ADVISORY COMMITTEE ON THE MICROBIOLOGICAL SAFETY OF BLOOD AND TISSUES FOR TRANSPLANTATION
MINUTES OF MEETING: 22 OCTOBER 2002
ROOM 102/124A, SKIPTON HOUSE

Chair: **Dr Vicki King**
Members:
Dr Cant
Dr Dash
Dr McClelland
Professor McMaster
Dr Perry
Dr Robinson
Dr Warren
Dr Wyatt
Professor Zuckerman

Observers:

Mr Stephen Lee	-	MDA
Dr Joyce Lawrence	-	MCA
Dr Lincloln Tsang	-	MCA
Mr Charles Lister	-	DH
Dr Peter Doyle	-	DH
Dr Philippa Edwards	-	DH
Dr John Stephenson	-	DH
Dr Peter Bennett	-	DH
Mr André Hare	-	DH
Miss Lynda Ewing	-	DH
Dr Aileen Keel	-	Scottish Executive
Dr Miriam McCarthy	-	Northern Ireland
Dr Tony Napier	-	Welsh Blood Service

Secretariat: Robert Finch, Linda Lazarus and Sara Johnston

ITEM 1: WELCOME AND APOLOGIES FOR ABSENCE

1. Members were informed that as Dr Troop was unwell, Dr King would be acting as Chair for the meeting. The Chair welcomed Professor Gordon-Smith, Dr Wallis and Dr Norfolk from the National Blood Transfusion Committee; Dr Napier from the Welsh Blood Service and Dr Miriam McCarthy from Northern Ireland.

2. Apologies were received from Dr Gorst, Dr Mortimer and Dr Doherty (Northern Ireland).

ITEM 2: MINUTES OF THE MEETING ON 25 JUNE 2002

3. The minutes of the last meeting had been circulated to members. The minutes were agreed subject to a correction on page 8, first paragraph, last line: "Scottish Office" to read "Scottish Executive".

Action 1: Secretariat to circulate list of attributed actions shortly after each meeting, ahead of the full minutes, as a reminder to Members of their designated actions.

ITEM 3: MATTERS ARISING

3.1 Safety of Blood Leaflet

i. ***EAGA Secretariat letter to Terrence Higgins Trust - MSBT 28/1 (Information paper)***

4. Members were circulated a copy letter from the Expert Advisory Group on AIDS to the Terrence Higgins Trust responding to comments and suggestions about the blood safety leaflet. The Trust was invited to join a new writing group chaired by NBS. Members were informed that a representative from the Commission for Racial Equality had also been invited to join the group and that work was already under way on a leaflet targeted at gay men to explain the reason for the deferral criteria.

ii. ***NBS update on the paper on blood donations and gay men***

5. NBS informed the Chair that an updated paper on blood donor deferral was available and would be forwarded to the Secretariat for circulation to EAGA and MSBT members.

Action 2: NBS to forward the update on the blood donor deferral paper to the **Secretariat** for circulation to Members and EAGA.

3.2 Storage of serum samples

6. NBS and PHLS advised that information on costs on storage would be provided. NBS guidelines (Red Book 5th edn) state that archived blood samples are kept for 11 years for lookbacks and stem cells for 15 years (post harvest). The British Association of Tissue Banks recommends storage of archives for 11 years. Samples from blood donors are stored for a minimum period of 2 years, but this is under review. The Association is already complying with the draft EC Directive on Quality and Safety of Organ and Tissue Banks.

7. Members agreed that while there were legal arguments against keeping archives, there were clinical governance arguments for doing so. In the case of vCJD, archives might need to be stored much longer (e.g. 30 years). It would be very costly to store archive samples of blood donations for 11 years, as there are 2.2 million donations per annum. This is an important topic for the new Cell, Organ and Tissue safety subgroup of MSBT (see Action 14) to look at in greater detail.

3.3 Screening for HTLV - Tissue and Organ donors – MSBT 28/6

8. Members noted that the Department of Health had sent a letter **(MSBT 28/2 Information paper)** on 8 October 2002 to all Directors of Tissue banks, NBS and

UK Transplant. The letter requested that testing of all new tissue donors for HTLV should start as soon as possible and that any stored tissue that had not been tested should, if issued, be clearly labelled as not tested for HTLV.

9. The Chair advised members that two action points from the last meeting had not been completed. The Secretariat hoped to receive advice from the Ocular Tissues Advisory Group and Organ Transplant Advisory Group of UK Transplant for discussion at the next MSBT meeting.

   [**Outstanding action from meeting 27**: Advice to be sought from Ocular Tissues Advisory Group and Organ Transplant Advisory Group of UK Transplant on whether all tissue (especially corneal) donors and organ donors should be tested for HTLV.]

