Importation of plasma: SaBTO review

Stephen Thomas PhD FRCPath

Disclosures / roles

- Associate Director, Manufacturing Development, NHSBT
- SaBTO member, Blood Service Manager
  - Chair of the Paediatric Components Working Group (task and finish)
- Deputy Professional Director, JPAC

Scope of the review

- The importation of plasma (for the manufacture of FFP and cryoprecipitate) and the use of apheresis platelets for patients born after 1995 or with TTP.
- This work will not consider the following:
  - leucodepletion, due to the many other benefits it brings in reducing adverse transfusion reactions and transmissions of infections such as CMV;
  - importation of fractionated plasma derivatives, as this is outside the remit of SaBTO;
  - exclusion of recipients of blood (after 1980) from donating, as this prevents the onward transmission of infections while having negligible impact on supply.

Collection

SaBTO reports and guidance documents

Reports published by the advisory committee on the Safety of Blood, Tissues and Organs (SaBTO).

Published 23 December 2016
Last updated 19 February 2018 — see all updates
From: Department of Health and Social Care

SaBTO advises UK ministers and health departments on the most appropriate ways to ensure the safety of blood, cells, tissues and organs for transfusion or transplantation.

Guidance reports

Risk reduction measures for variant Creutzfeldt-Jakob disease: PCWG report

Related content

SaBTO annual reports

Blood, tissue and cell donor selection criteria report: 2017

SaBTO microbiological safety guidelines 2017

Options considered

Option	Recipients of non-UK sourced plasma
U16 + TTP	Patients under 16 years of age Patients with TTP
U1 + TTP	Patients under 1 year of age Patients with TTP
None + TTP	Patients with TTP only
U16	Patients under 16 years of age only
U1	Patients under 1 year of age only
None	None

Option	Recipients of apheresis platelets
U16	Patients under 16 years of age
U1	Patients under 1 year of age
None	None

Workstreams

- Blood safety – risk assessment
- Contextual – ethics, social concern, perception
- Operations – hospitals and blood services
- Health economics
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Risk assessment – modelling

- Developed with oversight of expert ACDP TSE Subgroup:
  - Evidence, data, and interpretation
  - Assumptions, input parameters, and model calibration

"… Specific figures for the number of cases and infections, while uncertain and subject to revision in the light of further data, are considered to be of the right order of magnitude"

Risk assessment – key assumptions

- Highly precautionary
- Simple population based model – assumes subclinical carriers
  - Dietary BSE exposure 1978 – 2000 (Appendix III study)
  - Subclinical carriers: 1 in 1,800 (95% CI 1 in 1,000 to 1 in 3,700)

- Calibrated to clinical cases in under 76 year olds
  - All observed clinical cases to date
  - Large range of input parameters covering “worst case”
  - Calibration – allows for possible high levels of under-ascertainment in older population

- Main inputs (held constant)
  - Component numbers – 2017 values
  - Donor distributions – NHSBT
  - Recipient distributions – Multiple sources
  - Survival functions – EASTR study

Risk assessment – key assumptions

Plasma

- 50 year horizon (transfusions)
- 0-3 cases before 2018 in under 76s
- Negligible vCJD risk non-UK plasma
- TTP proportion of chronic recipients of FFP of all ages
- Includes leucodepletion

Platelets

- 60 year horizon (transfusions)
- 0-3 cases before 2018 in under 76s
- Apheresis used for younger patients
- Excludes HLA matching
- Relative risk apheresis/pooled 1:4 due to increased donor exposure
- Includes leucodepletion

