MEETING OF THE ADVISORY COMMITTEE ON THE MICROBIOLOGICAL SAFETY OF BLOOD AND TISSUES FOR TRANSPLANTATION

MINUTES OF 32nd MEETING: THURSDAY 11 MARCH 2004 AT AVONMOUTH HOUSE, 6 AVONMOUTH STREET, LONDON SE1

Chair: Professor Lindsey Davies

Members:
Dr Dash
Dr McClelland
Dr Mortimer
Dr Robinson
Dr Warren
Dr Wyatt
Professor Zuckerman
Dr Stainsby

Observers:

Dr Peter Bennett	-	DH
Mr Armin Kirthi-Singha	-	DH
Dr Philippa Edwards	-	DH
Mr Richard Gutowski	-	DH
Dr Denise O'Shaughnessy	-	DH
Dr John Stephenson	-	DH
Dr Peter Boyle	-	DH (part)
Triona Norman	-	DH (part)
Miss Kate Balmer	-	MHRA
Mr Bob Stock	-	Scottish Executive
Dr Miriam McCarthy	-	Northern Ireland
Dr Richard Jones	-	Welsh Blood Service

In attendance:

Dr Lorna Williamson	-	National Blood Service

Secretariat: Dr Linda Lazarus and Miss Zubeda Seedat

Agenda Item 1: Introductions and apologies

1. The Chair welcomed members and observers to the meeting, in particular Dr Stainsby, National Medical Co-ordinator for the Serious Hazards of Transfusion (SHOT) surveillance scheme, who was attending her first meeting. Apologies had been received from Dr Cant, Dr Perry, Dr Gorst and Dr Keel.

Agenda item 2: Minutes of the previous meetings

Minutes of 22 October 2003 (30th) meeting

2. Comments were invited on the accuracy of the minutes. The minutes of the 30th meeting were agreed with the following amendment to paragraph 12 (second sentence changed, third omitted):

> SNBTS reported that, during 2002, there had been 7 HIV positive donations detected among donors in Scotland, 5 of these in repeat donors. This contrasted with 1999 (2 donations), 2000 (none) and 2001 (1 donation).

Minutes of 22 January 2004 (31st) meeting

3. The minutes were agreed, with the following amendment to paragraph 5, 2nd sentence:

> At that time, the risk of vCJD transmission by blood transfusion had been a theoretical one. On the balance of risks (to the blood supply and public health), the need to defer previously transfused donors could not be ruled out.

Agenda Item 3: Matters arising

4. **Action 21(29)**: MSBT had asked the Health Protection Agency to set up a working group to develop standard operating procedures for centres providing microbiological screening of tissue and organ donors. The Secretariat reported that the working group held their first meeting on 23 February 2004 and would report back to MSBT in due course.

5. **Action 1(30):** NBS and EOR had been commissioned to review the risk assessment of HIV and other blood-borne viruses against the current donor selection criteria. A paper would be provided to MSBT before the end of the year.

6. **Action 2(30):** NBS reported that the reliability of their HIV testing was superior to that reported in an American comparison of antibody and NAT testing. In Scotland, where HIV NAT has been introduced, there have been no discordant (i.e. NAT positive, antibody negative) results, which would make the rate of missed positives far lower than the US figure of 1 in 6000. NBS experience of HIV testing in parallel (NAT and antibody) has also provided reassuring results.

7. **Action 7(30):** The Secretariat reported that work on reviewing/revising MSBT had been deferred, but it was hoped that this would be progressed later in the year.

8. **Actions 4, 10 & 13(29):** A member of the transplant policy team confirmed that HTLV testing of stored tissues was being taken forward and, as an interim measure, would be labelled according to whether they have been tested or not. In addition, UK Transplant had issued guidance on West Nile Virus deferral criteria for tissue donors and advice relating to organ donations.

Agenda Item 4: Exclusion of previously transfused donors

9. Members were informed that Ministers had accepted MSBT's advice to exclude donors who had received a transfusion since 1980. The new donor exclusion criterion would take effect from 5 April 2004. An announcement would be made in Parliament around 3 weeks before the implementation date (and simultaneously by Health Ministers in Wales, Scotland, and Northern Ireland), to allow the blood services time to prepare for possible shortages and to amend their procedures.

Agenda Item 5: Appropriate use of blood

10. At the last MSBT meeting, the Committee had discussed implementation of the Health Service Circular 2002/009 *Better Blood transfusion – Appropriate Use of Blood.* Members were informed that their views about giving greater prominence to *Better Blood Transfusion* had been made known to Ministers and Senior Officials. A strategy document was being drafted which aimed to re-invigorate implementation of *Better Blood Transfusion.* This would be a vehicle for highlighting good work to date and disseminating good practice.