10. NBS introduced a paper (MSBT 28/6) for this meeting on retrospective HTLV testing of stored tissues. The paper identified three types of stored tissue and three methods of tissue processing with different capacities for viral inactivation. MSBT endorsed the approach outlined in the paper as a pragmatic solution in the transition period, until routine testing all new tissue donors is established, with one amendment. Scarce/life-saving tissues that lack an archive sample should be issued but with an accompanying warning to clinicians and patients that HTLV testing has not been performed. It was recognised that some non-life-saving tissues would continue to be issued untested and that clinicians would prefer this to postponing operations due to lack of HTLV-tested tissue. Furthermore, a risk assessment, conducted centrally, should be provided with untested tissues.

11. MSBT was advised that there had been nine confirmed positive HTLV infections in blood donations since testing began in August 2002. These would be followed-up and lookbacks conducted as necessary. This was consistent with the prevalence found previously: overall, 1 in 50,000 ranging from 1 in 20,000 in London to 1 in 80,000 outside London.

    Action 3: NBS Tissue Strategy Group to be advised (by NBS member) that MSBT endorsed the approach outlined in their paper MSBT 28/6 with the addition that, for any tissues issued without HTLV testing, patients as well as clinicians should be alerted to the possibility of infection. In addition, centrally conducted risk assessment should be issued with the tissues.

3.4 vCJD transmission through blood components

12. At the last meeting members had been asked to forward any published or unpublished information that had been omitted from the Det Norsk Veritas (DNV) risk assessment of vCJD infectivity in blood and blood products to the CJD Incident Panel Secretariat. Some further papers and formal responses had been received. The DNV paper had also been seen by SEAC and the Committee on the Safety of Medicines (CSM) Biologicals Committee. The risk assessment on whole blood and red cells was supported but no consensus was reached on plasma derivatives. More reliable information was felt to be necessary on the yield of plasma from a single unit. DNV are revising their risk assessment.

13. Members were updated on the progress on the EOR paper presented at the last meeting "vCJD transmission through blood components; reconciling modelled risks with case evidence". Comments had been invited from independent experts and more data were awaited from NBS. The paper would then be put to the SEAC Epidemiological subcommittee and CSM Biological Committee.

3.5 Precautionary measures to mitigate risk of transmission of vCJD by blood and blood products

14. This item was covered under agenda item 5.

3.6 NAT HCV testing in the NBS

15. NBS updated members on progress made since the last meeting. The current contract with the test suppliers expires in March 2003 and the NBS Chief Executive had written to DH about the current high-risk situation. An OJEC tender process had been initiated to ensure continuity of test provision, but flexibility would be built into the new contract.

16. The Scottish Executive reported that it would be very difficult to stop HCV NAT testing given the acknowledged epidemic of HCV. It was also observed that NAT HCV testing of plasma was being done twice - first because imported pooled plasma is NAT tested at source and second when derivatives are made.

    Action 4: NBS to provide urgent information to DH on the pros and cons of continuing NAT HCV testing (including implications for the cost of a unit of blood) to inform a Departmental decision.

ITEM 4: FRESH FROZEN PLASMA – MSBT 28/1

17. The Chair welcomed the members of the National Blood Transfusion Committee (NBTC) who were attending for discussion on this item. Members were informed that the NBTC reports to the Chief Medical Officer for England and is the successor to the National Blood Users Group. The NBTC has a role in considering the delivery and safe usage of blood.

18. Members were informed that NBTC had considered the risks, efficacy and availability of different types of fresh frozen plasma (FFP) and had reached a conclusion on the preferred usage, which it intended to promulgate to users. It was important that MSBT and NBTC agreed a joint position. NBTC introduced their paper and outlined a number of safety issues associated with the use of FFP.

19. **Virus transmission:** Transmission of enveloped viruses (e.g. HIV-1 and 2, hepatitis C and B and West Nile fever virus) may occur with untreated FFP. Non-enveloped viruses such as hepatitis A and parvovirus B19 may also be transmitted. Hepatitis A risk was considered to be small because the donor was likely be too ill during the incubation period to donate. Reduction of viral transmission risk relies on a combination of careful donor selection, sensitive donation testing and viral inactivation (methylene blue [MB] or solvent detergent [SD]). Parvovirus is not inactivated by MB or SD treatment but neutralising

antibodies in the plasma pool could reduce the risk of transmission. Commercial SD-treated pooled plasma is screened for parvovirus.