Risk assessment – clinical cases

Component	Option	Clinical cases (Infected after 2020)	
		Total	Additional
Plasma	Current practice	2.8 (<0.05 - 27.1)	-
	U16 + TTP	3.6 (0.1 - 36.9)	0.8 (<0.05 - 9.8)
	U1 + TTP	3.8 (0.1 - 38.7)	1.0 (<0.05 - 11.6)
	None + TTP	4.0 (0.1 - 41.2)	1.2 (<0.05 - 14.2)
	U16	3.7 (0.1 - 37.7)	0.9 (<0.05 - 10.6)
	U1	3.9 (0.1 - 39.6)	1.1 (<0.05 - 12.4)
	None	4.1 (0.1 - 42.2)	1.3 (<0.05 - 15.0)
Platelet	Current practice	5.7 (0.1 - 69.9)	-
	U16	8.1 (0.1 - 103.6)	2.4 (<0.05 - 34.0)
	U1	8.6 (0.1 - 110.7)	2.9 (<0.05 - 41.1)
	None	8.8 (0.1 - 114.6)	3.1 (<0.05 - 44.9)

Risk assessment –additional clinical cases

Plasma (No import)

- Median: 1 in 5.2m
- Upper 95% CI: 1 in 440,000

Platelets (All pooled)

- Median: 1 in 3.1m
- Upper 95% CI: 1 in 210,000

Comparison

- RBC: 1 in 11m (Upper 95% CI: 1 in 1.8m)
- Dietary: ~1 in 3m (176 in 66 million)

