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NOT FOR PUBLICATION

MSBT 6/9

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

MINUTES OF THE MEETING HELD ON 13 OCTOBER 1995

Chairman :	Dr J S Metters
Members present :	Dr A J Cant Dr D W Gorst Dr D B L McClelland Dr P Mortimer Dr R J Perry Dr A Robinson Dr T Snape Professor J D Williams Professor A Zuckerman
Observers :	Mrs J Dhell Dr P Doyle Dr A Keel Dr J Ludlow Dr G Mock Dr I H Nicholas Mr J S Sloggem
Secretariat :	Mr K J Guinness Dr A S M Rejman Mr P Pudlo Miss A Towner Mr L Levy

1. Chairman's introduction and welcome

1.1 The Chairman welcomed Dr Brian McClelland, Director of Edinburgh and South East Scotland Blood Transfusion Service, as Dr Ruthven Mitchell's successor on the Committee.

1.2 The Chairman thanked members of the Committee whose initial period of membership had expired for agreeing to be flexible about retirement dates, which would help in establishing a rolling pattern of membership. The Secretariat would write telling members currently affected when their retirement date would be. Retirements (or reappointments) would normally take effect from November of the relevant year.

ACTION – Secretariat to write to members currently affected

1.3 The Chairman introduced two new members of the Secretariat: Kevin Guinness, who replaced Roger Scofield, and

Ann Towner, who replaced David Burrage.

2. Apologies for absence

Apologies for absence were received from Dr Warren, Miss Lord and Professor McMaster. Mr Sloggem deputised for Dr Purves.

3. Minutes of the fifth MSBT meeting - 25 May 1995 (Paper MSBT 5/10)

The minutes were agreed.

4. Matters arising from the minutes, not dealt with as separate items:-

- minute 4.1: investigation of transfusion reactions suspected to be due to bacterial contamination (MSBT 5/9)

4.1 Dr Robinson reported on proposals from a group representing the transfusion services for reporting and collation of information about transfusion events, both infectious and due to other causes. This was intended to follow the pattern of other confidential enquiries. The findings of collated, anonymised incidents would be fed back and publicised, with the objective of informing and educating. A new post created in conjunction with PHLS would ensure co-ordination of reports and investigations between Transfusion Centres and the PHLS, and that results were disseminated in an annual report.

4.2 It was thought important to get the system operational quickly. The group had in minding involving the Royal Colleges and professional organisations, and liaising with those running other confidential enquiries. Dr Robinson explained that the existing system of reporting to the CDSC laboratory did not provide a complete data set. It was hoped that this initiative would achieve that aim.

4.3 Dr McClelland thought work was progressing well. They hoped to start the system in the next financial year. The report form would be kept simple. As many cross-links as possible would be built in - including with manufacturers whose products might be implicated.

4.4 The committee welcomed these developments. Dr Metters drew attention to potential legal problems and the need to maintain confidentiality. Problems could be avoided by separating personal details from comments about the causes of the incident. Legal advice on these aspects should be obtained.

- minute 4.3-5 : HIV1-O update

4.5 Dr Mortimer said that a small amount of work had been done at Colindale. PCR studies were planned and HIV1-O type primers had been prepared. The latest generation of several manufacturers' test kits had now been adjusted to take account of the HIV1-O sub-type and these covered all HIV screening tests being used by the UK Transfusion Services. Initial test had not demonstrated any HIV1-O infection in a selected group of UK individuals with African connections.

4.6 The Chairman drew attention to reports that HIV-O infection had now spread from Cameroon to Nigeria, increasing the potential for infection in the UK. In the committee's view, the risk remained small.

- minute 4.9 and 10 : revision of blood donor leaflets

4.7 Dr Robinson said the revised draft was deliberately focused blood safety, not just AIDS. Paper MSBT 6/7, was the culmination of 12 months work. The old drawings had been regarded as stereotyped, while the previous wording had been perceived as excluding virtually all black Africans from donating. In trying to address concerns expressed by the MSBT and others, a research report had been commissioned to look both at what information was available on epidemiology and at reactions to possible wording. The present draft reflected the conclusions. While the Commission for Racial Equality were not completely happy with the references to Africans, they did not dispute that they properly reflected the research findings. Wording had been modified to exclude anyone of any colour who had been sexually active in Africa, or with anyone of either gender from Africa. It did not refer to race. The NBA were also trying to reword the first line on page 3 - which was applicable to women as well as men. EAGA had recently seen the draft and been given 2 weeks to let NBA have any comments.

