CONFIDENTIAL TO COMMITTEE MEMBERS MSBT 16/

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

MINUTES OF THE MEETING HELD ON THURSDAY 29 OCTOBER 1998

Chairman:

Dr J S Metters

Members present:

Dr D W Gorst
Dr D B L McClelland
Dr R J Perry
Dr A Robinson
Dr T J Snape
Dr T Wyatt
Dr A Zuckerman

Observers
Dr A Keel
Ms E de Zoete
Dr H Nicholas
Dr F Rotblat
Dr N Wingfield

Secretariat
Dr M McGovern
Ms G Skinner

APOLOGIES FOR ABSENCE

1. Apologies had been received from Dr Cant, Dr Mairs, Dr Mortimer, Dr Warren and Dr Smith.

MINUTES OF THE FIFTEENTH MEETING HELD ON 4 JUNE 1998

2. The minutes were agreed subject to the following amendments:

para 6 to say that Octaplas was pooled from about 1,500 donors

para 24 to refer to the fact that the patient had donated eye tissue as well as cornea

nvCJD to be used instead of vCJD.

MATTERS ARISING

Leucodepletion

3. Dr Robinson reported that by January there would be 100% leucodepletion of platelets, through increasing apheresis collection. 10% of red cells would be leucodepleted by December. Structural work related to leucodepletion was needed in the London and South East zone, and the necessary approval had been sought from the Department. The Birmingham blood centre was at present piloting 100% red cell leucodepletion, to pinpoint potential difficulties. The most difficult aspect was in the statistical process control, and setting the parameters of the specification to determine the point at which a unit would be withdrawn because the white cell count was too high. There was a possible concern about the quality assurance and standards of the filter manufacturers. There was a huge demand for filters and the manufacturers had increased their capacity. They had passed audit, but this needed to be watched. Overall, however, the NBA anticipated reaching 100% leucodepletion by October 1999.

4. Dr McClelland advised that Scotland was aiming to leucodeplete the red cells first, platelets second. They anticipated full red cell leucodepletion by April 1999, and full leucodepletion by the end of the summer. They were still debating the use of apheresis for platelet procurement, because of the costs.

5. Dr Wyatt would enquire about the position in Northern Ireland, and the Secretariat would do the same in respect of Wales.

6. Dr Robinson flagged up a number of research projects being taken forward under the NBA's research strategy group for nvCJD. These included a study on the wider benefits of leucodepletion, and on the white cell counting methodology.

7. Dr Metters advised that the US was taking a close interest in the UK's nvCJD related activity. At the FDA's request he would be speaking to the FDA's TSE Advisory Committee on 18 December to explain the UK policy on leucodepletion and the importation of non-UK plasma. He would confine his presentation to information that is in the public domain.

8. Dr Wingfield advised that there were textual refinements to the risk assessment and he would be meeting Philip Comer that afternoon to review progress. There was a commitment to publish the report but no date had been set for this as yet.

HTLV1

9. Dr Metters reported that Ministers had carefully considered routine HTLV1 testing and had decided it should not be introduced on the basis of the evidence currently available. If the evidence changed, the issue would be reconsidered. Dr Robinson suggested that as HTLV1 was a cell associated virus, leucodepletion might remove or reduce the risk of transmission. Members supported Dr Metters' view that MSBT should review the position on HTLV1; some additional data are available and further prevalence studies could be considered to provide medium to longer term information. The Department would consider the options for further studies and report back to MSBT.

Blood products

10. Dr Snape reported that BPL was now manufacturing only from non-UK sourced plasma.The aim was to establish a three to four week stock of each product before release. There would be such a stock of immunoglobulins and clotting factors by mid December and therefore release could begin then. For albumin, a mid January date was forecast, and BPL expected hyperimmune products to be ready for release at the end of June 1999. They were proposing to continue the UK plasma sourced products in parallel with the release of the non-UK products. They took the view that this was necessary for a time, to ensure the continued availability of supply, and to enable clinicians to have a choice.

11. Dr Perry advised that PFC were importing 50% of their non UK plasma from the Bavarian Red Cross and 50% from the US. Their first non-UK plasma derived products would be released between December and the end of January; like BPL they were building up sufficient stocks before releasing. They were still negotiating with regard to the plasma for hyperimmune products, and those products would therefore be available no sooner than BPL's.

12. PFC's view was that the transition from UK plasma derived products to non-UK should be a clean move, with no duplicate supply of UK and non-UK plasma derived products, and that existing stocks should be recovered. Their approach was to respond practically to a theoretical risk with a prompt transition and strong effort to substitute stocks, even at remote sites, to guard against old UK plasma derived products emerging in in the future, perhaps at a time when a theoretical risk had become more substantial. The SNBTS expected that around March they would be able to guarantee continued supplies of all the non-hyperimmune products. Either at the same time, or shortly after, they intended to recover the UK derived stocks.

