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MSBT 7/6

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

MINUTES OF THE MEETING HELD ON 8 JANUARY 1996

Chairman :	Dr J S Metters
Members present :	Dr D W Gorst Dr D B L McClelland Dr P Mortimer Dr R J Perry Dr E A Robinson Dr T Snape Dr R E Warren Professor J D Williams Professor A Zuckerman
Also present	Professor H Thomas (Items 1-4 and 6 (minutes 11.1-11.2) only)
Observers :	Mrs J Dhell Dr P Doyle Dr J Ludlow Dr G Mock Dr I H Nicholas Dr J Purves Mr J S Sloggem Dr J Toy (Items 1-4 and 6 [minutes 11.1-11.2] only)
Secretariat :	Dr A S M Rejman Miss A Towner Mr L Levy

1. Chairman's Introduction and Welcome

The Chairman welcomed Professor Thomas and Dr Toy (Mrs Griffin's successor), who had been invited for the discussion of matters which related to the Working Party on the Hepatitis C Look-back.

2. Apologies for Absence

Apologies were received from Dr Cant, Dr Keel, Miss Lord, Professor McMaster, and also from Dr Gillon and Dr

Westmoreland who had been invited to attend the discussion about the Hepatitis C Look-back Working Party's work.

3. Minutes of the 5th Hepatitis C look back working party - 13 October 1995

Dr Gillon had written suggesting two amendments to the minutes :

para 6.3 : delete "infected" and substitute "positive by PCR"

para 7.5 : amend first sentence to read "The Chairman agreed that consistency was needed - RIBA indeterminates shown to be PCR positive had been included in all cases in Scotland but only some 2/3rds in England."

The minutes were agreed, subject to these amendments.

4. Hepatitis C look back programme

4.1 Dr Rejman provided a table summarising progress as at December 1995, and gave new figures received from Scotland that morning. Although there was a fair amount of work left to do, the original estimate of some 3,000 people who were still alive being identified as Hepatitis C positive would probably be about right. Officials would be making a submission to Ministers, but sought the benefit of MSBT's views first.

4.2 Dr Robinson said the NBA had some later figures to pass on. The difference between the numbers followed up and numbers counselled and tested could include some who refused testing, as well as cases where follow up was outstanding.

4.3 Dr Ludlow noted that because of the scattered population in Wales the exercise was organised in 2 stages; first tracing, then counselling. The picture on tracing hospitals' records remained dismal despite the help of an NBA secondee. Dr Mock said that in Northern Ireland they suspected a problem in tracing records in the bigger hospitals. The fact that the deputy director of the transfusion service was herself doing all the counselling could also be causing delays. Dr Mock would investigate why Northern Ireland figures showed a much higher average of donations per donor than for the other countries.

4.4 The Chairman mentioned increasing press enquiries about why the exercise was going slowly and asking why Ministers were not taking action. One option was to abandon the lookback and offer Hepatitis C tests to anyone who had been transfused. Members were not in favour of this as the lookback exercise had been planned to ensure the right patients were identified, properly counselled and as appropriate referred for further investigation after a

positive test. In addition, the lookback was expected to produce important information about Hepatitis C. The alternative to simply letting the exercise run on as it was, was action to try and speed up completion. Simply sending out messages of exhortation from the centre seemed unlikely to produce action in the field.

4.5 Hospital records, and counselling, for which there was shortage of suitably trained staff, were identified as key bottlenecks. The Chairman re-emphasised the initial conclusion that counselling must be done well; patients must not be misinformed. Dr Robinson reported that counselling was being done effectively by transfusion staff, but they faced a heavy load because many GPs were unable or unwilling to undertake that role. Dr Rejman mentioned that for the CJD/hGH lookback counsellors trained in other fields had been used after being taught the necessary facts about CJD.

4.6 Suggestions for relieving the bottleneck at the hospital records stage included :

- establishing a task force
- representatives of the blood service visiting or phoning hospitals where there were particular problems,
- approaches to medical directors to emphasise the need for action to expedite the lookback (along similar lines to the approach taken by the Leukaemia Research Fund)
- using nurses with special experience in this field, eg epidemiological research, or the infection control nurses in post in most hospitals.

4.7 The Chairman asked whether some delay in completing the exercise could adversely effect patient health. Professor Thomas and Professor Zuckerman thought that about 7 years would be the earliest time at which cirrhosis might develop; 20-30 years was more common. It was unlikely the delay of some months in identifying patients would result in significant adverse effects. The exercise would also produce important results which must not be jeopardised by abandoning the methodology. But there was a risk of the exercise grinding to a halt if no action was taken to ensure completion was achieved during 1996.

