IN STRICT CONFIDENCE

An assessment of strategies, including leucocyte depletion, to minimise the risk of transmission of new variant CJD by transfusion.

1. Introduction

This paper considers ways of minimising the theoretical risk of transmission of nvCJD by transfusion.

The potential risk that this disorder might pose to the blood supply cannot yet be assessed. In particular data are not yet available on the transmissability of nvCJD by blood transfusion. Experimental and epidemiological evidence on the transmissability of TSEs by blood were reviewed at a recent WHO consultation.

It was concluded that "there is no proven or even probable instance of transmission of CJD by blood, blood components and blood products". However, recent evidence suggests that the transmissability of nvCJD in an experimental system differs from that of classical CJD. Thus nvCJD may differ significantly in its behaviour from classical CJD in respect of its ability to be transmitted by transfusion.

2. Possible approaches whereby the theoretical risk of transmission of nvCJD by transfusion might be minimised.

The UK Transfusion Services use five generic approaches to minimise the risk of transmission of any infectious agent by transfusion.

- **Exclusion of donors who could be at higher than average risk of acquiring the infection.** A number of exclusion criteria have already been implemented in the UK with regard to CJD:-
  - recipients of pituitary hormones of human origin
  - recipients of corneal transplants
  - family members of sporadic and iatrogenic CJD cases
  - recipients of dura mater (to be implemented shortly).

  These are kept under regular review.

  On the basis of our current understanding of nvCJD it is not possible to define effective donor exclusion criteria.

- **The application of screening tests to blood donations.** There are currently no tests which could be utilised in the blood screening environment.

- **The application of physical or chemical processes to inactivate or remove infectious agent.**

  A. Plasma fractions. The safety of products fractionated from large pools of plasma depends on the effects of the traditional cold ethanol (Cohn) process, and, more recently, the introduction of chemical and physical methods which further reduce viral infectivity. None of these processes can be expected to impact on the safety of these products in respect of CJD.

  B. Blood Components (whole blood, red cells, platelets, fresh frozen plasma/cryoprecipitate). Chemical and physical methods of virus-inactivation are being introduced for fresh frozen plasma and developed for other components. These are unlikely to be effective against nvCJD.

  C. Leucocyte depletion is already used as an effective means of preventing transmission of CMV. Given the experimental evidence that appears to identify TSE infectivity in the buffy coat it is possible that leucocyte depletion would be an effective mechanism to reduce the likelihood of transmission of nvCJD by blood.

- **Promotion of Good Transfusion Practice (GTP).** Despite the dissemination of clinical guidelines, transfusion continues to be utilised in clinical settings where limited benefit will accrue. Investment in the promotion of effective clinical practice is required to reinforce the principles of good transfusion practice. Randomised, controlled clinical trials are essential if peri-operative transfusion is to be applied only if clinical benefit is likely. In the context of reducing the risk of nvCJD by transfusion this should include a reassessment of alternative therapeutic approaches including autologous transfusion.

- **Substitutes or alternatives to human blood products.** Investment by industry and the transfusion services has lead to some new therapeutic approaches that reduce dependence on blood derived products. Public investment is needed to allow these to develop, especially in areas that are unlikely to be commercially viable.

A summary of possible interventions whereby the risk of nvCJD transmission might be minimised is contained in Appendix 1.

3. **Leucocyte depletion.**

3.1. Background.

More than 99% of the 2.25 million blood donations collected in the UK annually are processed into plasma and red cells. The plasma is either administered as whole fresh frozen plasma/cryoprecipitate (400,000 units/year), or forwarded for fractionation at BPL and PFC (625 tonnes). No steps are currently taken to specifically deplete plasma of leucocytes. Approximately 35% of donations are used for platelet production, resulting in a red cell product from which the buffy coat, containing >80% of the leucocytes, has been removed. Leucocyte depletion achieves 3-4 log reduction of leucocyte removal, to $<1 \times 10^6$ leucocytes /red cell unit or adult dose of platelets. This may be achieved either by filtration or by certain apheresis techniques for platelet collection eg COBE LRS. The numbers of leucocytes in standard and leucocyte depleted components are shown in Appendix 2, Table 1.
A number of specific indications already exist for the use of leucocyte depleted components. A recent survey of hospitals revealed that 9% of red cells and 23% of platelets transfused are currently leucocyte depleted.