4.8 Dr Rejman, and Dr McClelland, thought there might be an inconsistency in quoting a one year deferral period in the proposed leaflet, when 180 days was cited in the proposed guidance on the use of tissues. However, the meeting concluded that given the different audience - the public on the one hand, and health professionals on the other - and the need to finalise the leaflet, the draft need not be altered.

4.9 Dr McClelland asked why high risk areas other than Africa were not mentioned. Dr Robinson said that epidemiological studies showed that these did not rank significantly as sources of infection in the UK. She agreed that attempts to keep wording simple, if it was taken too literally, could arguably lead to unnecessary exclusions. It was best to err on the side of safety. The trigger questions approach was intended to lead to discussion with staff where there was room for doubt.

4.10 Although clinics for sexually transmitted diseases were now correctly known as GUM clinics, and listed as such in phone books, the general view was that the older more widely understood wording should be retained.

4.11 Dr Robinson said that recipients of blood were not directly excluded from donating, but as questions were asked about any surgery undergone this could lead to exclusion.

4.12 Dr Keel thought the draft represented a useful compromise and dealt with the anxieties of Afro-Caribbeans.

4.13 The Chairman asked that if members had any further comments they should send these to Dr Robinson by 24 October, to arrive sufficiently in advance of the staff training days about the handling of this sensitive issue planned for 6 November.

ACTION - any further comments from members to Dr Robinson by 24 October.

- minute 8.1-8.3 : quarantining or viral inactivation of FFP

4.14 The Chairman reported that having recently received a submission from officials, Ministers had asked that MSBT be asked to confirm whether their recommendations remained as in para 8.3 of the minute of the 5th meeting, ie not to introduce quarantining or viral inactivation of FFP at present.

4.15 Problems with the SD-VIP trials were reported. Dr Sloggem said it looked as if Octaplas could well be refused a product licence by the MCA. There were a number of points at issue, including viral safety.

4.16 In the absence of other comment from the committee, the Chairman summarised the committee's position as being that **there was at present insufficient information on which to recommend the adoption of quarantining or viral inactivation measures.**

4.17 Dr Rejman reported that Dr Robinson had agreed to prepare draft material for a CMO Update, reminding doctors about the optimal use of FFP. There had already been a reference to existing guidelines in a recent BMJ article on red-cell transfusion. Dr Keel thought Scotland would reflect that by an item in their health bulletin, supplementing a recently published Scottish Report on Optimal Use of Donor Blood.

ACTION - Dr Robinson to prepare material for Update, and Dr Keel to arrange for material for Scottish health bulletin. Officials to advise Ministers of committee's views.

- minute 11 : tissue banking review

4.18 Dr Doyle said that not much progress could be made on the tissue banking review while discussions were being held in the EU on the possible extension of the general Medical Devices Directive to include tissues. It seemed doubtful if the UK should go it alone in the meantime. However, Dr Robinson felt strongly that there was an urgent need for some regulation, including inspection, and auditing, even if this did mean the UK going it alone. Tissues were sometimes poorly handled at present.

4.19 Dr Metters agreed there was a need for regulation. There was continuing legal discussion over whether tissue was legally a product for the purposes of that directive. A separate directive seemed preferable to inclusion in the general Medical Devices Directive. At one time some human tissues had been covered by the Medicines Act. Since it had been removed from the scope of the Act in order to comply with EC law, the UK could not now adopt the suggestion of the MCA inspection system inspecting work on tissues. If guidance was issued now, even though this did not have direct force in law, it would carry substantial weight both with the courts and those to whom it was addressed.

4.20 Dr Doyle undertook to take back MSBT's views on the need for urgent action, and feed these into the European discussions.

ACTION : Dr Doyle to feed back MSBT's views

- minute 4.6- 4.8 : intra-muscular immunoglobulins

4.21 Dr Cant raised the question of viral inactivation of intra-muscular immunoglobulins. Transmission of Hepatitis by a commercial intravenous immunoglobulin which was licensed in the US but not the UK had been reported. Mr Sloggem reported that while CPMP had state clearly that no safety problems had been found with intra-muscular immunoglobulins it required Member States to either adopt a validated inactivation step, or to do HCV PCR testing until such steps were in place. Members were concerned that this position, which was not based on robust scientific findings, could raise unnecessary fears about safety. There was a very good safety record for intra-muscular immunoglobulins. Properly manufactured they were thought never to have transmitted infection; problems only arose if there were deviations from expected standards of Cohn fractionation. If there were no risk, there was no point in inactivation, and even a risk that any change in processing might reduce safety.