20. **Prion transmission:** There is a theoretical but unknown risk of transmission of vCJD by FFP. The key step to mitigate this risk is sourcing plasma from a country with a low BSE incidence (e.g. USA). There is no screening test available for the presence of infective prion protein nor methods for large-scale inactivation. US-derived plasma, however, may carry a higher risk of viral infection (due to higher population levels of infection).

21. **Transfusion-related acute lung injury (TRALI):** TRALI is caused by the presence of antibodies to HLA antigens or antigranulocyte antibodies in donor plasma and is the most common transfusion-related adverse event reported to SHOT (around 20 cases annually). Onset of symptoms, which are identical to those of acute respiratory distress syndrome (ARDS), usually occurs within a few hours of transfusion and may require long periods on a ventilator in intensive care. FFP from parous females is implicated in the majority of cases of TRALI; the high mortality rate is compounded by the generally poor state of health of FFP recipients. Pooling plasma (to dilute harmful antibodies) and sourcing from untransfused male donors are both known to reduce the TRALI risk. There is evidence that the incidence of TRALI is rising in the USA and it is likely that cases of TRALI in the UK are underreported.

22. Members agreed with the recommendation that the most vulnerable group of FFP recipients (neonates and children born since 1996) should receive virally inactivated (MB-treated), US-sourced, single-unit FFP, ideally from untransfused male donors. It was noted that single-unit SD-treated plasma is not currently available.

23. Based on survival data for FFP recipients, it was proposed that the second category of recipients to receive US-sourced virally inactivated FFP should be extended to include those up to age 30. Age 16 was felt to be an artificial cut-off; the numbers of adolescents and young adults (ages 17-30) requiring FFP would approximately double the volume of FFP required, but the potential life years gained would be high.

24. Members recommended that this re-defined group of children and young adults (up to age 30) should also receive US-sourced virally inactivated FFP if funding and sufficient supplies were available. It was considered important to maintain a choice of products for clinicians to use i.e. pooled versus single-unit FFP. Either product would be acceptable for this second category of recipients.

Action 5: NBS to investigate whether 'male only' donors could be part of the specification (rather than a preference) for procuring US methylene blue (MB)-treated single-unit FFP as a measure to reduce the TRALI risk.

Action 6: NBS to consider the option of extending the age range for the second category of vulnerable patients (who should receive US-sourced FFP) to age 30, taking account of the survival data supplied by Dr Wallis.

Action 7: NBS to keep MSBT updated on the its work examining options for preventing TRALI associated with use of plasma and platelets.

Action 8: NBTC chair to forward to the Secretariat evidence from the literature (e.g. case reports from Neil Young at NIH) supporting a role for neutralizing antibodies in reducing transmission risk of parvovirus B19 from pooled FFP.

Action 9: Secretariat to ensure the chairman of the National Blood Transfusion Committee receives relevant extract of the minutes detailing the consensus reached by MSBT on sourcing of FFP.

ITEM 5: THE IMPLICATIONS OF vCJD FOR BLOOD SAFETY AND SUPPLY IN ENGLAND [MSBT 28/2]

25. Members were asked to consider paper MSBT 28/2 prepared by EOR in consultation with the NBS, reviewing potential measures to reduce the risk of transmitting vCJD via blood components (e.g. more extensive use of imported FFP and excluding blood component recipients from donating) and their interactions with other blood safety and supply issues.

26. A number of key factors remain unknown, such as the infectivity of vCJD in blood, the number of primary infections that have occurred and the length of the secondary incubation period. On the assumption that blood is infective, quite a number of secondary infections will already have occurred. Therefor risk-reduction strategies can only affect the minority of infections. The most robust measure for reducing vCJD risk was reducing blood use.

27. Considering the DNV scenario, many blood-borne secondary infections can be expected, of the same order or slightly more than primary infections, even when discounting individuals with a short life expectancy (2 years or less). Blood transmission could add substantially to the primary outbreak, with an estimated 1200 secondary infections for every 1000 primary infections. The DNV model assumes that blood is infective throughout the incubation period. However, if blood is only infective in the later stages, this could make a big difference to the estimates.

28. The infectivity of leucodepleted red blood cells remains uncertain. The DNV model assumes that transfusion of a single unit leads to certain infection. Because of the high volume of red cells transfused, if the model exaggerates the infectivity of this component, it will make a major difference to the estimates of secondary infections. Calculating the percentage of infections avoided provides the most robust analysis. Any transmission risk is proportional to the amount of blood used, e.g. a 10% reduction in blood use will achieve a 10% reduction in infections. Reducing blood use is the only guaranteed way to reduce transmission risk.