11. MSBT discussed some proposals. These included auditing the supply and consumption of blood in hospitals, comparing usage by the same specialty in different hospitals and economic analyses to underpin cost comparisons with cell salvage. It was felt that a major investment in IT would be needed to gather meaningful data on blood usage. Other steps that could be taken to encourage appropriate use of blood include devising a performance framework, engaging with Trust Chief Executives and manipulating the price of blood.

> **Action 32(1):** Members were invited to forward their comments for the strategy document to the Secretariat.

Agenda Item 6: Reducing plasma in red cell components – MSBT 32/1

12. EOR had examined the relative risks of transmitting vCJD through transfusion of red cell products manufactured in different ways. While standard whole blood packs have a plasma residue of up to 25 ml, this might be reduced to 7-10 ml by 'bottom and top' (BAT) pack processing. Using standard processing, plasma content could not be reduced below around 18 ml. EOR have begun to look at the implications of scaling up BAT production from the current 40% level to 100% of donations. Besides the additional costs associated with purchasing the packs and filters, there is a potential clinical impact because BAT production results in loss of around 30-40 ml of red cells. For a minority of transfusion-dependent patients, such a cell loss would result in exposure to a higher number of donors. More donors might also need to be recruited to compensate for the loss. NBS will look at ways to limit this red cell loss.

13. The other area for consideration was plasma-reduced red cells used for exchange transfusion in neonates and children. This product has been preferred, because the red cells are not suspended in additive solution, despite the lack of evidence

of adverse effects associated with additive solution. Continued use of plasma-reduced red cells (with their relatively high plasma content) for this most vulnerable group of patients is anomalous given that FFP is being imported to reduce exposure to UK plasma of children born after 1 January 1996.

Action 31(2): NBS to progress work on red cell processing and report back to the next MSBT meeting.

Agenda Item 7: Proposals to increase the number of platelet doses through apheresis donation procedures – MSBT 32/2

14. The NBS presented its two-part strategy for increasing the proportion of platelets prepared from apheresis (as opposed to pooling platelets recovered from four whole blood donations) as a vCJD risk reduction measure. Apheresis production could be raised from the current 38% to 50% of the total platelet supply within 18 months by maximising the potential of existing apheresis units, and by introducing apheresis into current whole blood only static units (Part 1). A further increase in platelet supply from platelet apheresis procedures would probably require a mix of locating and establishing more static sites and moving apheresis services into the mobile collection environment (Part 2).

15. A summary of current platelet procurement activity and apheresis donor panel characteristics was provided at Annex A of MSBT 32/2. There was some concern that there were fewer active apheresis donors than the actual numbers on the panel and further analysis would be undertaken. To make apheresis platelets a more cost-effective option, the NBS has moved towards only accepting donors able to donate a double adult dose on each occasion. This requirement limits the number of eligible donors, who also need to be highly motivated because of the time commitment for completing the donation and attending regularly (e.g. 6 times a year). A number of issues around recruiting and retaining apheresis donors also needed to be explored. The NHS was suggested as a target for recruitment.

16. MSBT supported implementing Part 1 of the strategy to maximise output of apheresis platelets provided costs could be met from existing funding. Members also endorsed the NBS's recommendation to undertake further in-depth analysis for Part 2 (expansion to new static sites and moving apheresis into the mobile environment), and report back progress to MSBT.

Action 32(3): NBS to progress work for increasing the proportion of platelets provided from apheresis donations (Part 1), and undertake further work on expansion of new sites (Part 2) and report back to MSBT.

Agenda Item 8: Importation of US plasma

(i) Update on vCJD risks – MSBT 32/3 (information paper)

17. MSBT 32/3 summarised the main conclusions of previous analyses by EOR on the vCJD risk reduction that could be achieved through importation of FFP. The

recent discovery of a BSE-infected cow in the US had not altered the conclusions, as the analysis had never assumed a zero prevalence of BSE (or vCJD) in the US. Continued use of UK-sourced FFP could act as a significant multiplier of the primary vCJD infection. Even taking a pessimistic view, the risk associated with US plasma is at least 100 times lower than for UK plasma. From a vCJD point of view, even a pooled US product would be preferable to unpooled UK FFP.