4.22 Members were concerned that if additional viral inactivation steps were introduced this would be interpreted as qualifying any statements about safety. If the UK did not adopt the measures specified it could find itself unable to release products onto the home market and lose valuable

supplies, eg of anti-D. The Chairman asked Mr Sloggem to take back to CPMP the committee's strong concerns about the position. Members were also encouraged to write to Mr Sloggem setting out their concerns, as this would help him argue the UK case. The committee were concerned that any action taken by the EU should be taken on soundly based scientic evidence.

ACTION - Mr Sloggem to take back MSBT's views. Members invited to write to him setting out their concerns.

5. EU activities relevant to the committee

5.1 Mr Sloggem reported that the CPMP's ad hoc working party on Biotechnology had been considering the evaluation of the performance of test kits for viral markers. The Working Party would continue its discussion at its November meeting, with the aim of harmonising, through the CPMP and the European Commission, the evaluation of the suitability of these test kits for their purpose.

5.2 Mrs Dhell explained that a meeting of experts and Departmental officials had been proposed to look at aspects of the control of assays through standards to underpin the In Vitro Diagnostic Devices Directive. There was scope within it for standards on performance criteria, although there was the possibility that some EU countries would not want to relinquish national regulatory control of tests. The view of the the World Health Organisation had been sought.

5.3 The Chairman advised that the UK would need to handle discussions carefully, so as not to appear to be trying to impose its views on others, particularly the European Commission, France, Germany and the World Health Organisation, who all have an interest in this subject.

5.4 Mr Sloggem also reported that :

(a) revised CPMP Guidelines on Virus Validation Studies and on Medicinal Products derived from human blood and plasma were sent out for consultation in July, with a 1 November deadline for comments;

(b) the Member States' review of the adequacy of viral inactivation/removal procedures for IV Immunoglobulins was ongoing;

(c) the Biotechnology Working Party was pressing for the implementation of quality assurance systems, inspection and approval of donation centres and associated testing sites;

(d) Dr Rejman, the MCA and the MDA have commented on a proposed revision of the European Pharmacopoeia monograph on Plasma for Fractionation, which was to include a new section on donor selection and exclusion criteria and screening tests.

6. CJD and blood transfusion (paper MSBT 6/5)

6.1 Introducing paper MSBT 6/5, Dr Rejman pointed out that the fifth paragraph and Annex 2 should have referred to a "**draft** position statement" by the EPFA. He explained that the information in the tables gave what information was known about the line being taken or being proposed in Europe and North America. Some members of the European Pharmacopoeia were known not to favour the line set out in the draft monograph. CPMP and MSBT's views were in line with those of the Council of Europe. Dr Rejman had undertaken to explain to the Council of Europe MSBT's view that Dura Mater recipients should not be excluded from donating blood.

6.2 Dr Snape asked whether a distinction was made between those at risk and those actually infected.

6.3 Mr Sloggem explained that the CPMP were revisiting their stance on CJD following a voluntary withdrawal of products in USA, Canada and Germany after the death of an HGH recipient, and withdrawals also in France. (They had also reviewed other criteria for exclusion, but decided to follow the Council of Europe line.) **The biotechnology group considered there was no new evidence requiring a change in stance.** If donations had been made over a longer period there was little to be gained from withdrawing only recent donations. If albumin were withdrawn, all other blood products should logically be withdrawn too, as well as products contaning albumin as a carrier, eg vaccines. If quarantining were adopted how would risk/benefits be explained to patients ? It had been decided to liaise with the Council of Europe. A study was proposed to see if blood products were implicated at all.

6.4 The Chairman noted that the withdrawal in Canada had been without reference to Health Canada. **The committee agreed that the deferral criteria for dura mater should not be altered.** Dr Perry said that the EAPPI draft paper he would pass to the Secretariat stated that they were not recommending withdrawal if a batch proved to be contaminated - that would produce major problems.

ACTION - Dr Perry to send EAPPI document to Secretariat for circulation to committee members.

7. Promoting the safety of transplantation of human tissues and organs (paper MSBT 6/1)

7.1 Dr Rejman thanked the sub-group which had considered the 32 replies received to the consultation on the draft document. Only 2 sets of comments on fairly minor points had since been received from MSBT members. Key differences in the present draft from that previously seen by the full MSBT were that it was now accepted that if a patient needed a life-saving bone marrow transplant, it could be acceptable to use a Hep C positive autologous donation provided all the appropriate precautions were taken and patients and others were fully aware of the risks (page 8). A similar line on risk versus

benefits in relation to other infected donations was reflected in the material on serological testing of donors (page 5). The first paragraph of the introduction to the document stressed the scope for the exercise of discretion. Annex 2 had been amended to bring it into line with the current blood donor AIDS leaflets. The previous draft of Annex 4 had been dropped in view of the need to progress the document and in the face of the often contradictory comments received on that part of the material. A simple guide to potentially relevant diseases had been substituted, with the intention that knowledgeable microbiologists should be consulted in cases of doubt.