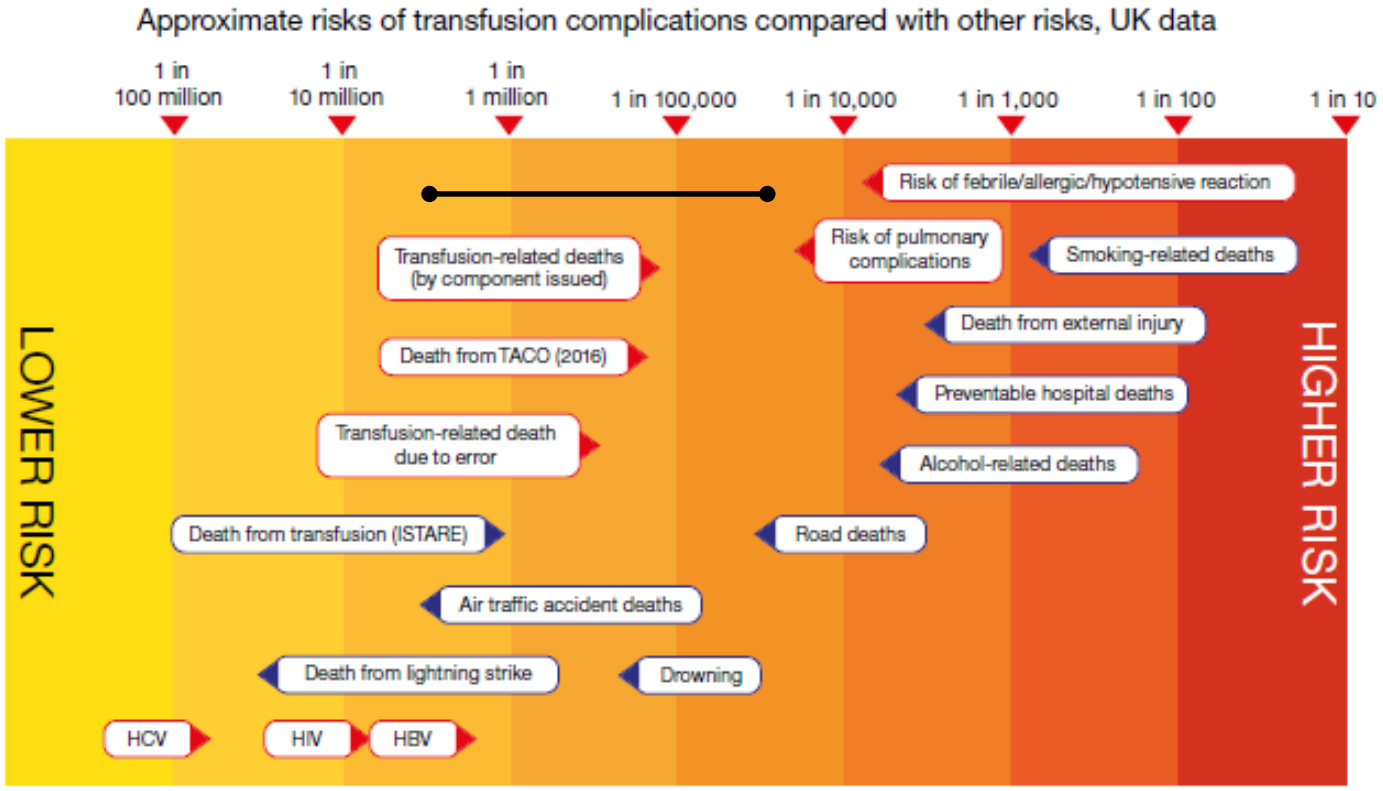

Figure from SHOT Annual Report 2017
www.shotuk.org

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Contextual issues

- Please refer to published report for full discussion

- Briefly:
  - Duty to protect patients from harm
  - Acceptable risk - sufficient to justify change in policy?
  - Treating different groups fairly
  - Fairness to all patients

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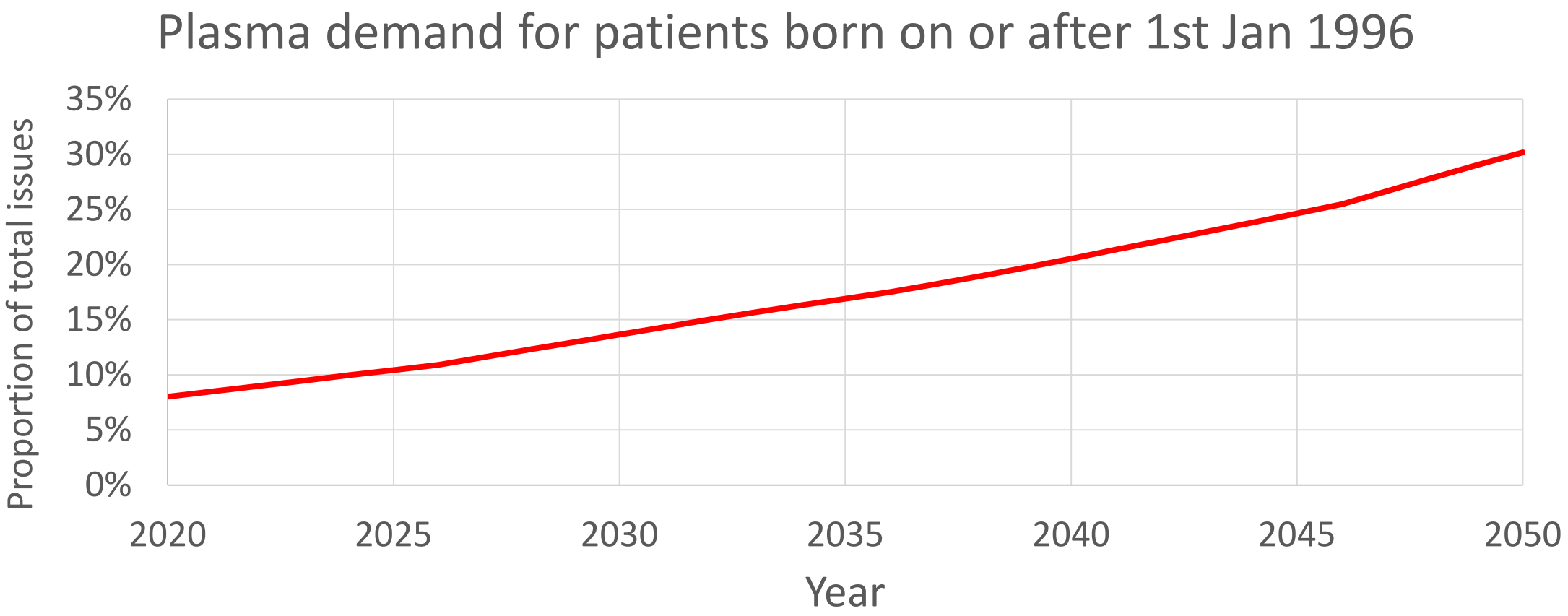
Challenges to importation

