Item 1: Welcome, introductions and apologies

1.1 The Chairman thanked members for attending. Apologies had been received from Professor Dark, Professor Martin, Dr Keel, Dr Mitchell, Dr Hayes and Dr Swann.

1.2 The Chairman welcomed Dr Watkins (replacing Dr Cardigan as UK Blood Services secondee to the secretariat), Ms Gronow (DH analytical team) and Dr Jones (standing in for Dr Hayes as representative of the Welsh Assembly).
1.3 The Chairman notified the committee that this would be Dr Ward’s last meeting. He thanked her for her significant contribution to the committee’s business since its inception.

1.4 The Chairman thanked Mr Dobra and Dr Cardigan for their contribution to the work of the committee since its inception.

Item 2: Minutes of the meeting held on 14/15 July 2009

2.1 The minutes were accepted as being a true record of the meeting.

Item 3: Action points from the meeting 14/15 July 2009

3.1 Action 07/01: Secretariat to: monitor developments and work with Professor Warrens and Dr Galea to produce a document for SaBTO

Professor Warrens informed the committee that he had identified a group of experts to discuss the issue of organ donation by those with CNS tumours and will bring a series of recommendations to SaBTO. It is hoped that the group will meet in the coming months to discuss the subject and begin work towards those recommendations.

3.2 Action 07/02: UK Blood Services to: perform an analysis on the potential ancillary benefits of pathogen inactivation

The analysis is underway, secretariat are being kept informed of progress.

3.3 Action 07/03: Secretariat to: monitor progress of the independent clinical trial into efficacy of PI platelets compared to untreated platelets, and to report its findings to SaBTO

Update due in January.

3.4 Action 07/04: Secretariat to: co-ordinate production of a document for the October public meeting which clearly explains the evidence for current donor deferral and exclusion.

Completed and to be provided to attendees of public meeting.

3.5 Action 07/05: Secretariat to: co-ordinate production of a paper on prion filtration for the October 2009 meeting of SaBTO

Provided, see item 6.

3.6 Action 07/06: Secretariat to: contact BCSH for their views on whether SD-FFP is suitable for all patients. Advice would also be sought from MHRA on post-marketing surveillance

Will be done following ministerial decision to proceed.

3.7 Action 07/07: Dr Potter/secretariat to: discuss licensing of fibrinogen concentrate with the manufacturer and MHRA

Update to be provided at future meeting.
3.8 **Action 07/08:** Dr Potter/secretariat to: obtain pathogen reduction data from manufacturer [of fibrinogen concentrate].

Update to be provided at future meeting.

3.9 **Action 07/09:** Dr Potter/Mrs Howell/secretariat to: produce leaflet for clinicians describing the hazards of platelets and cryoprecipitate

Draft to be provided to January meeting.

3.10 **Action point 07/10:** Dr Potter/secretariat to: write to specialist groups regarding inappropriate use of cryoprecipitate

Update to be provided at future meeting.

3.11 **Action 07/11:** Secretariat to: co-ordinate production of paper which will include cost-benefit analysis [of options for replacement of UK-derived cryoprecipitate] for future SaBTO meeting

To be provided at future meeting.

**Item 4:** Revision of MSBTO Guidance on the microbiological safety of human organs, tissues and cells used in transplantation - update

4.1 It had been intended that this document should be at a stage where widespread consultation on a draft document could be undertaken. Unfortunately the document is not yet completed but Richard Tedder and other members of the Working Group promised to take this further forward in the few weeks following the meeting.

**Item 5:** Consent for blood transfusion update

5.1 Members were provided with an update on progress. Mrs Howell spoke to this item. She informed the committee that she and the secretariat are hoping to commence a consultation on this issue as quickly as possible, acknowledging the guidelines from the Department of Health regarding consultation process. Mrs Howell noted that the necessary documentation is in place. The Chair reiterated the importance of this work and its timely completion, which should involve engagement of as wide a range of stakeholders as possible.

**Item 6:** Prion filtration of red cell components

6.1 Professor Turner presented this item. He reminded members that SaBTO substantively discussed prion filters in Jan 2009 (SaBTO5) and April 2009 (SaBTO6) meetings including data on red cell quality, clinical safety and efficacy studies. In April SaBTO recommended that the data from the independent efficacy studies be reviewed with HPA and the Manufacturer. The HPA data on the 263K studies is now complete, has been audited both internally and by external independent auditors and has been reviewed in detail by the UK Blood Services’ Prion Removal Working Group. Further data from the company and complementary independent data sets have been reviewed in detail. Further clinical safety data is also now available.
6.2 There are three filters currently in development. One is not CE-marked, the second is CE-marked but there is no independent efficacy data relating to infectivity available as yet, and the third is CE-marked and its efficacy has been widely assessed. It is this filter which was discussed.

