ADVISORY COMMITTEE ON THE SAFETY OF BLOOD, TISSUES AND ORGANS

FINAL MINUTES OF THE FIFTEENTH MEETING, 10 OCTOBER 2011

WELLINGTON HOUSE, LONDON

Present:			
Professor	John	Forsythe	Chair
Members			**Area of expertise**
Professor	Peter	Braude	IVF/Fertility/Stem Cell Specialist
Professor	John	Cairns	Health Economist
Professor	John	Dark	Solid Organ Transplant Surgeon
Dr	George	Galea	Blood/Transplant Service Manager
Mrs	Catherine	Howell	Nurse
Professor	Deirdre	Kelly	Physician
Professor	Richard	Knight	CJD Expert
Dr	Harpreet	Kohli	Epidemiology/Public Health
Professor	Joanne	Martin	NHS Management
Mr	Elwyn	Nichol	Patient Representative
Dr	Michael	Potter	Haematologist
Professor	Hamish	Simpson	Orthopaedic Surgeon
Professor	Richard	Tedder	Microbiologist/Bacteriologist/Virologist
Professor	Marc	Turner	Haematologist
Professor	Anthony	Warrens	Immunologist
Dr	Lorna	Williamson	Medical Director, Blood Services
Observers			
Dr	Liz	Reaney	Northern Ireland
Dr	Aileen	Keel	Scotland
Mr	Will	Scott	Scotland
Mrs	Jenny	Thorne	Wales
Dr	Sheila	MacLennan	UK Forum
Mr	Nigel	Goulding	MHRA
Ms	Victoria	Gauden	HTA
Secretariat			
Dr	Rowena	Jecock	DH
Mr	Mark	Noterman	DH
Dr	Stephen	Thomas	DH/NHS Blood and Transplant
Mrs	Tina	Lee	DH
Others			
Professor	Adrian	Newland	National Blood Transfusion Committee
Ms	Leonie	Austin	NHSBT
Dr	Peter	Bennett	DH
Dr	Maren	Daraktchiev	DH
Mr	Andrew	Parker	DH

Item 1: Welcome, introductions and apologies

1.1 The Chair welcomed members to the meeting. Apologies had been received from Dr MacMahon and Ms Norman.

1.2 The Chair welcomed Ms Gauden, who was attending her first meeting as official observer for the Human Tissue Authority. Mrs Lee was also welcomed, having joined the Secretariat.

Item 2: Minutes of the meeting held on 3 May 2011

2.1 It was agreed that at page 3, the minutes should be amended to capture further detail of the discussion on the report back and recommendations of the Blood Donor Selection Steering Group, which gave rise to actions including the Communications Strategy.

2.2 Otherwise, the minutes were accepted as being a true record of the meeting.

2.3 **Action 15/01: Secretariat to amend and circulate the minutes.**

Item 3: Action points from the meeting on 3 May 2011

3.1 There were no action points outstanding.

Item 4: Donor Deferral

4.1 MSM (men who have had sex with men): Update on the announcement and media / stakeholder reactions

4.1.1 The Chair thanked Professor Kelly, Dr Williamson, Sir Nick Partridge of the Terrence Higgins Trust and Ms Elaine Miller of the UK Thalassaemia Society in particular for their part in successfully communicating Ministers' decisions, taken in response to SaBTO's recommendation. He noted that NHSBT's Communications Group had provided considerable help, and that the presence of Dr Pippa Grenfell and Dr Will Nutland at the press briefing had contributed to the positive responses of scientific and interest groups. He appreciated the way sensitive information had been managed over a long period, until the announcement was made.

4.1.2 A selection of press cuttings on the announcement was tabled. The response had been generally positive, with balanced and accurate coverage, though some interest groups had called for individual risk assessment.

4.1.3 The Minister for Health in Northern Ireland had yet to decide on SaBTO's recommendation. It was noted that if other blood services were to supply blood to Northern Ireland in an emergency, it might not comply with their current policy, and NIBTS have been advised of this.

4.1.4 The monitoring of compliance with deferral criteria by the blood services, in accordance with paragraph 4.13 of the minutes of SaBTO 14, was raised. It was noted that all infection-related criteria are routinely monitored.