7.2 In answer to questions raised by members of the committee, Dr Rejman said that :

* he thought that the material in para 2 of page 5 should stand, in view of concerns about geno-types;

* in Annex 2, it was not wished to exclude recipients of blood as this could exclude perfectly healthy young donors eg post-1985 haemophiliacs;

* it was convenient to treat bone marrow as a tissue for the present purpose;

7.3 Dr McClelland was concerned that guidance now might make it more difficult subsequently to endorse the outcome of the tissue banking review. Dr Rejman stated that this guidance related only to safety aspects of tissues and organs and not to more general aspects of organisation of tissue banking. Current transplantation questions needed to be addressed now. There was no reason to expect any conflict with the tissue banking guidance, which had a much wider scope.

7.4 Dr Cant raised the question of donors, particularly of Asian origin, who tested antibody positive but antigen negative for Hepatitis B. Should the last line on page 14 refer to past as well as to current infection ? Professor Zuckerman advised that the present wording was acceptable. Conventional wisdom was that antigen negative cases could not transmit infection. Nor should the material at present attempt to reflect new strains of hepatitis which were not yet detectable.

7.5 Dr Robinson questioned whether the guidance should attempt to deal with organs and tissues in the same document. The Chairman advised against reopening earlier discussions on that point. He felt we now needed to get out the guidance, which had been in preparation for 2 years, unless there were very strong objections. Some compromise had been necessary, but the guidance went a long way. He saw it as a sub-set to the later guidance on tissue banking.

7.6 It was decided to put the 4th sentence of the introductory paragraph in bold to highlight it. Any final comments should be sent to Dr Rejman by 23 October, after

which the text would be finalised for distribution.

ACTION – Members to send any final comment to Dr Rejman by 23 October.

8. Guidance notes on the collection, storage and infusion of bone marrow and stem cells (Paper MSBT 6/2)

8.1 Dr Rejman confirmed that members' comments on the Notes would be conveyed to the Expert Advisory Group which was preparing the guidance. The final version would be sent out as a CMO letter or Health Service Guidance, targeted at haematologists, obstetricians and Blood Transfusion Services.

8.2 Addressing concerns about the membership of the Expert Advisory Group, Dr Rejman assured MSBT members that Dr Pegg and Col Thomas were directly involved in the blood transfusion service, and Professor Tedder and Dr Mortimer had close links with it.

8.3 The Chairman's asked that any further comments would be sent to Dr Rejman within 10 days. Outstanding points would be resolved with the person who raised them or incorporated in the Notes, which would then be published as quickly as possible.

ACTION – Members to send any further comments to Dr Rejman y within 10 days

9. Hepatitis C look back programme

9.1 The Chairman reported that the working party on the Hepatitis C look-back exercise had effectively concluded it's work. It would not meet again separately, but members would be invited to attend any future discussions on the subject at the full MSBT.

9.2 The Chairman cited figures received so far which indicated that substantial progress had been made with the exercise in all 4 countries. Figures were currently incomplete but the Secretariat would be asking for these to be updated. They would then be circulated to MSBT members and included in a report to Ministers. The figures showed that the hospital records system was having difficulty coping with the requirements of the exercise.

9.3 Questions arising were whether stored samples should be tested, and whether indeterminates should be included. The data so far suggested that testing stored samples was unlikely to produce much benefit in relation to the effort expended and should not be advised, unless there were overriding legal reasons for it. Tests should be available for those who asked for them, but it did not seem likely to be cost-effective to test everyone who had ever been transfused.

9.4 However, the working group proposed that England and

Wales - where there had been particular problems - should look again at some indeterminates which were selected on the basis of high probability of being true positives. Cases could be identified from transfusion records; they were expected to add only about 10% to the current numbers of cases. To avoid overburdening hospitals currently, this would be done as the second wave of the exercise. The NBA's proposed criteria for selecting which indetereminates should be further investigated would be circulated, taking account of minor amendments proposed at the working group.

9.5 The Chairman reported that the working group had strongly supported PHLS/NBA/SNBTS proposals for a joint archive. Absence of consent might be a problem, but this could be overcome if hepatologists requested such permission retrospectively when next seeing patients. Other research studies could be piggy-backed on this. All the research proposals would be considered by the Departments Research and Development branch, but it seemed hopeful that funding would be made available.