13. Members agreed that the availability of choice and the nature of a recovery programme were significant policy issues. Dr Metters advised that careful account had to be taken of the position of the blood services and other authorities if they knowingly allowed continued supply when there was a possible risk, however theoretical. There were several strands: the issue of concurrent supply of non-UK derived and UK derived stocks; the role of the Committee on Safety of Medicines; the recovery of stocks from remote sites, including patients' fridges.

14. Dr Rotblat advised that once non-UK plasma derived products were issued, then UK-derived should not be issued (except that the hyperimmune products would come on stream later). This was the only position consistent with the CSM advice, and it was not a matter of clinical choice. The Committee agreed that it was not appropriate for BPL/PFC to continue to issue UK sourced products once adequate supplies of non-UK sourced products were available.

15. The position with regard to the recovery of UK plasma derived stocks was less clear cut. Whilst it was reasonable to replace existing stocks, the extent of a recovery programme needed to be addressed. Considerations included the range of locations where old stock might be held, the need to apply the same recovery arrangements to stocks held abroad, and the need for openness in line with Government policy. Dr Metters stressed

that Ministers would expect to see proper and open action taken.

16. Dr Gorst and Dr Wyatt stressed that clinicians needed clear advice. It was agreed that prompt guidance would help to reduce further the issue of large quantities of UK plasma derived products for storage in patients' fridges. Whilst there was a case for leaving the recovery decisions to clinicians at local level, it was recognised that it was important to prevent unnecessary continued use of the UK plasma derived products.

17. It was agreed that in the light of CSM's advice Dr Rotblat and MCA colleagues would discuss the arrangements for recovering products with BPL and PFC and that when the position was clear an article would appear in CMO's Update.

Record keeping and CMOs' initiative

18. Dr McGovern reported that these two issues would be picked up in a Health Service Circular due to be issued on 27 November, and that all the major points would be included. The other UK countries would be sent the draft before issue, so that they could make their corresponding preparations.

HCV Lookback study

19. Dr Keel reported that following the discussions at the June MSBT meeting when the Committee had stressed the need to account for the full trail of those untraced, she had passed the information on to SNBTS. The documentation and traceability work was under way.

NAT testing

20. Paper MSBT 16/11 was tabled and Dr Robinson reported on the progress of NAT testing. The UK countries were trying to move forward in parallel. It was now possible to propose the introduction of HCV PCR testing of frozen blood components by minipooling. These components had a long shelf life and therefore stocks could be held back without compromising the blood supply. For short shelf life cellular blood components there was more difficulty. Platelets had a 5 day shelf life. Although red cells had a longer shelf life, holding up issue would present a stock problem. HCV PCR testing of red cells and platelets would not be before April 2000. However Germany would be releasing NAT tested red cells and platelets by April 1999 as they were far ahead of other European countries in this area.

21. The UK Blood Services wanted to get the system running efficiently for the frozen components, and MSBT's view was sought on whether the 1 April 1999 target for NAT testing implementation should be for frozen components produced after that date, issued after that date, or transfused after that date. Dr Robinson's preference was for the latter, as it would make sure that components in hospitals were withdrawn and exchanged. It was not imperative from a regulatory viewpoint. She had a remaining anxiety, as the system had not been totally validated.

22. The Committee agreed that implementation should be for frozen components transfused after 1 April unless this preferred option creates logistical problems in which

case the target should still relate to transfused products. The start date might need to be deferred but should be no later than 1 July 1999. There would be a further MSBT meeting before then if further discussion was needed.

Deferral of donors who were blood transfusion recipients

23. As MSBT had wished, Dr Metters had presented the supply related problem to SEAC, who had not pressed for further developments. The matter had not re-emerged as a SEAC agenda item. Dr McClelland referred to the recent publicity about a recommendation from a Bayer advisory group to the Canadian blood services that blood should not be accepted from donors who had lived in the UK since 1980. The response of the Canadian government had been that this would be premature. In practice, to take such a step would leave them with supply difficulties. Dr Robinson reported that the French authorities had already deferred donors who had been recipients, and were now finding it difficult to manage.

MSBT guidance

24. Dr McGovern presented a brief paper, MSBT (16)2, on the proposals for the review. Dr Naomi Brecker, a public health trainee trainee seconded to the Department, would be helping to take the review forward. Over the next six to nine months, two or possibly three meetings would be held. The aim would be to consider the updating of the existing guidance. The group of members listed in the paper would be brought together as soon as possible. It was agreed that Audrey Todd (Edinburgh) would be invited to join the group; she was expert in issues relating to seeking information and gaining consent in relation to cadaver and organ donors. A practising haematologist might also be needed, and Dr Gorst would discuss this with Dr McGovern. It was noted that Dr Wregitt's name was wrongly spelt in the paper.