4.1.5 **Action 15/02: NHSBT to** consider whether compliance with donor deferral criteria could be measured by the blood services using information currently available, or whether a research study would need to be commissioned (funding for which would need to be applied for).

4.2 CSW (commercial sex workers): Update

4.2.1 The Steering Group had investigated current and prospective sources of data on blood borne infections in CSW. Key data are lacking from both published reports and Health Protection Agency data. The Group is hoping to obtain more information from relevant out-reach projects. If any additional data is identified, it will be reviewed by the Steering Group and potentially submitted to SaBTO.

Item 5: Report from the CMV Transmission Steering Group

5.1 SaBTO received a presentation on the outcome of the work of the Cytomegalovirus (CMV) Transmission Steering Group, and modelling data on the impact of removing CMV screening.

5.2 CMV causes a chronic, persistent and usually asymptomatic infection for most adults, and around 50-60% of UK adults are CMV seropositive. Transmission of CMV in blood products can cause primary infection in CMV-naïve recipients or re-infection in previously infected individuals.

5.3 Groups at risk of transfusion-transmitted CMV include CMV seronegative recipients of a haemopoietic stem cell or solid organ transplant, patients with malignant disease, low birth weight and/or premature neonates of CMV seronegative mothers, foetal transfusion recipients and foetuses of pregnant (CMV seronegative and seropositive) women.

5.4 Universal leucodepletion, which provides a measure of CMV reduction, was implemented by all four UK Blood Services in 1999, primarily as a vCJD risk reduction measure. Leucodepletion does not completely eliminate the risk of CMV transmission; there is a small risk that CMV could be transmitted in blood components from recently infected donors, due to the presence of plasma or the remaining white cell fraction. However, it is estimated that no more than 0.01 – 0.1 viral copies per mL would remain in leucodepleted blood from a CMV infected donor. Currently, a proportion of donations are screened for CMV antibodies to provide 'CMV negative' cellular components for transfusion. The demand for, and cost of, such components are rising, and significant savings would be made if leucodepleted components, as currently provided, were accepted as 'CMV safe'.

5.5 For seronegative adult and paediatric recipients of haemopoietic stem cell transplants, studies show that CMV screened/seronegative blood and platelet support and the use of leucodepleted products using a bedside filter were equally efficient as methods of mitigating transfusion transmission of CMV. Both approaches have a low failure rate, and CMV monitoring and/or pre-emptive therapy are highly effective in mitigating against the potential clinical effects.

5.6 Though the risk of transfusion transmitted CMV following leucodepletion is low, there is a high risk of congenital CMV infection following primary maternal infection. It was suggested that it would be appropriate to continue to reduce this risk by the use of CMV negative blood products in addition to leucodepletion for elective transfusions in all pregnant women, and for intrauterine transfusions. Transfusions in pregnancy are most commonly for mothers with thalassaemia or sickle cell disease, who are usually treated in specialist centres, which makes the separate inventory easier to manage.

5.7 It is very rare for HIV positive patients to be CMV negative, and there is no evidence to support the continued use of CMV negative blood for these patients. There is similarly a lack of evidence to support the use of CMV negative blood for immunodeficient patients. These groups of patients are rarely transfused.

5.8 CMV positive organs are transplanted into CMV negative patients due to the greater risk of remaining untransplanted, but there is limited evidence of transfusion transmitted CMV in the solid organ transplant population. Of solid organ transplants, the lung is most seriously affected by CMV infection; however, while the risk of primary, donor-acquired infection at a time of high immunosuppression used to be a major concern, studies suggest that transfusion-acquired infection is of little concern, even for children, now that effective viral prophylaxis is available. It is highly unlikely to be different for other organ transplant groups.

5.9 The impact of removing CMV screening on the CMV infectivity of leucodepleted blood components was modelled, with variations in seroconversion rates and lengths of phase with both antibodies and CMV DNA. The basic model showed that the number of potentially infectious units (red cells, pooled platelets and apheresis platelets) in 141,600 units issued may rise from 226 to 486.