6.3 Laboratory tests on the quality of filtered blood have shown no significant detrimental impact on red cell quality or immunohaematological parameters.

6.4 20 patients in Ireland have received single units of prion filtered red cells with no ill effects. 6 have received a second transfusion. No recipients have produced alloantibodies to prion filtered red cells. IBTS have switched the red cell inventory of one hospital to prion filtered red cells: a further 130 units have been transfused to adults. [Post meeting clarification: IBTS issued prion filtered red cells to one hospital as part of routine supply, with full follow up of recipients by the transfusion nurse at the hospital. Approximately 130 units were issued and transfused, with no reports of adverse events. The objective was to increase the number of units transfused to adults before seeking to use prion filtered red cells for transfusions in children. IBTS will now apply for ethics approval to transfuse this product to children requiring transfusions.] The PRISM study A in surgical patients is continuing. 74 patients have been transfused with 203 units in single transfusion episodes. No imputable adverse events and no evidence of increased incidence of red cell alloantibodies have been observed. A study in multiply-transfused patients (PRISM study B) is not currently planned to commence until PRISM study A is completed.

6.5 **Question 1:** Is the committee satisfied that sufficient data exist to demonstrate the safety of prion filtered red cells in humans?

6.6 **vCJD Review Group Recommendation:**

The filters can be considered safe in broad general terms with the caveats that rare adverse events may not have been detected as yet and the filters have not been studied in subsets of transfusion recipients such as children and multi-transfused patients.

If implementation is recommended it should be supported by revisiting the timetable for PRISM study B, and enhanced ‘post-marketing’ surveillance through the SHOT system.

6.7 During the discussion that followed, the following points were made:

- Many patients would need to be transfused to spot rare adverse events, in numbers (1000's) that would not be practical in a clinical trial;
- Any post-marketing surveillance would need to be carefully formulated and developed in a formal fashion;
- The Irish Blood Transfusion Service (IBTS) have applied for ethical approval to trial filtered blood in transfusion-dependent children;
- It was noted that the IBTS have not monitored alloantibody formation in the recipients of the 130 units of filtered red blood cells;
- Clinical trials have limitations, and post-marketing surveillance will be highly significant;
• Members were reminded that clinical trials have been performed following extensive laboratory studies on quality of filtered red blood cells;
• No adverse effects have been identified on the *in vitro* properties of filtered red blood cells;
• Concern was raised that implementation should not proceed until the PRISM trial is complete. Implementation before the completion of the PRISM trial may not be justifiable on issues relating to safety. Members were informed that UK Blood Services set the clinical safety studies up on a precautionary basis and that they are powered only to detect an increase in the rate of red cell alloimmunisation.
• Production of antibodies in recipients of filtered red blood cells could be mitigated by selecting blood that is matched for minor blood groups;
• The PRISM trial was initiated partly because of fears that recipients may (i) become immune to filtered red blood cells and (ii) may develop alloantibodies to normal red cells (as observed in 1-2% of recipients). In such an event their transfusion support may be compromised;
• Recruitment to PRISM has been slow due to reduced use of red cells in surgery;
• CE marking is a different process to licensing;
• There is a tension between awaiting the completion of the PRISM study, and implementing an available product which may improve blood safety;
• **In response to question 1, the committee stated that implementation of prion filtration was dependent on the satisfactory completion of the PRISM study A.**

6.8 The manufacturer had generated a combinatorial library of several million potential ligands. These were screened for affinity binding of PrP using Western Blotting on the resin-bound protein and ELISA on the flow through. Eight ligands were studied using a set of columns in series in order to study the kinetics of prion removal. ‘Stochastic’ removal would have resulted in the same proportion of the infectivity being removed at each passage independent of scale. ‘Selective’ removal results in removal of infectivity to the limit of capacity. SaBTO was shown data on removal of infectivity in a sarkosyl treated sonicated spike by 4 resins. A small fraction of infectivity (1/10,000) was not removed by serial passage. No reduction in infectivity was seen using a chemically modified negative control. This data was reviewed by PRWG.

6.9 The final results from the independent assessment of efficacy carried out by HPA were shared. It was found that, using exogenous bioassay of 263K hamster brain homogenate, the filter removed infectivity from crude brain homogenate and sarkosyl treated, sonicated brain homogenate, though not to the same extent as in the studies reported by the manufacturer.

6.10 The data and differences therein have been reviewed in detail by the PRWG efficacy subgroup and discussed with PRWG, the manufacturer and HPA. The features of concern were variability of intra-experimental runs and between different spikes in the HPA studies, differences between the HPA and PRDT studies and that the titre of the challenge may exceed the capacity of the resin. PRWG’s conclusions were:
“We feel that differences in results between the [manufacturer's] study and the HPA study may be explained by differences in methodology, differences in the performance of the manufactured filter compared with the prototypic columns, or, perhaps more likely, a combination of the two.