- Source country must appear on a DHSC-approved list of nine countries with sufficiently low risk of vCJD
- Source must comply with the EU Directive 2002/98/EC (effectively reducing this list to four EU countries)
- Supplier must have spare capacity to meet its domestic needs as well as the volume required for export
- Collection and supply services must conform to UK regulatory standards and national guidelines eg pre-donation health check and post donation microbiology screening eg HEV
- The electronic data file and label barcodes must be compatible with NHSBT's IT system.
- The Blood Establishment had to implement the process to MB treat the plasma at source
- Only one bid was received in response to the 2018 invitation to tender; incumbent supplier did not bid.
  - Likely that other potential suppliers felt that the terms of the specification were too onerous to meet
  - There are many alternative buyers for plasma – these are mostly plasma fractionation companies based in the same jurisdiction and having less demanding specifications.
  - It is expected that obtaining a supply from suitable European countries will become increasingly difficult as countries move to become self-sufficient in the supply of plasma

Blood service provision

	Paediatric plasma components	Apheresis platelets
NHSBT	Import 20 to 30K pa units of MBFFP from Poland Issue some as MBFFP (60 mL split or 250 mL bag) The majority is manufactured into MB Cryo (single or pools of 6). Supply other UKBS	50 % apheresis Provided as splits or ATD for paeds and HLA-matched adults.
WBS	Wholesale for OctaplasLG and fibrinogen concentrate also import a small amount of MBcryo from NHSBT	40 % apheresis
NIBTS	Import MBFFP and MBcryo from NHSBT Supply OctaplasLG for renal transplant patients	80 % apheresis
SNBTS	Import 60 mL MBFFP from NHSBT and single MBcryo (not pools). Supply OctaplasLG for adults	80% apheresis, reducing to 60% Provided as splits or ATD for paeds and HLA-matched adults
IBTS	Supply fibrinogen, manufacture very small amounts of cryo Wholesale for OctaplasLG and fibrinogen concentrate	70% apheresis, under review

Increasing demand



Hospital feedback - trauma centres

- 18/23 Major Trauma Centres and 4/4 children's MTC responded
- Four MTCs use UK FFP in the pre-hospital setting
- For the initial stage of resuscitation, 60% said that they use UK FFP, and later on they move to non-UK plasma.
- Most trauma centres indicated that rapid provision of plasma is more important

Hospital feedback – imported cryo

- Survey of paediatric cardiac / high-use non-cardiac hospitals
  - 14 in total
  - 3 non-compliant (UK or off-label Fgn)
  - 3 compliant, no complaints
  - 5 mentioned supply issues
  - 5 mentioned cost issues

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Cost-effectiveness – Overview

- Convert clinical cases to QALY loss
- Unit costs from NHSBT and indicative cost of SD-FFP
- All discounting @1.5%
- Plasma CE two scenarios:
  1. Hospitals continue using MB-FFP or SD-FFP
  2. Hospitals all use SD-FFP only

Cost-effectiveness – Plasma

Option	Additional QALY loss	Savings (£m)		ICER (£m per QALY)	
		MB-FFP / SD-FFP	SD-FFP only	MB-FFP / SD-FFP	SD-FFP only
U16 + TTP	8.9 (0.1 - 87.6)	413	418	46 (5 - 3,183)	47 (5 - 3,222)
U1 + TTP	11.5 (0.2 - 115.3)	448	452	39 (4 - 2,705)	39 (4 - 2,728)
None + TTP	15.7 (0.2 - 159.7)	497	501	32 (3 - 2,201)	32 (3 - 2,218)
U16	9.9 (0.1 - 94.1)	435	437	44 (5 - 3,010)	44 (5 - 3,018)
U1	12.5 (0.2 - 121.9)	471	471	38 (4 - 2,585)	38 (4 - 2,584)
None	16.8 (0.2 - 166.4)	520		31 (3 - 2,143)	