18. Uncertainty remains about the number of people who may be incubating the disease (regardless of whether they go on to develop clinical disease) and the absolute risks associated with blood components. Some models suggest there may be only 40 more UK cases of vCJD, whereas extrapolation from the retrospective appendix study (which found roughly a 1 in 4,000 prevalence in the age group covered) suggests a figure of 5-6000 cases. For the general population, it may be reasonable to consider prevalence scenarios ranging from 1 in 100,000 to 1 in 1,000. Transfusion experiments in sheep found that animals at both clinical and pre-clinical stages of disease can transmit. A prospective tissue study is under way (collection of tonsil specimens has been slow), but it will take 2-3 years before good data are available. Tonsils from patients aged 16-29 will be the primary focus, although the archive will include tissue from individuals of all ages.

19. Of the three potential target groups for receiving imported FFP (described in paragraph 7 of the paper), agreement had been reached to import US plasma for neonates and children born after 1 January 1996. NBS reported that the first shipments were undergoing pathogen inactivation (methylene blue, MB) and non-UK MB-FFP would be issued for neonates from the end of March 2004 and for all children in the group by the summer, once adequate stocks had built up.

20. A further consideration is to reduce overall usage of FFP to indications for which it is known to be effective. A systematic review of randomised controlled trials involving the use of FFP was due to be published shortly[1]. This provided little evidence of clinical effectiveness of FFP other than for plasma exchange in thrombotic thrombocytopenic purpura (TTP). This finding was reflected in the British Committee for Standards in Haematology guidelines on FFP use, which need to be promoted to ensure greater consistency in clinical practice. A plea for research on the use of FFP and to demonstrate the safety and efficacy of alternatives, such as fibrinogen, was made by NBS.

(ii) Extending the provision of non-UK plasma to include other high-risk groups – MSBT 32/4

21. NBS presented MSBT 32/4, which explored the feasibility and financial implications of extending non-UK sourced FFP to a second tranche of patients including children born before 1 January 1996 and up to age 16 and high-use adults e.g. those with TTP. In terms of cost-effectiveness, life expectancy for

[1] Stanworth SJ *et al.* Is fresh frozen plasma clinically effective? A systematic review of randomized controlled trials. *Br J Haematol* 2004; **126**: 139-52.

the older children is still good, albeit shorter than for those in the first tranche. The high-user adults also have good life-expectancy (given the treatment). For this group, there are issues to do with acceptable individual risk as well as QALYs saved within the population.

22. The NBS option appraisal considered: (i) extending procurement of voluntary non-remunerated male plasma from non-UK sources with subsequent methylene blue (MB) treatment in-house and (ii) procurement of solvent detergent (SD)-FFP. (A third option, to contract out MB treatment of imported plasma, was ruled out as being non-viable unless meeting 100% of NBS's FFP needs through importation was under consideration.)

23. NBS estimated that an additional 2.5 tonnes of plasma per year would need to be imported to supply the older children (on top of the 2 tonnes already imported for younger children). This allowed for their greater numbers and larger body size. Estimating the volume required for adult use is less straightforward; Octapharma (the sole supplier of SD-FFP) claim to supply 23,000 units per year to hospitals, of which >90% is likely to be used for TTP. A further 6.5-13.8 tonnes of FFP would probably be needed on top of this because although the number of TTP patients is small, they may need as much as 3 litres of FFP per day for several weeks. Further work is being undertaken to refine this estimate.

24. NBS had ascertained that sufficient volumes of both SD-FFP and raw plasma for MB treatment are available from US suppliers. Clinical preferences and uses were being sought through a survey of the top 20 users of paediatric FFP in England. As some (younger) children are already receiving MB-FFP, this is likely to be the preferred option for all children. There are, however, valid clinical differences between the products. SD-FFP for example, has a von Willebrand factor (vWf) profile like cryo-supernatant and is low in some anti-clotting factors. SD-FFP is firmly favoured for treating TTP as there is little experience of using MB-FFP.

25. From the options analysis, NBS concluded that there was little difference in either cost or time to implementation between importing MB-FFP or SD-FFP for both patient populations or having a mixed economy of MB-FFP for children and SD-FFP for TTP patients. However, the availability of male-only plasma may become a limiting factor should the option of MB-FFP for all users be pursued.

26. MSBT asked the NBS to undertake some further work, incorporating the results of the key users survey and making clear what the costs and benefits of extending the importation of FFP would be or of not doing so. Also to consider what new risks might be introduced and the diminishing returns for the older children group (as those born after 1 January 1996 approach their sixteenth birthdays).