We see no reason to believe that either assessment has inherently more legitimacy than the other and also note that in our opinion the currently available data supports the proposition that prion infectivity can be removed by the filter at levels in excess of that predicted to be present in the peripheral blood of patients with variant CJD.”

6.11 An efficacy evaluation has also been carried out by a research group in France and results recently presented in poster form at an international conference. Two spikes were used to challenge the CE marked filter, the supernatant from 263K sonicated hamster brain homogenate centrifuged at 14000g, and the supernatant from 263K sonicated hamster brain homogenate ultracentrifuged at 188000g. Reduction in infectivity was shown in both spikes.

6.12 The resin used in the filter was also studied in 50ml of leucoreduced whole blood from hamsters with 263K scrapie. Leucoreduction was more effective at removing infectivity than shown in previous studies. The resin removed remaining infectivity to the point of detection. The full data had been reviewed by PRWG.

6.13 Results from further independent studies in 263K endogenously infected hamsters and BSE infected sheep will be available in 2012 and 2014 respectively.

6.14 The committee were reminded that removal of abnormal prion by a filter must be at a sufficient level to reduce infectivity of the unit of blood to be transfused.

6.15 Question 2: Does the committee believe that sufficient data exist to demonstrate that prion filtration is likely to remove the infectivity thought to be present in blood of individuals with subclinical infection to a level that would be likely to prevent the transmission of vCJD through a single unit of red cells?

6.16 vCJD Review Group Recommendation:

“The balance of currently available data supports the proposition that the affinity filter has the capacity to remove prion infectivity in excess of that predicted to be present in the peripheral blood of patients with subclinical variant CJD and therefore reduce the risk of transmission of infection by red cell concentrates.

The group recommends that, if recommended, the policy is kept under review as further data emerges on, inter alia, prevalence, infectivity and susceptibility and the efficacy of the filters.”

6.17 During the discussion which followed, the following points were made:

- There was discussion on the distinction between the specificity and the stochastic removal of the prion by the ligand, and how applicable...
this distinction is. It was noted that this approach has a lengthy history in plasma fractionation. An alternative view was that the real issue in the efficacy of the removal is the on-off rate of the abnormal prion to the ligand.

- There would be a difference in transit time between column and filter;
- The data from the assessment of the filter may be more valid than that from the ligand in column format;
- If similar log removal rates were observed for virus removal from blood they would be regarded as disappointing;
- SEAC have previously noted that the level of infectivity in blood is uncertain, and may range from 1 to 300 infectious doses/ml of blood.
- The efficacy of removal is below that of 3 logs of spike as recommended by SEAC; however, the filter need only remove the level of infectivity found in the residual plasma in a bag of red cells to impact on transmissibility;
- The reported capacity of any filter will be dependent partly on the physical characteristics of the agent used to challenge it. Data obtained from use of a spiked homogenate is therefore limited in its usefulness.
- For operational reasons, the animal models used have a restricted (~2 log\(_{10}\)) reduction limit of detection
- In response to Question 2, the committee agreed with vCJD review group’s recommendation that while no filter would ever be likely to be proven to entirely remove infectivity, there is sufficient evidence to suggest that this filter reduces infectivity.

6.18 The UK Blood Services have prepared project plans for implementation as requested by SaBTO in April 2009. Broadly, implementation for the under-16s (around 3% of red cells) could be achieved within current processing facilities, albeit some additional staff and equipment will be required. The time frame for this would be 6-9 months from the point at which authorisation is received. Implementation for all red cells may require additional space as well as a significant increase in staff and equipment. The time frame would be 12-15 months from the point at which authorisation is received.

6.19 Work is ongoing on validation of process control using Prothrombin and Factor IX. A solution is required for neonatal exchange transfusion, which will probably involve remanufacture of prion filtered red cells with pathogen reduced imported plasma. There will be some negative impact on supply due to additional red cell loss from filtered units (leading to some multi-transfused patients requiring more units) and increased wastage due to filter blockage etc.

6.20 PRWG advise that universal implementation is best achieved by a phased process and that implementation by smaller Blood Services is not artificially delayed, but that a date by which all 4 services will complete implementation is agreed.