Cost-effectiveness – Conclusion

- Under all options the saving per QALY lost is greater than:
  - NHS marginal threshold: £15k per QALY
  - NICE threshold: £20k - £30k per QALY

  - Societal value (WTP): £60k per QALY (WTA £360k per QALY)

- Move to UK sourced plasma and pooled platelets for all

- **Only considers clinical cases of vCJD and direct blood costs**

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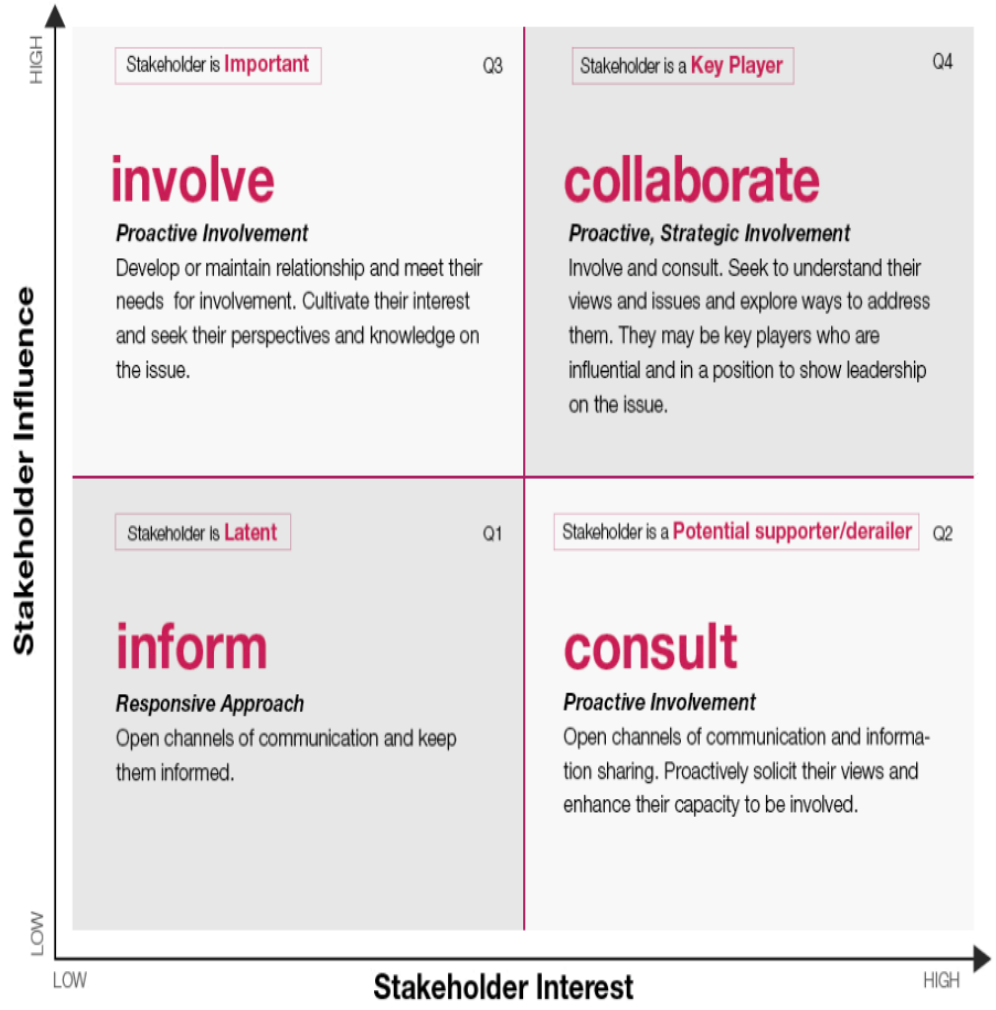
Stakeholder engagement

- The ABO risk based decision making framework identifies four types of stakeholder depending on influence and interest.
  - Involve, and Collaborate groups are represented by the composition of the working group or established communication routes
  - Inform and Consult are less well represented and engagement with these groups is required before final recommendations can be made.



