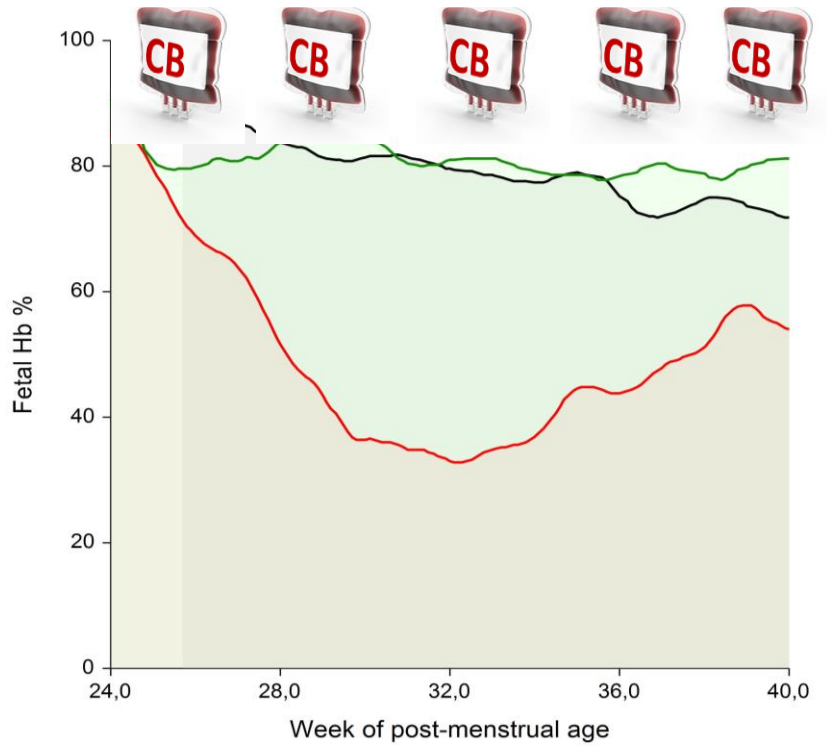
Insights for reflection (2)

Longer storage
Alternative sterility testing

Quality assessment

Donor suitability

Patient monitoring



Thank you!

AZIENDA OSPEDALIERO - UNIVERSITARIA
Città della Salute e della Scienza di Torino

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Sistema Socio Sanitario
Fondazione IRCCS Policlinico San Matteo
Regione Lombardia

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Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

Azienda Ospedaliero Universitaria Careggi
UNIVERSITÀ DEGLI STUDI FIRENZE
Da un secolo, oltre.

Sistema Socio Sanitario
Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico
Regione Lombardia

FRESENIUS KABI
caring for life

GRANDE OSPEDALE METROPOLITANO
BIANCHI MELACRINO MORELLI
REGGIO CALABRIA

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OSPEDALE PEDIATRICO
SANTOBONO PAUSILIPON
"curiamo i bambini, curiamo il futuro"

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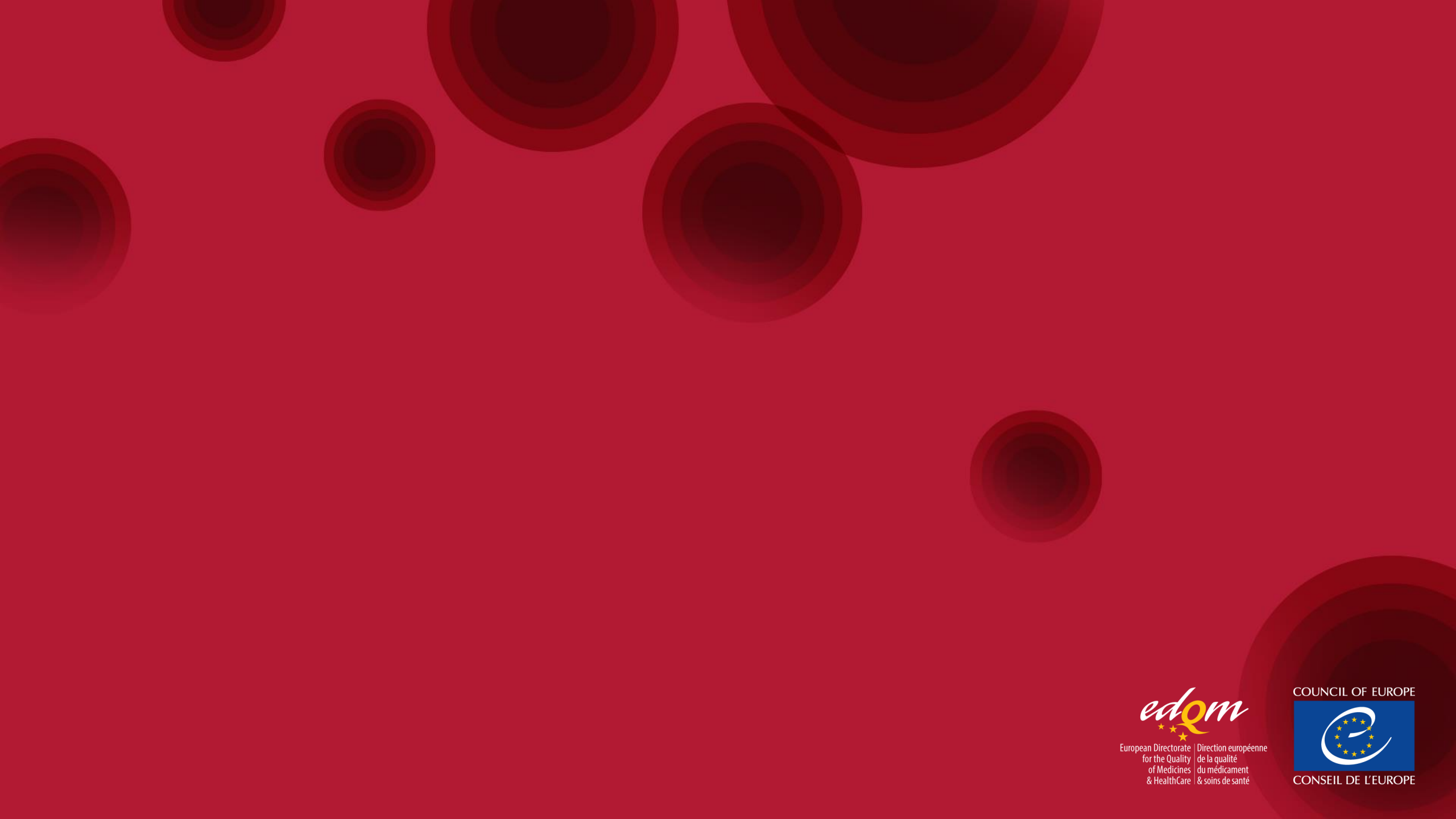
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