3.2. Potential effect on CJD agent.

The rationale for considering leucocyte depletion of the blood supply is based on a possible association of the CJD agent with the buffy coat, and B lymphocytes in particular. However, the transmissable dose is unknown, and therefore the reduction in risk offered by leucocyte depletion cannot be calculated with any certainty.

Data on removal of different leucocyte populations from donor blood are very limited at present, and results depend on the technique used. However, investigators are agreed that granulocytes and monocytes are removed most effectively by filters, and lymphocytes least well. An example of this is included in Appendix 2, Table 2.

3.3 Logistics of leucocyte depletion.

At the present time, the technology exists to leucocyte deplete all blood components (red cells, platelets, and plasma), with leucocyte depleted red cells and platelets regularly produced in UK Transfusion Centres to meet clinical demand. A number of strategies might be employed to implement universal leucodepletion . A detailed financial and logistical review would be required to determine the optimal approach. On the assumption that filter manufacturers would be able to increase production to meet the demand then preliminary operational advice suggests that a twelve month period would be required for full implementation. A brief analysis of methodologies is provided in Appendix 2.

4. Leucocyte depletion - clinical evaluation.

4.1 Benefits.

The British Committee for Standards in Haematology Transfusion Task Force has just completed a guideline for the use of leucocyte depleted components (Transfusion Medicine, in press). The guideline attempted to provide an evidence-based set of recommendations for the use of such components in a variety of clinical settings, and has incorporated MSBT's previous recommendation on the provision of leucocyte depleted components for infants under 1 year. Recommendations have been grouped on the basis of the strength of available evidence into definite, possible and not indicated. A summary is provided in Appendix 2. A few points are worth emphasising:-

- Leucocyte depletion has been by proposed as a means of reducing the immunomodulatory effect of transfusion. However, evidence of reduction of post-operative infection and tumour recurrence following surgery was considered to be conflicting and leucocyte depletion has not been recommended in these clinical settings.

- Leucocyte depleted components may provide benefit to patients with HIV infection, and studies which should provide a definitive answer are ongoing.

- The role of leucocyte depletion in the prevention of transfusion-transmitted HTLV infection was considered, but in the absence of any published data, no recommendation could be made.

4.2 Are there disadvantages of leucocyte depletion?

Two possible disadvantages should be borne in mind, although hard data are lacking.

- Filtration methods results in some loss of red cells, particularly when combined with buffy coat removal. As this may particularly affect the younger (lighter) red cell populations, there may be a cumulative effect over a period of months on the requirements of transfusion -dependent patients such as those with thalassaemia.

- There has been concern that components which have been leucocyte depleted during or soon after collection, may not have had the opportunity to 'self-sterilise', with a possible increase in risk of bacterial transmission, particularly from platelets. Bacterial transmissions involving platelets have not so far involved an excess of leucocyte depleted components. However a monitoring study on COBE LRS platelets is in progress, and good surveillance systems currently exist to review all bacterial transmissions from blood components.

5. Actions

The information currently available is inadequate to enable an informed view to be developed on the potential value of leucocyte depletion, or other measures, to reduce the likelihood of nvCJD being transmitted through transfusion of blood or blood products. If on the basis of this initial assessment it is considered appropriate to undertake further investigation then the following actions should be considered.

1. A number of nvCJD cases are reported to have donated blood. Further information on the fate of donated units should be obtained as a matter of urgency.

2. Effective regular collaboration between blood transfusion experts and experts in TSEs is required to ensure that transfusion services are kept informed of scientific progress in this area, and to ensure that appropriate research effort is directed into establishing the role of leucocytes in possible transmission of nvCJD.

3. An operational and financial assessment of the introduction of universal leucocyte depletion of all blood components should be undertaken by the 4 UK Transfusion Services.

4. The desirability of introducing a pooled solvent/detergent treated fresh frozen plasma product derived from UK donor plasma should be reassessed (see Appendix 3).