Action 32(4): NBS and EOR to undertake further work on the options so that MSBT can reach an informed decision about extending the availability of imported FFP to other patient groups.

27. A draft professional letter setting out advice for clinicians on the use of single-unit MB-treated FFP was tabled. It is intended that this will be issued to coincide with non-UK MB-FFP becoming available from the NBS for patients born after 1 January 1996. Members were invited to submit written comments to the Department.

Action 32(5): Members to submit comments on the draft professional letter to the Secretariat.

Agenda Item 9: Bone donation

(i) vCJD infection risks of bone products: a comparative assessment – MSBT 32/5

(ii) NBS overview to the EOR bone risk assessment paper – MSBT 32/6

28. At NBS's request, EOR had undertaken an analysis of the vCJD risk from transplanted bone products. The conclusions reached had been endorsed by the Spongiform Encephalopathy Advisory Committee (SEAC).

29. NBS Tissue Services are the largest, but not the only, supplier of bone products to England and North Wales. Most bone is ground up and used as 'filler' in revision hip surgery (i.e. replacement of worn-out artificial hips). Most of the patients are therefore elderly, but tend to be those with better post-operative survival prospects. In consequence , they might well live long enough to develop symptoms of vCJD if infected. There are also a small number of patients under 20.

30. Bone may be sourced from living or cadaveric donors. Either might be incubating vCJD and therefore are a potential source of transmission. EOR identified a number of factors that needed to be considered in the vCJD risk assessment including the infectivity of bone tissue itself (and the associated blood and marrow), the ability of processing to reduce any infectivity and the impact of pooling donations from several donors.

31. The expert view on the infectivity question is that marrow is likely to be at least as infective as blood and it is possible that bone may carry infectivity. In the latter case, because of the substantial volume used in bone implants, the risk could outweigh that from residual blood or marrow (around 15-20 ml per minimally processed femoral head). In addition to the absolute risk of infection, higher doses may reduce the incubation time to developing symptoms.

32. Processed bone supplied by NBS Tissue Services, either from a single cadaveric donor or pooled from living donors (typically 17), is ground up (morcellised), thoroughly washed and then freeze-dried or frozen. Most is also gamma-

irradiated after processing: this may reduce prion infectivity by around 1 log though experimental evidence is based on higher levels of radiation. This processing also removes at least 99% of blood and marrow. Alternatively, individual femoral heads may be collected and stored locally by surgeons, ground up in the operating theatre at the time of the recipient's operation either with no further processing or with more limited washing and/or irradiation.

33. In terms of vCJD risk, unless bone contains a very high dose of infectivity, processing to remove blood and marrow is likely to reduce the risk. In high infectivity scenarios, pooling of material from a number of donors is disadvantageous as it increases the risk of an infected donation being included in the pool (i.e. the dilution effect is unable to reduce infectivity to below the threshold [2 x ID_{50}] required for certain infection of the recipient).

34. EOR's assessment concluded that the most robust processing options for vCJD risk reduction are those that use cadaveric sources, remove bone and marrow without pooling, or achieve high-efficiency washing of single femoral heads. However, there are insufficient cadavers to meet demand, there are limited synthetic alternatives available, and many surgeons prefer material from living donors.

35. Some valuable points were made about revision grafting and ways in which demand for bone might be reduced. It was observed that revision arthroplasty is often postponed and that such delays increase the likelihood that bone grafting will be needed. As infection is often the underlying reason, lowering sepsis rates could be key. Bacteriological risks could be reduced by removing and washing donated bone in clean air theatres and using ethylene for terminal sterilisation. There is also potential for the biofilm created on bone by water treatment to be colonised by bacteria. Information on the sepsis rates associated with different bone products was needed to feed into the risk assessment.

36. The EOR risk assessment is based on individuals having a single arthroplasty, but those with rheumatoid arthritis may undergo as many as six procedures and those with osteoarthritis have a predictable risk of needing both hips replaced (so pre-depositing femoral heads for future use might be a risk reduction option).

37. It was clear from the discussion that a wide range of issues need to be considered in devising practical risk reduction strategies for bone products and that expert input would be required. Issues to consider include likely infectivity in donors of different age groups (cadaveric donors being younger and possibly higher risk than living donors), the possibility of importing bone, the mechanical properties of different bone products, convenience of local supply versus bone bank, reducing bacterial risks and maintaining adequate supplies to meet surgical need. One proposal for improving safety was to perform biopsies on cadavers to test for vCJD with quarantining of retrieved material until testing had been completed. Technical difficulties with performing brain biopsies in the mortuary setting, patchy distribution of prions in the brain and lack of sensitivity of the alternative tonsil assay were some of the obstacles identified.