5.10 The following recommendations were proposed by the Group:

1. CMV seronegative red cell and platelet components should be provided for intra-uterine transfusions and for neonates (ie up to 28 days post expected date of delivery), and therefore all small sized blood packs and other cellular blood components intended for neonates should be provided as CMV seronegative;

2. Granulocyte components should continue to be provided as CMV seronegative for CMV seronegative patients;

3. CMV seronegative blood components should be provided, where possible, for pregnant women, regardless of their CMV serostatus, who require repeat elective transfusions *during* the course of pregnancy (not labour and delivery). This mainly applies to patients with haemoglobinopathies who are managed in specialist centres. However CMV seronegative blood components are not expected to be generally available in all hospitals, and therefore for emergency transfusions in pregnant women leucodepleted components are recommended;

4. All blood components (other than granulocytes) in the UK now undergo leucodepletion, which provides a measure of CMV risk reduction. This measure is considered adequate risk reduction for all other patients requiring transfusion without the requirement for CMV seronegative components in addition; and

5. CMV PCR testing should be considered for all patients (even CMV negative/negative transplant patients) to allow early detection of any possible CMV infection (whether transfusion transmitted or primary acquired infection).

5.11 The following questions were considered by Members:

5.12 Does SaBTO agree with each of the recommendations made by the CMV Steering Group?

5.13 **If not, are there any amendments or alternative recommendations which SaBTO would make? If so, on what evidence or grounds do SaBTO make any amendment or alternative recommendation?**

5.14 During discussion the following general points were raised:

- Transfusion of red cells or apheresis platelets carries a risk of c 1 in 1,000 of transmitting CMV infection. If a recipient receives 10 products, the risk would be 1 in 100. This needs to be compared with the high risk of acquiring the infection naturally (in the UK c 50-60% of adults are CMV seropositive);
- Viral load is important, but the level in blood that will cause infection is not known;
- The modelling did not take into account factors such as the fact that in pooled platelets, one donor's contribution predominates; or that the group who are NAT negative and antibody seronegative are not a homogeneous group. Data were not available to carry out eg age / gender stratification;
- It could be expected that in stem cell donation for a bone-marrow transplant, stem cells from a proportion of donors would be infectious, but this is not found;
- The Blood Services would benefit if dual inventories ceased;
- The Blood Services' 80% apheresis target would be more achievable if CMV serostatus did not have to be considered;
- The reduction of waste would be an important element in any recommended change to current practice;
- The major transplant centre in Seattle uses leucodepleted products rather than seronegative screened products, but data on outcomes is lacking.

5.15 The following points were raised in relation to specific recommendations:

5.15.1 Recommendation One: SaBTO accepted this recommendation.

5.15.2 Recommendation Two: SaBTO accepted this recommendation.

5.15.3 Recommendation Three: SaBTO accepted this recommendation.

5.15.4 **Recommendation Four**:

- The recommendation was discussed specifically in relation to CMV seronegative recipients of a stem cell transplant, or a solid organ transplant; and patients with immunodeficiencies and/or malignant disease.
- Currently, a seronegative recipient of a seronegative (seronegative to seronegative) haemopoietic stem cell transplant is not always monitored;
- Nor is the recipient of a seronegative to seronegative organ transplant monitored, unless they develop a visible infection;
- In the case of a haemopoietic stem cell transplant, if leucodepletion alone were accepted, the recipient of a seronegative to seronegative transplant should be monitored for the risk period;
- It was noted some units monitor / give prophylaxis to all seronegative to seronegative recipients as the numbers are small. It is simpler to have one protocol covering all cases to avoid the risk of oversight.

5.15.5 **SaBTO accepted recommendation four, but noted that testing and monitoring (as per recommendation five) would be important.**

5.15.6 Recommendation Five:

- It was noted that epidemiological monitoring of outcomes is also needed;
- There are relevant WHO regulations and European Directives;

- From next summer, when the European Union Organ Donation Directive takes effect, there will be an obligation for serious outcomes to be reported. Regulations are in preparation;
- The blood services will consider what form of monitoring is pragmatically possible;
- It is not possible to prove that a transfusion was the route of an infection; only that it might have been.

5.15.7 **SaBTO accepted recommendation five**.

5.15.8 The status of SaBTO's recommendations in general was discussed. It was clarified that the recommendations concerning CMV, noted above, would be published via a Position Statement.