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October 1997

Appendix 1
TSE TRANSMISSION BY BLOOD: APPROACHES TO REDUCING A THEORETICAL RISK

Approach	Present Position
Donors and Donations	
• Exclude donors who may have an increased risk of CJD	• Implemented for pituitary hormone recipients and relatives of CJD cases; dura mater shortly.
• Exclude donors who may have an increased risk of nv CJD	• No credible exclusion criteria identified Not clear if dietary history is relevant
• Screen blood donations for infectivity	• No blood test is available
• Screen donations for "surrogate" markers	• No such marker has been identified
• Use larger donations from single donors to minimise number of donors required for a patient's treatment	• Apheresis collections
Blood Components	
• Inactivate infectivity in blood components	• No effective inactivation procedure is known
• **Remove leucocyte from blood components before infusion**	• Depends on assumption that leucocytes (or a subfraction) are relatively more infective than red cells, platelets and plasma. • Depletion techniques are available commercially • May reduce transmission of other cell associated agents • Reduce transfusion reactions • Avoids some instances of platelet refractoriness • **Uncertainty - could either reduce or increase the risk of bacterial growth in blood components**
• Reconsider introduction of pooled plasma products	• Methods are available to reduce virus infectivity in single donations
Plasma Fractions	
• Alter manufacturing of plasma fractions to maximise "partitioning" of prion protein into discard fractions	• Work in progress
• Change inactivation procedures for plasma fractions	• No evidence to suggest an effective method
• Reduce batch sizes of plasma for fractionation to minimise dissemination of a contaminant from a single donation	• Under active consideration by FDA (US), but has large cost and process implications
Clinical Practice	
• Effective use of aprotinin, tranexamic acid and DDAVP	• Publicly attractive risk/benefits uncertain - targeted approach appropriate
• Autologous transfusion	
• Erythropoietin	
• Implement rigorous standards of blood production prescribing based on evidence of clinical effectiveness	• Evidence available only for new products • Large practice variations persist • Trials needed - urgently, meanwhile invest in implementing *existing* guidelines
• Use recombinant plasma protein substitutes where available Factor VIII, (IX, when licensed)	• Unknown risks due to animal virus contaminants • Little evidence of clinical effectiveness
• Restrict use of human albumin to proven indications **[Do not substitute gelatine]**	• But risks of other "colloid" solutions

Approach	Present Position
Clinical Practice (Continued) • Minimise use of human immunoglobulin - review overall benefits/risks of antenatal administration of Anti-D immunoglobulin - use hepatitis vaccine in place of Hm IgG for all traveller indications - review effectiveness and need for HB IgG, eg by extended HBV vaccination programmes - critical control of non-proven uses of IV IgG (especially young patients) • Review plasma fraction innovations for risk/benefit - fibrin sealant, fibrinogen concentrate	
New Products From Industry • Haemoglobins • Other oxygen carriers • Platelet substitutes • Thrombopoietin	• Clinical trials in progress • When they approach licensing ensure early economic and effectiveness assessment
New Products From UK Transfusion Service • Monoclonal (in vitro produced) Anti-D IgG Anti Zoster IgG	• Trials in progress • Pre trial • Assessment as above

Appendix 2

LEUCOCYTE DEPLETION OF BLOOD COMPONENTS - OPTIONS.

1. Background.

More than 99% of the 2.25 million blood donations collected in the UK annually are processed into plasma and red cells. The plasma is either administered unaltered as fresh frozen plasma (200,000 units/year), or forwarded for fractionation at BPL or PFC. Approximately 30-40% of units are further processed for platelet production, via either 'top and bottom' production via buffy coats, or from platelet rich plasma. Removal of the buffy coat results in a red cell product from which 80-90% of the leucocytes have been removed. Leucocyte depletion implies greater levels of leucocyte removal, to $< 5 \times 10^6$ leucocytes /red cell unit or adult dose of platelets. (This figure is under review as Council of Europe mandates $< 1 \times 10^6$ /unit). The numbers of leucocytes in different blood components are shown in Table 1.

2. Potential effect on CJD agent.

The rationale for considering leucocyte depletion of the blood supply is based on a possible association of the CJD agent with the B lymphocyte. However, the transmissable dose is unknown, and therefore the reduction in risk offered by leucocyte depletion cannot be calculated with any certainty.

Data on removal of different leucocyte populations are very limited at present. However, investigators are agreed that granulocytes and monocytes are removed most effectively by filters, and lymphocytes least well. The study shown below (Table 2)on platelet concentrates also suggests that filters from different manufacturers, with different physico-chemical properties, do not behave identically, and that the COBE LRS apheresis technique again results in a different leucocyte profile.