29. A number of risk reduction measures were considered:

- Procuring all platelets from apheresis: this would avoid the need for pooling products from 4 donors, thereby reducing risk of exposure to an infected donor (assuming quarter of a unit would be infective). The analysis is reasonably robust. The measure appears feasible and worth considering.

- Modify processing of red cells. Depending on the method of production, the infective dose can be above or slightly below 2 ID_{50}s. If below 2 ID_{50}s, then a substantial number of infections would be avoided. This is a relatively straightforward option, but the benefits are very dependent on the assumptions about infectivity of red cells.

- Importing FFP from a presumed vCJD-free source: risk calculation is reasonably robust as residual risk of infection if not zero will be small.

- Exclude previous component recipients. The effect would depend on the secondary incubation period and any impact would be reduced by importing all FFP – these are competing risk reduction measures.

- The use of accredited donors for specific groups would amount to redistribution of risk and result in ethical concerns. However, as precedents have already been set, this should not be an issue (e.g. CMV-screened blood for special risk groups). The estimates for reductions in secondary infections are dependent on the DNV model, which represents the worst case scenario.

30. It was reported that CMO's Better Blood Use campaign was being taken seriously but would take some time to impact on blood usage. A 2% reduction in red blood cell usage was projected for 2002 but FFP use had not decreased and platelet use was up slightly.

31. The SNBTS tabled a paper [MSBT 28/7] on the impact on the blood supply of a ban on donation by previously transfused individuals. vCJD presents a threat of unknown magnitude. Efforts to counteract vCJD must make blood safer and reduce patients' exposure to blood. The national Effective Use of Blood programme is committed to a 10% decrease in red blood cell use over 3 years. Deferring blood component recipients would be expected to results in a loss of 10-15% of donors and possibly a greater proportion of donations. It might be possible to maintain the current level by stepwise increases in efforts to recruit and retain donors. The paper focussed on improving current practice (e.g. reducing wastage) rather than relying on new blood-sparing techniques. The rapid introduction of a ban on previously transfused donors would cause an acute shortage of red cells and platelets. However, given adequate lead time (around 6 months) and commitment from all sides, the impact would be manageable. The introduction of a screening test for vCJD could have a similar impact on supply.

32. Relying on donor recall of whether and when they received blood components is an imperfect measure and could affect many more people. Older donors would be disproportionately affected, with a knock-on effect on platelet collection (more apheresis donors in older age group).

33. DNV is cautious about the effect of leucodepletion on infectivity of red cells. If the actual infectivity of red cells is much lower, this would dramatically reduce the number of secondary infections. Back calculations from the number of recipients of blood among the vCJD patient cohort leads to a low estimate of infectivity risk. More information is needed on survival rates of patients who received implicated blood. It is possible to reconcile the calculations by assuming carriers of vCJD are only infective towards the end of the incubation period.

    Action 10: SNBTS to provide information on the Effective Use of Blood Programme in Scotland to EOR to help develop the section of the paper considering the impact of appropriate use. EOR and SNBTS to harmonise calendar cut-offs for deferral in their models for predicting the impact of a ban on donations from transfused donors.

    Action 11: EOR/NBS to continue refining the options as set out in paper MSBT 28/2.

    Action 12: NBS to report back to MSBT on the risks, benefits and practicalities of the option to modify the processing of red cells to reduce vCJD risks.

ITEM 6: SCREENING BLOOD DONATIONS FOR vCJD [MSBT 28/3]

34. A DH official presented paper MSBT 28/3 which provided a chronology of discussions that had been ongoing between DH and the NBS around establishing facilities for evaluating potential vCJD blood screening assays. A research proposal was submitted and peer-reviewed. Although the majority of reviewers agreed on the importance of NBS undertaking contingency planning and that DH should assist with that process, there were concerns, backed by peer reviewers' comments, that the proposal did not represent good value for money and might be over-ambitious.

35. To take the work forward, MSBT agreed that a small steering group should be established, involving all the key stakeholders (e.g. NIBSC, PHLS, the other UK blood services and MDA) to ensure that the final design meets the needs of all interested parties. The steering group's remit will include supporting the design of a proposal and its implementation.

    Action 13: Members to forward their suggestions to the Secretariat of organisations that should be consultees to the steering group comprising key stakeholders.

ITEM 7: UPDATE ON NEW BLOOD-BORNE VIRUSES [MSBT 28/4]

36. TT virus (TTV) was isolated from a Japanese patient in 1997 (and is named after the patient i.e. TT does not stand for transfusion-transmitted). It displays remarkable diversity with numerous genotypes arising through recombination. TTV replicates in many tissues, particularly the liver, and is shed into blood and faeces. It is found in 20-90% of the general population but there is no published evidence that it causes liver disease in humans (it may be commensal), but

continued monitoring remains important. In chickens it causes anaemia; zoonotic or digestive acquisition are possible. TTV is not an enveloped virus and is therefore not inactivated by solvent detergent or methylene blue treatment.