5.15.9 It is not for SaBTO to implement these recommendations, but the responsibility of the UK Blood Services, the organ transplant community and others. SaBTO Secretariat would draw the position statement to the attention of the UK Blood Services and relevant personnel within NHSBT (for the organ transplant community).

5.15.10 Publication in an academic journal is also a possibility, as was done for the work on higher risk organs.

5.15.11 **Action 15/03: Secretariat to draft** a Position Statement for approval by SaBTO.

Item 6: Consent to Blood Transfusion: update and public meeting

6.1 The Chair thanked Catherine Howell and the Consent Sub Group, which included Elwyn Nicol, for the tremendous amount of work they had done.

6.2 SaBTO agreed that taking valid consent should be a discussion, recorded in the patient record. There were 14 recommendations, which were detailed in the Report and the Action Plan, many of them designed to help health professionals. The Action Plan set out the work of the Consent Sub Group in detailing actions, identifying who was to take them and agreeing a timeline. The resources included a standard for consent (with SaBTO's thanks to Health Improvement Scotland, who had developed it); guidance for clinical staff, on which feedback was currently being sought; and good practice guidance on taking consent retrospectively.

6.3 This point marked the end of SaBTO's work, and the beginning of work by the blood community to implement the recommendations.

6.4 The work had been discussed with Better Blood Transfusion teams in Northern Ireland, Scotland and Wales. Scotland and Northern Ireland undertook to highlight the work to other equivalent organisations in their countries.

Item 7: Fresh Frozen Plasma – vCJD Risk Management Strategies – ongoing review of SaBTO's 2009 recommendations

7.1 SaBTO received a presentation on this item. This noted that the basis of experimental evidence is shifting constantly, especially in relation to the question of why there are so few cases of transfusion-transmitted vCJD if the assumptions are correct. Much is unchanged, however: incidence and prevalence are at the

levels noted before; only infectivity and susceptibility have been questioned. DH has taken a precautionary approach to vCJD, but the effect of being precautionary on all fronts is overly pessimistic. A new position has emerged on how many cases could be expected if there were no further risk reduction interventions.

7.2 The following points were raised in discussion:

- It is not clear whether bone and tissues will be separately modelled, as for the first report, but they will be borne in mind;
- The HPA appendix study is currently due to be completed during summer 2012. Summaries of information on interim findings were included in the Minutes of the Advisory Committee on Dangerous Pathogens (ACDP) Transmissible Spongiform Encephalopathy (TSE) Risk Assessment Sub-Group from its first meeting on 14 July 2011. Findings will go to the ACDP TSE Risk Assessment Sub-Group in the first instance; they will take a scientific view of the interpretation and implications of the data. The Sub-Group's outcomes will go to the SaBTO vCJD Sub-Group, for assessment of the effectiveness of available risk reduction measures. SaBTO members made clear they would wish to discuss unexpurgated data rather than just 'digested' findings.

7.3 **Action 15/04: The SaBTO vCJD Sub-Group Chair undertook** that the vCJD Sub Group would review the information and bring a considered view back to SaBTO at the next meeting.

Item 8: Prion filtration of red cells

8.1 Members were reminded that in October 2009, SaBTO recommended the use of the PCapt prion removal filter for red cell concentrates for those born after 1 January 1996, subject to the satisfactory completion of the PRISM clinical trial. PRISM A is due to report in December 2011, and the results will be presented to SaBTO's meeting in January 2012. PRISM B is to be replaced by a post-marketing surveillance study, to look for unexpected reactions and alloimmunisation, with baseline data being collected for six months prior to any implementation of prion filtration.

8.2 In addition, studies in sheep of the efficacy of the PCapt filter are ongoing and are likely to last into 2014. The latest data will be considered by the Prion Working Group of the UK Blood Services in November. Relevant data will be passed to the SaBTO vCJD Sub Group, for consideration alongside the outcomes of the ACDP TSE Risk Assessment Sub Group.

8.3 The report of the Health Technology Assessment, which used the methods developed for SaBTO's work, of prion filtration of red cell concentrates to reduce the risk of vCJD transmission in Ireland had been circulated. It was reported that based on this, the Irish Government had decided not to proceed with prion filtration of red cell concentrates in Ireland. It was noted that vCJD incidence in Ireland is lower than in the UK.