3. Logistics of leucocyte depletion.

At the present time, the technology exists to leucocyte deplete all blood components (red cells, platelets, and plasma), with leucocyte depleted red cells and platelets regularly produced in UK Transfusion Centres to meet clinical demand (see below). A number of strategies may be employed, depending on the production system in use.

3. 1 Whole blood filtration

This method is suitable only for units which will be processed to red cells and FFP/plasma for fractionation ie not for units from which buffy coats or PRP will be taken for platelet production.
The method works with both warm and cold held units held for 6-24 hours.
Suitable filters are available from Pall (WBF1) and Asahi. A recent Cambridge/Bristol evaluation was done of the Pall filter.

Red cell residuals - all $<0.5 \times 10^6$ /unit.

Plasma WBC (Nageotte) - pre filtration 2.67 +/- 1.19 x 10^6/unit
- post filtration < 2.5 x 10^3/unit (ie below detection limit, counted on a sample concentrated x 25 by centrifugation).

There was some loss of factor VIII, but within acceptable limits for FFP. BPL is now accepting the plasma for fractionation.

This is probably the most cost-effective option for the majority of units. For units intended for platelet production, the 3 components have to be leucocyte depleted separately.

3.2. Filtration of processed red cells

Filters are available from several manufacturers, some with integral blood bags. The Pall BPF4 reliably filters down to 10^5/unit.

3.3 Platelets

Filters are available for use either during processing of pooled buffy coats (eg Pall Autostop) or on the finished product (either PRP or buffy coat derived). The leucocyte residuals are 5 x 10^5/adult dose or less. Increasing use is being made of COBE LRS apheresis technology, which provides reliable leucocyte depletion without filtration. Although UK experience is limited so far, the system is reliable, with 100% units containing < 1 x 10^6 leucocytes and many < 5 x 10^5 or less.

3.4. Processed plasma

Neither fresh frozen plasma nor plasma for fractionation is routinely leucocyte depleted at present. However, this product can be generated as a result of whole blood filtration, as described above, or by filtration of processed plasma. Pall manufacture a filter specifically designed for plasma (LPS2), with residuals down to the detection limit (10^{3-4} /unit). COBE have no data on the plasma from their system.
Note that the methylene blue viral inactivation system for FFP has an integral filter which has been evaluated at Bristol, and which leucocyte depletes to < 2 x 10^3 /L.

4.0 Clinical aspects of leucocyte depletion.

4.1 Benefits.

The British Society for Haematology Transfusion Task Force has just completed a UK Guideline for the use of leucocyte depleted components (Transfusion Medicine, in press). The guideline attempted to provide an evidence based set of recommendations for the use of such components in a variety of clinical settings, and has incorporated MSBT's previous recommendation on the provision of leucocyte depleted components for infants under 1 year. Because the evidence for some indications is stronger than others, the recommendations were grouped as listed below. In certain areas such as post-operative immunomodulation, the peer-reviewed evidence is contradictory, while in others, such as HIV infection, studies which should provide a definitive answer are ongoing. Prevention of HTLV infection was

considered, but in the absence of any published data on the possible degree of protection afforded by leucocyte depletion, no recommendation could be made.

RECOMMENDED

Febrile non-haemolytic transfusion reactions (FNHTRs)

1) To prevent recurrent FNHTRs after red cell transfusions, buffy coat-depleted red cell concentrates should be used, if they are available, or alternatively red cell concentrates filtered at the bedside.

2) If FNHTRs continue despite these measures, leucocyte-depleted red cell concentrates should be used.

3) To prevent FNHTRs in patients likely to be dependent on long-term red cell support, the use of buffy-coat-depleted or bedside filtered red cell concentrates should be considered from the outset of transfusion support.

4) The routine use of pooled platelets derived from buffy coats is associated with a low incidence of FNHTRs. The use of platelet concentrates leucocyte-depleted prior to storage is recommended for patients with reactions despite the use of such components. Bedside filtration of platelet concentrates is not recommended for the prevention of FNHTRs associated with platelet transfusions.

Reducing graft rejection after haemopoietic cell transplantation

Patients with severe aplastic anaemia who are potential haemopoietic cell transplant recipients should receive leucocyte-depleted blood components from the beginning of transfusion support. The same might apply to patients with haemoglobinopathies, but more evidence is required before a definite recommendation can be made.