HIV testing and organ donation

25. MSBT(16)3 attached a letter from the UK Transplant Coordinators Association attaching a draft protocol on the referral of anencephalic infants for organ donation and raising the question, after consultation with the Terence Higgins Trust, of the requirement in the MSBT guidelines to tell the family that an HIV test would be carried out. It was agreed that the group revising the guidance would consider the issues, and that it would then be appropriate to refer the matter to EAGA.

Sir William Stuart enquiry

26. Dr Keel reported a number of action points had been identified at a meeting of the UK Health Departments in the summer. An article around the issue of delay in post mortem results in cases of CJD would appear in the Bulletin of the Royal College of Pathologists and the College might set up a working party if necessary.

27. Emma de Zoete was introduced as a new member of the DH team dealing with the review of tissue banking.

TESTING FOR HEPATITIS B CORE ANTIBODY

28. Dr Nicholas reported that when the question of advice on core antibody testing of potential organ donors was raised, advice had been sought from Professor McMaster. The issue had then been taken to the Advisory Group on Hepatitis. However, the issue was primarily one for MSBT and the matter needed to be addressed in advance of the revision of the MSBT guidance. Professor Zuckerman set out the perspective. In the past, MSBT did not support the tests because they were not specific. Matters had now changed, and there was evidence that hepatitis B was introduced into the liver recipient if the donor was hepatitis B immune. However, it was not necessarily the case that anti core testing was the answer.

29. Mathematical modelling had been carried out by the Oxford group, who had found that the wild type hepatitis B virus was being replaced by a mutant. Looking back at hepatitis B immunised infants, 99 out of 1,000 had acquired the mutant virus. Routine core testing would miss a substantial number of these, and therefore PCR testing was needed.

30. Members supported Professor Zuckerman's view, and agreed that there should be tests but with a leapfrog over core antibody to PCR. The money and effort should go to this, pressing ahead as soon as possible. Dr McClelland suggested that looking to the future, there was a logical extension to blood donors, and Professor Zuckerman supported this but advised that the present urgency was in transplantation, because of the risk of hepatitis B being introduced into an immunosuppressed person.

31. Dr Metters confirmed that the advice on liver donors would be issued as a pressing matter, and the Committee would return to the wider issues at the next meeting. Professor Zuckerman agreed to present a paper on hepatitis B core testing and the science behind it for that meeting.

PROGRESS REPORT ON nvCJD

Lookback study

32. Dr Robinson introduced paper MSBT (16) 4, which was a detailed report of what had been achieved in the collection of data for the transfusion medicine epidemiology review between the NBS's London and South East zone and the CJD surveillance unit. This had entailed a great deal of work, for a small number of returns. The study included information from the blood product recalls when products were implicated by plasma from donors found to have nvCJD. The study looked two ways - at donations previously made by CJD infected patients (including subsequently confirmed or suspected nvCJD cases) and the recipients of implicated components/products. All the retrospective work had been completed and the team would like to continue the prospective work. The NBA had agreed to fund this, and the sums involved were relatively small. Dr Metters expressed MSBT's thanks for the information.

Research

33. Dr Wingfield advised that a substantial budget of some £25 million p.a. was being given to for TSE research, and that there was a large portfolio under the TSE funders group. Several areas were being addressed, and a study of haemophiliacs was being

proposed. For research, the area was a difficult one as there was no pre mortem diagnostic test. The first aim was to try to understand the target agent. Much effort was being made to get a good diagnostic test. Bio assays were being used, which were not ideal. On therapeutics, work was being done on the effect of Pentosan Polysulphate on nvCJD. Some data suggested that it might be prophylactic against the passage of scrapie.

34. There were proposals for a prevalence study to look at tonsil and appendix material collected in the usual way. It was not known whether the aberrant prion protein could be identified in the pre clinical phase, so it would be difficult to know the meaning of a negative result.

35. There were about 10,000 samples involved in the total number of studies. Dr McClelland suggested that there would be a raft of blood donors in that number, and hence a risk of chance associations. Careful scenario planning was needed. There were also future ethical questions relating to informing people of results. There was a possibility, also, that treatment processes for blood components and products might have removed the infective agent. It was agreed that there were many factors to take into account but that research work was essential. Dr Metters alerted members to the option of suggesting areas of work to Dr Wingfield, who could pursue the funding possibilities.