9.6 The Chairman noted that with hindsight it was easy to say that questions such as indeterminates should have been resolved at the outset, but at the time it was not obvious to the working group. The look back programme had achieved a lot in the 6 month since the exercise started, and each stage inevitably took time. Dr Robinson mentioned the interest other European countries had shown in what the UK had been doing.

ACTION - Secretariat to obtain updated figures and circulate summary to MSBT members. Dr Robinson to circulate criteria for selecting indeterminates for further investigation.

10. <u>Virological Screening of UK blood donations, including HTLV screening (paper MSBT 6/6)</u>

10.1 The Chairman reported that MSBT were being asked to review their decision not to recommend screening for HTLV I/II. If there was any doubt in members minds, should a sub-group be set to examine it ?

10.2 Professor Zuckerman considered nothing had happened to change MSBT's previous advice, unless they wished to pursue combined HTLV/HIV testing. Dr Mortimer felt it would be hard to demonstrate that screening for HTLV was cost-effective ; there seemed better ways of spending NHS monies. But this was more of a political issue.

10.3 Dr Cant suggested that neo-nates and young children might be a special case, even though infection might take years to develop. A selective approach, testing only those at particular risk, might be warranted. One approach might be the use for such groups of a special donor pool who tested negative, as in the case of CMV. Other members raised the need to consider how any age-grouping adopted should be decided.

10.4 Dr McClelland agreed that the evidence had not changed, although he could make available evidence from a huge study in the USA which suggested that neurological disorder appeared earlier than had previously been thought. He agreed that a selective policy was a possibility that merited serious consideration and offered to draft proposals. Specialised panels might not be feasible in some parts of the country, a graded response might need to be considered. Dr Robinson offered to co-operate with Dr McClelland in working up proposals. Special panels were only one of several options.

10.5 The Chairman agreed that Drs McClelland and Robinson co-operate in producing a paper on how the needs of special groups might be met, without the introduction of general screening, for discussion at the next MSBT meeting. Other concerns raised by members could be pursued at that time, such as whether "double standards" on testing were acceptable, despite existing precedents in cases where testing was not cost-effective. **The Chairman summarised the Committee's current view as being that the scientific evidence had not changed and the current recommendation to Ministers remained unaltered.**

ACTION - Dr McClelland and Dr Robinson to prepare paper for next meeting

11. New hepatitis viruses, 1995 (Paper MSBT 6/3)

11.1 Commenting on his paper which had been circulated to members, Dr Mortimer said that HGV is potentially as serious as HCV, but there was no information about associated morbidity and mortality. It is prevalent in the UK, possibly in 1-2% of blood donors. However, he confirmed that the current viral inactivation steps would remove it from plasma.

11.2 The Chairman said that there seems to be an unending stream of new viruses, and the Committee were very likely to need to consider carefully how much screening was appropriate.

12. HHV-6 (paper MSBT 6/4)

12.1 Dr Rejman drew attention to the editorial in AIDS Weekly (paper MSBT 6/4) which recommended screening for HHV-6 where blood was given to immuno-suppressed (particularly AIDS) patients. MSBT needed to be aware of this, and to consider whether this was appropriate. Other recent articles had linked the virus with Multiple Sclerosis. An article on epidemiology in blood donors rated the incidence of HHV-6 infection as between 5.4% and 90% in healthy donors.

12. 2 Dr Cant mentioned 2 cases of child deaths from pneumonitis where HHV-6 was present, although not proven as the cause of death. There were other erports of deaths in immunodeficient children who had received multiple transplants, in which HHV-6 was said to be implicated, as evidenced by large numbers of white cells. This was

potentially worrying in the case of bone narrow transplants. Protection should be provided by the white cell filters which were now used for all bone marrow transplants, primarily to reduce CMV infection.

12.3 Dr Mortimer suggested that virtually everyone over 10 was infected with HHV-6 - perhaps 99% of the population, so finding negative donors would be impossible. Hence the importance of protection.

12.4 The Chairman summarised the committee's view as being that **no immediate measures were necessary.** But the issue could be considered in the context of the special panels and procedures to be discussed in the paper being prepared, as in paragraph 10.6 above.

13. Any Other Business

13.1 Dr Robinson tabled paper MSBT 6/8 on Autologous Blood Transfusion, for information.

13.2 There was a brief discussion about the appropriate use of blood transfusion.

14. Date of next meeting

The next meeting would be held in January ,on a date to be arranged. It was agreed that the meeting would start at 11 am, now that the Ad Hoc Working Party on the Hepatitis C Look Back Programme has been dissolved.

ACTION - Secretariat to arrange next meeting