Prevention of transmission of viral infections by blood transfusion

Leucocyte-depletion of blood components is an effective alternative to the use of CMV-seronegative blood components for the prevention of transfusion-transmitted CMV infection to at risk patients.

Fetal/neonatal transfusions

Leucocyte-depleted blood components should be used for intra-uterine transfusions and for all transfusions to infants below 1 year of age.

POSSIBLE

Platelet refractoriness

There is currently no convincing evidence that routine leucocyte-depletion of blood components produces clinical benefits for patients receiving multiple platelet transfusions, although HLA alloimmunisation and platelet refractoriness are reduced.

Kidney transplants

Pretransplant blood transfusion may confer some benefit to renal transplant recipients, although some patients will become alloimmunised leading to difficulties in the selection of donor kidneys. Consideration should be given to the leucocyte-depletion of transfusions to renal transplant patients to prevent HLA alloimmunisation unless they are part of a deliberate pre-transplant immunosuppression protocol.

Immunomodulation

There is insufficient evidence to recommend the routine use of leucocyte-depleted blood components for surgical patients for the prevention of either post-operative infection or tumour recurrence.

Progression of HIV infection

There is insufficient evidence to recommend the use of leucocyte-depleted blood components for reducing the progression of HIV infection.

NON-INDICATIONS

A significant number of recipients of blood components receive a limited number of transfusions over a short period of time e.g. most general medical and surgical patients. Leucocyte-depletion of blood components is not indicated for these recipients unless there is an additional acceptable indication discussed in one of the other sections in this guideline.

Prevention of TA-GvHD is not an indication for leucocyte-depleted blood components. Gamma-irradiation of blood components is the standard method for avoiding TA-GvHD.

There is no need to leucocyte-deplete non-cellular blood components such as fresh frozen plasma, cryoprecipitate, and blood products prepared from pooled plasma.

4.2 Are there disadvantages of leucocyte depletion?

Two points should be borne in mind. Firstly, all filtration methods results in some loss of product. Usually, this is acceptable (5-10%), but for red cell units which have been buffy coat removed prior to filtration, this loss may become clinically important (up to 50 mls). Particular loss of young red cells may impact over a period of months on the requirements of transfusion -dependent patients such as those with thalssaemia. Secondly, there has been concern that components which have been leucocyte depleted during or soon after collection may not have had the opportunity to 'self-sterilise', with a possible increase in risk of bacterial transmission. This is of particular concern with regard to platelets, although there are no data to support this theory as yet. Bacterial transmissions involving platelets have not so

far involved an excess of leucocyte depleted components. However a monitoring study on COBE LRS platelets is in progress.

Lorna Williamson 20/10/97

TABLE 1
LEUCOCYTE NUMBERS IN RED CELL AND PLATELET COMPONENTS

RED CELLS

	Red cells	Red cells, buffy coat removed	Red cells, leucocyte depleted
WBC/unit	$> 2 \times 10^9$	$5\text{-}10 \times 10^8$	$5\text{-}10 \times 10^5$

PLATELETS

	Derived from platelet rich plasma (PRP)	Derived from buffy coat pools (BCD)	Apheresis	Leucodepleted*
Donors/ adult dose	5	4	1	4 or 1
WBC/dose	$<10^9$	$<10^8$	$<0.8 \times 10^9$	$< 5\text{-}10 \times 10^5$

* Can be produced from PRP, BCD or apheresis platelets

PLASMA

Pre-filtration- $1\text{-}10 \times 10^6$/unit

Post-filtration $<2.5 \times 10^3$/unit (ie below limits of detection). This level of leucocyte depletion is also offered by the filter in the methylene blue system.

Table 2. WBC populations in leucocyte depleted platelet concentrates (Wenz et al, ISBT, October 1997).

	WBC (CD45)	(CD3)	B lymphs (CD4)	T4 (CD8)	T8 (CD14)	Monos (CD15)	PMN's
Unfiltered (x 10^6/unit)							
Whole blood (500mls) 2000		3,000	75-200		Total = 2,700		200
PRP platelets	100	?	?	?	?	?	
Buffy coat derived platelets	10	?	?	?	?	?	
Filtered (x 10^3/adult dose)							
Pall LRF (used in Haemonetics harnesses)	220	18	124	77.9	0	0	
Pall PXL (post-processing)	24	0.55	0.10	12.9	0	0	
Asahi PLS	200	4.6	114.8	75.2	4.8	0.6	
Terumo/Immunogard	80	6.48	52.88	14.96	4.72	0.96	
COBE LRS	220	23.1	110.88	65.34	18.48	2.2	

Appendix 3

To: Dr Angela Robinson cc Dr Peter Flanagan 8th October 1997

From: Dr Lorna Williamson

VIRALLY INACTIVATED PLASMA.