Item 9: Publication of a report on the use of higher risk organs, including those from donors with central nervous system tumours

9.1 It was reported that the paper had been submitted for publication in the journal Transplantation. The response was positive, but some questions had been raised, resulting in re-drafting of the paper. The journal's decision was awaited.

9.2 It was confirmed that SaBTO will publish the paper on its website when it is in the public domain. In discussion, the following points were made:

- Waiting for publication meant the benefit of work reported in the paper was not yet available to the transplant community;
- In this instance, SaBTO had 'hitchhiked' work already in progress, and given it impetus.

9.3 **Action 15/05: The Working Group Chair undertook** to request publication should be expedited, if/when the paper was accepted.

Item 10: Advanced Therapy Medicinal Products

10.1 The Secretariat has commissioned the Medicines and Healthcare Products Regulatory Agency (MHRA) and the Human Tissue Authority (HTA) jointly to draw up a paper outlining the regulatory network for tissues, stem cells and advanced therapy medicinal products (ATMPs), and present it to SaBTO at the meeting in January 2012.

10.2 This was welcomed, in light of concern about the possibility of unexpected pathogens being present in cell lines before they are expanded.

Item 11: SaBTO work plan for 2012/13

11.1 Members were asked to suggest / comment on prioritisation of topics for future consideration by SaBTO.

11.2 Suggestions included:

- Testing of donors of stem cells vs testing of products.
    - Currently testing of donors of human embryonic stem cells is limited, but a clinical grade stem cell line means a vast quantity of cells are distributed to a great many people. It would be helpful to quantify any risk, eg to meet potential criticism of British products when they start to be marketed;
    - The HTA Observer reported a paper on whether stem cell lines, rather than donors, should be tested was due to be reviewed by the Committee for Advanced Therapy;
    - Doubts were raised whether suitable methods for such testing exist;
    - Some provisions of the Tissue and Cells Directive 2004/23/EC do not fit the case for stem cells;
    - Consideration of the type/quality of reagents used to cultivate cells is also needed, again with a view to potential criticism of British products in future.
    - There are similar issues in microbiology.
    - It was noted that there are UK regulatory authorities for human tissue and cells, medicinal products and medical devices, and SaBTO must not step into such bodies' remits. However, the MHRA/HTA paper will enable SaBTO to understand the regulatory framework, including where the regulators have work in hand. SaBTO will then be able to consider whether it needs to undertake any further work itself; or whether members with pertinent expertise might be able to contribute to the work of other bodies.
- The threat to the sufficiency of the blood supply which could result if large numbers of donors are deferred due to geographical spread of West Nile Virus

infections, since the EU Directive requires deferral of donors returning from affected areas rather than testing of donations.
    - The MHRA Observer reported they planned to share a position paper with the EU on the possible alternative of NAT testing donations for West Nile Virus.
- Consideration of the restrictions on MSM donors of tissues and organs.
    - The Secretariat reported this had been discussed within DH.
    - It was noted that this subject would be reviewed by JPAC in the near future. It was felt that SaBTO needed to work with JPAC in making a decision as to whether this issue should be reviewed by a small shortlife working party of SaBTO.

11.3 Action 15/06: SaBTO members to suggest any other topics for consideration.

Item 12: SaBTO Annual Report

12.1 It was agreed that a relatively brief report could be a useful vehicle to publicise SaBTO's work and its recommendations in a large number of different areas.

12.1 Action 15/07: Secretariat to draft an Annual Report for consideration by SaBTO.

Item 13: Any other business

13.1 It was noted that SaBTO's recommendations are not always disseminated sufficiently widely, despite a significant consultation process. An example was given of the lack of knowledge within certain microbiology laboratories concerning the recently updated Guidance on the Microbiological Safety of Human Organs, Tissues and Cells Used in Transplantation. Members of SaBTO and the Secretariat briefly reviewed the management of promulgation of some of the recent SaBTO recommendations. It was felt that this action had been appropriate but that all measures must be taken in the future in an attempt to make sure that SaBTO recommendations penetrate throughout the NHS.