Informal Sessions

- Haemophilia Scotland
- The Haemophilia Society
- TTP Network

Email responses received

- Sickle Cell Society
- The Platelet Society
- TTP Network

Formal Sessions

- Haemophilia Wales
- The Haemophilia Society
- Haemophilia Scotland
- CJD Support Network
- Great Ormand Street Hospital
- Bristol Royal Infirmary
- Birmingham Children's Hospital
- Octapharma
- Macopharma

Patient groups, including charities and clinical networks representing patients

Hospital transfusion laboratories

Commercial suppliers

Patient groups, including charities and clinical networks representing patients → Do not support the recommendation

Clinicians treating individuals affected by the proposals → No objection to the recommendation*

Hospital transfusion laboratories → Support the recommendation

*TTP Network wrt SD-FFP

Recommendations

- **Based only on vCJD risk, the current risk reduction measures of the provision of imported plasma and apheresis platelets for individuals born on or after 1st January 1996 or with TTP be withdrawn.**
- This is due to the revised risk assessment showing that the total number of deaths due to vCJD transmitted by plasma or platelets is predicted to be very low and these risk reduction measures would only prevent a small number of additional deaths.
- Removing the current risk reduction measures (importation of plasma and provision of apheresis platelets) will provide benefits in terms of more equitable provision of components, less operational complexity and risk, and will allow more resources to be deployed to save lives elsewhere in the NHS.
- Clinicians will still be expected to follow local and national guidelines on managing individual conditions (such as the British Society for Haematology Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies).
- It is important to note that the conclusions from the analysis on plasma cannot be extrapolated to the manufacture of plasma derived medicinal products from fractionation of plasma sourced in the UK. Further work would be required to determine the risks and benefits of using UK plasma for fractionation.

What next?

- Instructions received from ministers of health to implement these changes (not NI)
- Risk assessment regarding viral risk of UK components
  - Re removal of PI process
  - Under review by UK Blood Services (JPAC)
- Blood service – hospital discussions…

NHSBT response

Towards UK plasma self-sufficiency

- NHSBT has advised DHSC that transition to UK plasma self-sufficiency will take c.8 months
- This transition includes NHSBT planning for the transfer of EXISTING Imported/MB demand to UKFFP/cryo
- Considerations over viral risks/PI requirements for vulnerable patient groups are being considered by a number of safety groups
- Final determination by JPAC/SaBTO will inform NHSBT's implementation to meet patient component requirements

Maintaining sufficiency of supply through the transition to UK plasma self-sufficiency must be treated as an NHS-wide joint endeavour; NHSBT will move as quickly as possible to establish self-sufficiency but stable hospital ordering and demand is an essential prerequisite.