Given the very recent data on the transmissability of nvCJD, and the high level interest over prevention of possible transmission via transfusion, I would like to propose that the NBS seriously reviews the decision to introduce pooled solvent/detergent treated plasma in early 1998. The relevant points are as follows:-

1. The remit which MSBT gave to UK Transfusion Services earlier this year was to be in a position to offer a proportion of FFP in a virally inactivated form to coincide with licencing and launch of the Octapharma product, estimated to take place by the end of 1997. It had been agreed earlier that 'no action' was not an option, since if Octaplas gained a product licence, Octapharma would be in a position to market this product in the UK, manufactured from plasma collected outside the control of the UK Transfusion Services.

2. In choosing between the available options, NBS took the view that provision of this product should not be limited and that NBS should be able to meet all demand, even if that turned out to be 100% of current FFP usage. This ruled out the methylene blue option, at least in the short term, since the current generation of light boxes allowed only very low throughput. Given the current pattern of blood collection and processing, it was considered that it would prove very difficult to methylene blue treat all FFP within the time allowed prior to freezing. It was thus agreed that general introduction of methylene blue plasma should wait until equipment suitable for high throughput became available, and that the SD FFP option should be pursued in the short term.

3. It was recognised that there were theoretical risks associated with pooling of up to 1000 donations to produce a batch suitable for SD treatment, although no excess risk of clinically apparent transmission of non-lipid coated viruses has so far been identified. Surveillance data of recipients on a large scale are not yet available. Some reassurance was obtained from the fact that plasma pools contain neutralising levels of antibodies to hepatitis A and probably to parvovirus B19, and that plasma pools are tested for HAV genome before SD treatment. Thus it was agreed that the balance of risks did not weigh unduly against the introduction of pooled SD FFP as a means of controlling the source of Octaplas in the UK. It was recognised, however, that NBS would probably wish to convert to single unit methylene blue FFP once appropriate technology was available. Thus it was agreed to pursue a short-term contract with Octapharma; this is not yet signed.

4. Although the SD process removes cells and cellular debris from the final product, there is no information on the likely partitioning of prion protein during downstream processing. Thus, at the present time, the potential risk of prion transmission from pooled SD plasma cannot be assumed to be less than that of single unit untreated plasma. The balance of risks of Octaplas introduction should therefore be reviewed. It should also be noted that the

methylene blue process includes an initial filtration step to remove leucocytes; this may be advantageous in the context of prion removal.

5. Early indications from user hospitals suggest that demand for a virally inactivated FFP may be between 30 and 40% of total use. Discussions with Operations staff suggest that this could perhaps be met by the current generation of methylene blue technology, provided a sufficient number of light boxes could be made available. The effect on demand of providing a single unit, as opposed to pooled, plasma is unknown at present. The possible effects of raising undue concern over CJD and transfusion by any change of policy on FFP should also be considered.

Suggested actions.

1. Review options at next Clinical Directors meeting .

2. Discuss with MSBT whether it is acceptable at this point to delay introduction of virally inactivated FFP till methylene blue technology can be introduced using current low throughput light boxes , with the caveat that it may not be possible to offer 100% VIP in the first instance. This option includes the liklihood that Octapharma will then proceed to market Octaplas manufactured from non-UK plasma (provided a product licence is granted).

3. Urgently investigate resources, costs and possible timescale of providing 20%, 50% and 100% of total FFP issues as methylene blue plasma using current light boxes (Terry Male has already agreed to do this as part of the ongoing VIP project, but this review could be accelerated).

4. Investigate longer term options for introduction of 100% methylene blue treatment - these include the use of either low or high throughput light boxes from Baxter, direct in-licencing of the Springe technology, or contract large scale contract methylene blue treatment of plasma (Grifols).

5. Discuss at BCSH Transfusion Task Force the rapid production of a clinical guideline to help clinicians prioritise the use of methylene blue FFP