6.21 Members were provided with a full cost-benefit analysis for all scenarios. In summary:

Prion filtration of red blood cells for <16s
Extra 2000 units per annum required due to Hb loss
One off costs: £211k
Recurring costs: £5.9m per annum
Cost effectiveness: £5k – £839k

**Prion filtration for <16s and haemoglobinopathies**
Extra 2000 units per annum required due to Hb loss
One off costs: £211k
Recurring costs: £8.7m per annum
Cost effectiveness: £8k - £1.02m

**Prion filtration for all red blood cells**
Extra 10000 units per annum required due to Hb loss
One off costs: £1.7m
Recurring costs: £87m per annum
Cost effectiveness: £3k - £856k

6.22 Targeting of safety measures which could be implemented universally towards a subset of patients (e.g. <16s or haemoglobinopathy) raises some ethical / societal issues:

- The desire to protect the ‘most vulnerable’ first;
- Targeted implementation of prion filters for some groups does not convey an increase in risk for the remainder of the patient population;
- The desire not to expose the ‘most vulnerable’ first to a new product;
- What to do about liminal cases;
- On what grounds do we justify our decision not to provide ‘safer’ product to other patients;
- How to handle the principles of autonomy.

6.23 **Question 3:** Taking account of cost-effectiveness analyses, would the committee recommend prion filtration of red cells be implemented either universally or for selected patient groups?

6.24 **Question 4:** If for selected patient groups, then which ones?

6.25 **vCJD Review Group Recommendation:**

“Universal in principle, because:

The ethical principles of equity, autonomy and non-maleficence.

Efficacy and cost effectiveness are of similar magnitude across different groups though overall cost obviously varies significantly.

If selected patient groups then children <16 and patients with haemoglobinopathies would leverage the most benefit on a population basis.

Targeted clinical safety studies will need to be done in these groups.”

6.26 In the discussion which followed, the following points were made:

- Members were made aware that a change to the scenarios concerning possible infectivity, prevalence and susceptibility of vCJD which inform their discussions on cost-effectiveness of measures may
be forthcoming over the next few months. This is because some of the modelled scenarios may be inconsistent with what has been observed.

- To recommend measures that have low cost-effectiveness would represent a disparity in approach compared to the wider NHS. However, some other blood safety measures are not cost-effective.
- Should very few further cases of vCJD present then there will be uncertainty as to whether this is due either to mitigating measures or incorrect assumptions about prevalence, infectivity and susceptibility;
- Certain groups may be more at risk of contracting transfusion-transmitted vCJD. These include those born after 1 January 1996 who have not been exposed through diet and multi-transfused patients;
- It was noted that although the risk appeared to be low, those who have been resident in the UK are not permitted to donate blood, stem cells etc in many countries;
- The UK Blood Services have in the past faced significant difficulties due to transfusion-transmitted infections. UK Blood Services are harmed legally, reputationally and ethically by such incidents;
- An instruction to implement may provide impetus for competition and a subsequent reduction in price;
- Many young blood recipients were not exposed to BSE through diet;
- The lack of data from animal models makes decision-making difficult;
- There is a possibility that the filter would not be wholly effective when challenged with blood from very high risk donors;
- There is no new information on prevalence, although studies are continuing;
- It was noted that, under certain conditions, the introduction of double dose red cells was more cost effective than prion filtration;
- **In response to questions 3 and 4, the committee recommended that filtration of red cells be implemented, for those not exposed to BSE through diet (i.e. those born after 1996). The option to remove this measure should be exercised in the event of (i) further data on prevalence or (ii) filters proven to not be efficacious when used widely;**
- This recommendation will be kept under review as further data emerges on prevalence, infectivity and susceptibility and the efficacy of the filters

6.27 In April 2009, SaBTO recommended double dose red cells should be provided for under-16s and patients with haemoglobinopathies. Prion filters have not yet been tested on apheresis red cells – but there is no particular reason to believe there would be a problem. The volume of residual plasma is higher in some products.

6.28 Prion filtration has the potential to provide a higher level of vCJD risk reduction compared to DDRC. Implementing filtration and DDRC would be more expensive and less cost effective than either alone. It would be operationally very challenging to implement DDRC and Prion Filtration simultaneously.

6.29 **Question 5: If implementation is recommended for any group that includes children or haemoglobinopathy patients, is this in addition to, or instead of double dose red cells?**
6.30 vCJD Review Group Recommendation:

“Instead of double dose red cells, because:

Operationally very difficult to implement both initiatives in a timely manner.

Of the two, prion filters offer the potential for a complete solution whilst double-dose red cells offer at best partial mitigation of risk on both an individual and a population basis.”

6.31 In response to question 5, the committee recommended that under-16s not be supplied with DDRC.

Item 7: Donor selection/Public Meeting

7.1 Members were provided with a paper detailing an amendment to the summary document which was given to members at the 7th meeting of SaBTO.

7.2 Question 1: Does the committee consider that such a change merits a review of the amended document?

7.3 Members agreed to revisit the new data in January 2010, along with a review of the views expressed at the Public Meeting.

Item 8: Any other business

8.1 The dates of forthcoming meetings are:

- 26 January 2010
- 27 April 2010
- 6 July 2010