38. It was agreed that a time-limited subgroup of MSBT should be established, involving appropriate experts (e.g. the Hip Society, British Orthopaedic Society) to advise on how vCJD risk may best be reduced.

> **Action 32(6):** Blood Policy Team to set up the expert subgroup to consider practical risk reduction strategies for bone products. Subgroup to report back to MSBT.

Agenda item 10: Tissue donation

(i) Risk of vCJD transmission via tissue transplantation – MSBT 32/7

39. Having prioritised the bone risk assessment, because bone implants are by far the most numerous, NBS and EOR have begun to examine vCJD risks associated with other tissues used for transplantation. However, there is scarce evidence of whether particular tissues might carry vCJD infectivity and sensitive tests will be needed to rule out infection given the relatively large masses of tissue transplanted.

40. EOR considered three levels of risk:
    (i) Individual risk: what is the risk for a recipient of being infected if the donor has vCJD (CJD Incidents Panel territory)?
    (ii) Group risk: does the fact of having been a tissue recipient (regardless of the donor's status) increase the risk of infection sufficiently to warrant extra precautions to reduce onward transmission?
    (iii) Public health risk: could person-to-person transmission via tissues act a significant multiplier of the initial outbreak, thereby possibly perpetuating it?

41. The table (pgs 6-7) summarises the available information on the scale and range of current tissue transplant practice, including batching issues and typical ages of donors and recipients. Assigning the relative infectivity of different tissues was based on a combination of expert judgement, commonsense and available evidence. Information is needed on matters such as clinical need, allogeneic versus autologous transplants and whether importing tissue might be practicable (if risk high enough and quantity needed small enough) to inform risk management decisions.

42. The paper concluded that there was insufficient scientific evidence on which to base a quantitative risk assessment of vCJD transmission via tissues. Nevertheless, enough information had been gathered for a consideration of precautionary measures to be appropriate.

(ii) Proposals for action from the NBS Tissue Services – MSBT 32/8

43. NBS presented a paper discussing options for action with regard to previously transfused tissue donors. Currently, NBS Tissue Services retrieve tissue from

around 350 cadavers and 4000 surgical donors per year. Deferring previously transfused tissue donors would result in significant losses (16-33% of surgical donors and 38-52% of cadaveric donors). UK Transplant advised that such a ban would exclude all multi-organ donors as a source of tissue donations and cadaveric donors who died traumatically and required emergency transfusions.

44. Options to compensate for a shortfall in available tissue if deferral were introduced include: importing tissues from low incidence countries; collecting more femoral heads from additional sites; relaxing some of the selection criteria for cadaveric donors (e.g. raising the upper age limit for donation from 60; extending the retrieval time limit from 24 to 48 hours; using NAT testing to reduce deferral windows for those with potential blood-borne virus exposures); reserving low-risk donations for specific recipients and minimising the use of tissue allografts.

45. MSBT agreed that further work was needed and that an expert subgroup should be set up to consider practical risk reduction strategies for tissue transplants.

> **Action 32(7):** Blood Policy Team to set up the expert subgroup to consider the practical risk reduction strategies for tissue transplant. Subgroup to report back to MSBT.

Agenda item 11: Any other Business

46. There was no other business.

Agenda item 12: Date of the next meeting

47. The next meeting will be held on 15 June 2004. [This meeting was subsequently cancelled and an extraordinary meeting scheduled for 29 June 2004.]

ACTION POINTS

Action 32(1): Members were invited to forward their comments for the strategy document to the Secretariat.

Action 31(2): NBS to progress work on red cell processing and report back to the next MSBT meeting.

Action 32(3): NBS to progress work for increasing the proportion of platelets provided from apheresis donations (Part 1), and undertake further work on expansion of new sites (Part 2) and report back to MSBT.

Action 32(4): NBS and EOR to undertake further work on the options so that MSBT can reach an informed decision about extending the availability of imported FFP to other patient groups.

Action 32(5): Members to submit comments on the draft professional letter to the Secretariat.

Action 32(6): Blood Policy Team to set up the expert subgroup to consider practical risk reduction strategies for bone products. Subgroup to report back to MSBT.

Action 32(7): Blood Policy Team to set up the expert sub-group to consider the practical risk reduction strategies for tissue transplant. Subgroup to report back to MSBT.