TTV

36. Professor Zuckerman introduced his paper, MSBT (16)5, which was a summary of the range of papers produced. He stressed that although "TTV" was being translated as "transfusion transmitted virus", the "TT" was in fact the initials of the patient in Japan found to have the virus. It was clear that it was a new DNA virus, probably in the parvovirus group. Unlike others in the parvovirus group, it was excreted in faeces. In some countries there appeared to be a wide dissemination among the population - eg, from sample studies, 62% of blood donors in Brazil, 38% in Thailand, (1.0% - 1.9% in the USA and UK). An association with hepatitis was not firmly established, but the virus was probably spread in the same way as hepatitis A. It was common in haemodialysis patients and in those with haemophilia because the inactivation procedures do not destroy the virus in plasma products. Dr Rotblat advised that TTV was on the agenda for the next Biotech Working Party. Dr Metters advised that at a recent European CMOs meeting the CMO of France had drawn attention to the virus.

37. MSBT noted the position carefully. They had considered the available evidence and for the present concluded that they should watch the data on this virus as it emerged. There was no justification at this time for the introduction of donor screening. They regretted the use of "transfusion transmitted", which was a misnomer. Professor Zuckerman would consider how this inaccurate terminology could be stemmed.

SCREENING FOR OTHER TRANSMISSIBLE AGENTS

38. Dr Metters suggested that it was appropriate to revisit the other factors for which the Committee had not recommended screening. There was no general screening for malaria in blood donors, although selected individuals were screened. Citing two incidents

involving bacterial contamination involving apheresis platelets, Dr Robinson raised the issue of whether there should be bacteriological screening. It was agreed that Dr Robinson and Dr McClelland would liaise with Dr McGovern on the production of a paper for the next MSBT meeting, focussing on potential screening gaps.

GB VIRUS C

39. Professor Zuckerman had provided a copy of an article published in the journal of Medical Virology on the clinical implications of GB Virus C. The Committee considered this most up to date position and concluded that at present there was no justification for screening donors. The position would be reviewed from time to time.

NBA ITEMS

Fresh frozen plasma/Octaplas

40. Dr Robinson reviewed the position on clinical FFP and Octoplas. Octapharm were taking legal action against the NBA alleging unfair pricing to retain the market. They had also contacted some MPs, who had made representations on safety grounds. Octaplas currently had 4% of the market.

41. The NBA had been preparing to contract with a company in Spain for the Methylene Blue UV light processing of plasma, but this had not proved viable. Options were being considered. The NBA had written to the MCA to see if there were toxicity issues with Methylene Blue, as it was not in the European Pharmacopoeia.

42. Dr Metters asked the Committee to revisit the question of the availability of clinical FFP from single donor UK plasma. At the previous MSBT meeting it had been agreed that clinicians should retain the choice of using this single donor, UK derived non licensed product, even though the licensed Octaplas, made from pooled non-UK plasma, was now available. Dr Gorst expressed the view that most haematologists would prefer the UK FFP. Dr McClelland pointed to the relative absence of safety evidence. Dr McGovern advised that that the National Blood Service User Group had discussed this issue. They had suggested the establishment of a sub group to provide guidance to the profession.

43. Dr Metters enquired whether the NBA's clinical FFP could be licensed. Dr Rotblat advised, however, that it would be the first time that single unit donations had been licensed, for any purpose.

44. The Committee concluded that it would expect the NBA to keep the supply of its clinical FFP available. The pooled product brought the risks of dispersal; the potential for transmission of infection through the UK sourced product was reduced by the fact that it was in single donor units. The National Blood Service User Group would prepare guidance to the profession.

National Guidelines/Standards for Investigation of Bacterial Contamination of Blood Components

45. Dr Robinson advised that the NBA had issued the guidelines, as there had been

incidents associated with transfusion, and practices needed to be addressed. The next report of SHOT would be in early 1999.

DRAFT PAPER ON NEW RCOG ANTI-D GUIDELINES

46. Paper MSBT (16)8 on the use of anti-D immunoglobulin for Rhesus prophylaxis was presented for information. The guidelines recommended routine use of antenatally Anti-D immunoglobulin in pregnant Rhesus D negative women. Members expressed concern that it was not timely to issue the guidelines. Anti-D immunoglobulin was currently derived from UK plasma and until non UK sources were secure the guidelines should be put on hold.

47. There was a balance of risk, and although the nvCJD risk was theoretical, it had been given a reality in public understanding. Dr Robinson pointed out that primagravidae who became sensitised in the first pregnancy might never have live children. Dr Rotblat advised that the CSM had allowed UK plasma derived anti-D immunoglobulin to stay on the market for a longer time if replacement products could not easily be found, because of the huge benefit of post natal prophylaxis. For pre natal use there was a non-UK licensed product on the market which could be used. It was agreed that the Department would write to the RCOG.

ANY OTHER BUSINESS

48. The policy on openness and transparency required public summaries of the proceedings of Advisory Committees, and this would be applied to MSBT for its next meeting. Members would see the summary before its issue.

DATE OF NEXT MEETING

49. The 25 February date already arranged needed to be changed because of a conflicting meeting which would affect a number of members. **16 February** was chosen instead.