37. Other viruses possibly related to TTV include TTV-like minivirus (TLMV) and SEN virus. At least eight genotypes of the SEN virus have been identified (SENV-A – H). Some claim an association between SENV-C, D and H genotypes and post-transfusion hepatitis. However, SENV does not appear to cause liver damage or identifiable disease in man, so these should not be regarded as candidate hepatitis viruses.

ITEM 8: EUROPEAN BLOOD DIRECTIVE

38. Members were updated on the progress of the draft Directive. All issues that had been of concern had been resolved. Formal adoption of the Directive was expected by the end of the year (2002).

ITEM 9: UPDATE ON WEST NILE FEVER AND BLOOD TRANSFUSION [MSBT 28/5]

39. To date in the current US epidemic there have been over 2500 cases of West Nile virus (WNV) reported, resulting in over 100 deaths. US blood services are deferring donors who are not in good health. Similar deferral would apply in the UK, so there is no case for excluding donors who are well and have recently travelled to the US. WNV is an enveloped virus and current pathogen inactivation should eliminate risk of transmission through blood products derived from US-sourced plasma. There have been no identified cases of WNV in the UK in humans or animals. BTSAG and SACCTI are keeping the issue under review.

ITEM 10: REVISION OF MSBT REMIT [MSBT 28/8]

40. A paper was tabled outlining the need to revise the MSBT's remit. The Secretariat identified the need for a wider range of expertise to advise on vCJD issues, non-microbiological aspects of blood safety such as TRALI and others identified in the SHOT report. A separate group would be established, initially as a subcommittee, to look at issues around the transplantation of cells, tissues and organs. Adequate cross-representation and co-ordination between the two groups would be necessary to ensure consistent advice.

    Action 14: Secretariat to instigate the changes necessary to establishing a 'Blood Safety Advisory Group' and a subcommittee (with some joint membership) to advise on cell, tissue and organ safety issues.

ITEM 11: ANY OTHER BUSINESS

41. The date of the next meeting is Tuesday 25 February 2003.

ACTION POINTS

Outstanding action from meeting 27: Peter Doyle to seek advice from Ocular Tissues Advisory Group and Organ Transplant Advisory Group of UK Transplant on whether all tissue (especially corneal) donors and organ donors should be tested for HTLV.

Action 1: Secretariat to circulate list of attributed actions shortly after each meeting, ahead of the full minutes, as a reminder to Members of their designated actions.

Action 2: Dr Robinson to forward Kate Soldan's update on the blood donor deferral paper to the **Secretariat** for circulation to members of MSBT and EAGA.

Action 3: Dr Robinson to report back to the NBS Tissue Strategy Group that MSBT endorsed the approach outlined in paper 28/6 from Dr Warwick *et al.* with the addition that, for any tissues issued without HTLV testing, patients as well as clinicians should be alerted to the possibility of infection. Centrally conducted risk assessment should be issued with the tissues.

Action 4: Dr Robinson and NBS colleagues: to provide urgent information to Charles Lister on the pros and cons of continuing NAT HCV testing (including implications for the cost of a unit of blood) to inform a departmental decision.

Action 5: Dr Robinson to investigate whether 'male only' donors could be part of the specification (rather than a preference) for procuring US methylene blue (MB)-treated single-unit FFP as a measure to reduce the TRALI risk.

Action 6: NBS (Lorna Williamson) to consider the option of extending the age range for the second category of vulnerable patients (who should receive US-sourced FFP) to age 30, taking account of the survival data supplied by Dr Wallis.

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Action 9: Secretariat to ensure the chairman of the National Blood Transfusion Committee receives relevant extract of the minutes detailing the consensus reached by MSBT on sourcing of FFP.

Action 10: Dr McClelland (SNBTS) to provide information on the Effective Use of Blood Programme in Scotland to EOR to help develop this section of the paper. EOR and SNBTS to harmonise calendar cut-offs for deferral in their models for predicting the impact of a ban on donations from transfused donors.

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Action 13: Members to forward their suggestions to the Secretariat of organisations that should be consultees to the steering group comprising key stakeholders (UK blood services, PHLS, NIBSC, MDA) whose remit will involve supporting the design of a proposal and its implementation.

Action 14: Secretariat to instigate the changes necessary to establishing a 'Blood Safety Advisory Group' and a subgroup (with some joint membership) to advise on cell, tissue and organ safety issues.