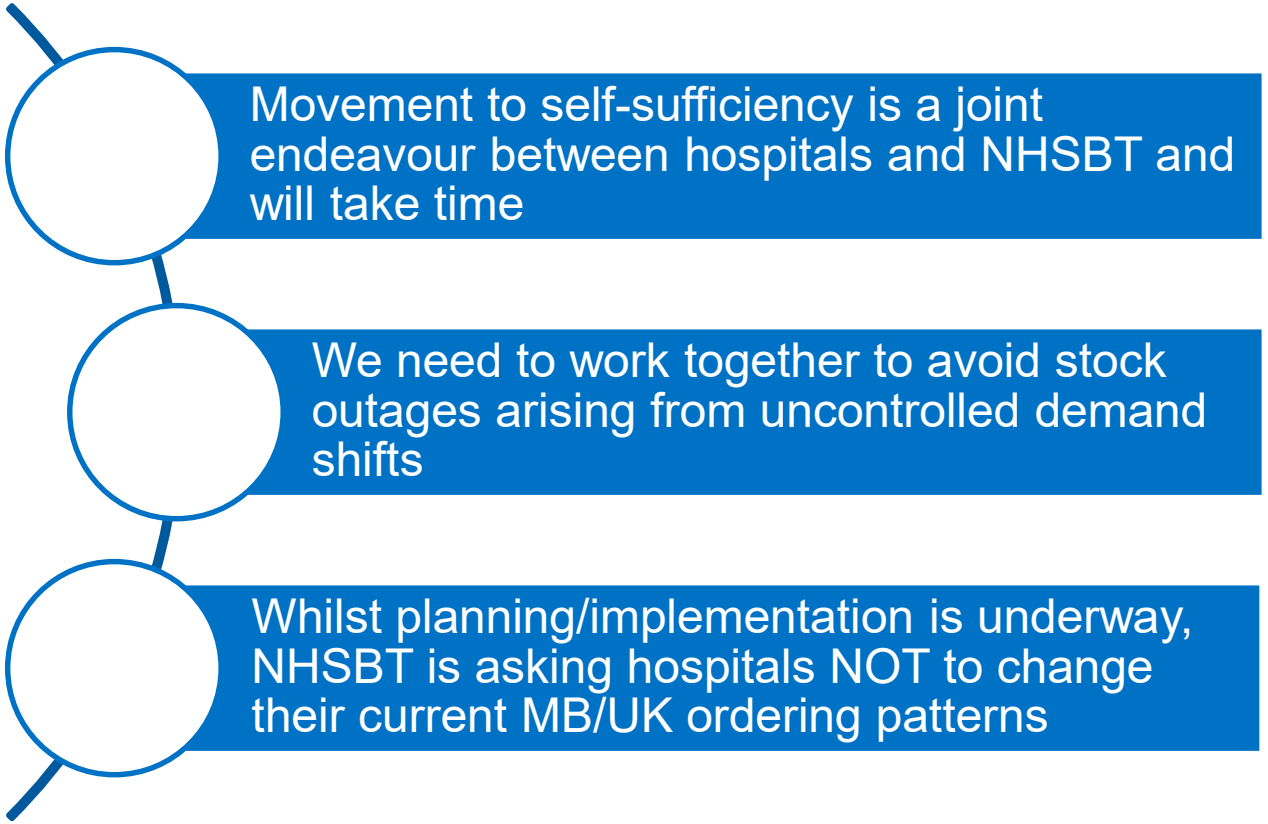
HOSPITAL response

Intelligence re: hospital intent

- NHSBT has asked hospitals to consider this change with their HTT to agree their intended response
- NHSBT will shortly survey hospitals to obtain that intelligence to underpin our demand planning to ensure sufficiency of supply:
  - level (and speed) of any demand changes to UK plasma components and
  - preferred blood group mix in which those components will be requested
- Demand and component specification will inform costs/prices
- SaBTO recommendations do not alter current treatment guidance for TTP, nor permit use of UK plasma for (medicinal) fractionation

This change came after the 2020/21 NCG commissioning round. Therefore, DHSC has agreed to an extraordinary NCG meeting specifically to commission 2020/21 plasma prices in an effort to better support hospital budget-setting

Summary of key challenges



Members of Paediatric Components Working Group

Dr Stephen Thomas Member of SaBTO; Blood Service Manager, NHSBT - Chair
Dr Susan Brailsford Member of SaBTO; Consultant in Epidemiology & Heath Protection NHSBT/PHE
Prof Richard Knight Member of SaBTO; Consultant Neurologist, National CJD Research & Surveillance Unit, Uni of Edinburgh
Dr Lynn Manson Member of SaBTO; Consultant Haematologist, SNBTS
Dr Gail Miflin Member of SaBTO; Medical & Research Director, NHSBT
Dr Helen New Cons ollege Hospital & NHSBT
Prof James Mason Heal
Dr Anne-Marie Slowther
Dr Jonathan Wallis Cons hair of NBTC
Gillian Hollis Men
Matthew Katz Anal

Thank you

Secretariat:
Dr Gary Mallinson SaBTO Secretariat/JPAC
Emily Coelho SaBTO secretariat; DHSC
Observer:
Dr Stephen Field, Medical & Scientific Director, IBTS