4.8 Professor Thomas pointed out that after identification through the look back exercise patients still had go through further stages of the NHS system, eg counselling, referral to a hepatologist for biopsy and treatment. The latter would create pressure at purchaser level. In his area only one purchaser was currently funding interferon treatment, despite the advance warning given of the demand the lookback exercise might generate. The suggestion of direct referral to liver units for testing and counselling might be feasible, but would still leave bottlenecks at the biopsy stage (about 40% of cases). The Chairman agreed that there was a limit to the

number of new referrals the NHS could deal with; this was an important point to make to Ministers.

4.9 Officials proposed to put to Ministers the various options suggested by members of MSBT. It could be helpful to be able to demonstrate that MSBT had considered how the lookback could be speeded up, and estimated the size of the problem. Officials would also make clear that even if that problem of patient identification was dealt with there could be delays at later stages. The Chairman proposed to circulate to members a summary of the options before a submission to Ministers, went forward. This would be shared with territorial health departments.

4.10 The Chairman asked that national blood services make contact with hospitals before April (a year after the issue of the CMO letter) enquiring about progress, and asking for estimates of when tracing might be completed. This approach might be better done personally by phone or visit than by letter.

4.11 Dr Rejman reported on recent discussions at the Leukaemia Steering Committee, the umbrella group of the MRC adult and childhood leukaemia working parties. Of 180 patients tested by a Glasgow paediatric haematologist, 13(7%) were found to be Hepatitis C positive, 9 of whom were also PCR positive. The highest proportion were bone marrow transplant recipients, who had the highest usage of blood products. The Steering Committee had agreed that it was not unreasonable for multiple blood transfusion recipients to be tested for Hepatitis C on request.

4.12 Members agreed with the Leukaemia Steering Committee's position, but thought that the 7% figure might be quite high, depending on the dates to which it related. Dr Rejman offered to send copies of the data to those who were interested, but confirmed that none had been transfused since 1991.

4.13 The Chairman summarised MSBT's views, as concurring with the Leukaemia Steering Committee's stance. There was no reason to recommend that all children who had leukaemia and had received a blood transfusion should be tested, unless identified through the lookback programme. Equally, there was no reason to limit clinicians' freedom to offer a test if they felt it appropriate.

4.14 Dr Mortimer wondered whether younger age-groups might be targeted, but was unsure how the lookback could accommodate these. This was a reason for completing the lookback exercise speedily. Consideration could then be given to whether any group should be given priority for investigation and treatment.

4.15 Dr Toy gave an update on research. He said DH was awaiting the amended protocol for a national HCV archive from Julia Heptenstall, which the MSBT supports. The National Research Register includes a large study on the vertical

transmission of HCV being conducted by the Blood Transfusion Centre in Cambridge. The R&D Division had received two proposals - one for a surveillance study in relation to children and the other for a cohort study of HCV infected patients in Trent. The research division is finalising research vignettes and hoped to advertise these to the research community very soon.

4.16 The NHS Health Technology Assessment programme has given priority to the study of interferon alpha in early stage HCV infection. The MRC has agreed to take this forward. Exceptionally the MRC has agreed to the setting up of a trial development group prior to the agreement of funding for a trial of the clinical and cost-effectiveness of interferon alpha and ribavirin in chronic HCV infection. As interferon was now licensed, the agreement of the various purchasers involved would need to be obtained.

4.17 Dr Gorst raised the earlier suggestion of a study of the efficacy of counselling. Dr Toy said this idea had merit as but had not been seen as a priority area, and no budget had been allocated.

4.18 Dr Robinson reported that the data base was being set up for the national archive. But she was unsighted on the Data Protection Act implications where there was no explicit patient consent.

4.19 PHLS had well established procedures for dealing with such questions which Dr Robinson might be able to draw on. Local ethics committees could also be approached. Annonymisation of data could avoid problems under the DP Act. In some cases consent could be obtained retrospectively, eg those where contact was made with the hepatology unit.

4.20 Dr McClelland reported that in Scotland the transfusion service had established systems for exchanging information with other organisations.

ACTION

- Officials to prepare submission to Ministers, including possible recommendations for speeding up completion of the exercise, after consulting MSBT/working group members (paragraph 4.9)

- All National Blood Services to obtain estimates from hospitals of likely timescales for completion of tracing of medical records (paragraph 4.10.)

-Dr Mock to investigate high proportion of donations per donor in Northern Ireland suggested by their entries in the tables (paragraph 4.3)

5. Minutes of the sixth MSBT meeting - 13 October 1995 (paper MSBT 6/9)

Following comments from Dr Cant, it was proposed that the following be substituted for paragraph 12 of the minutes :

" Dr Cant mentioned two child deaths following bone marrow transplantation where there had been a failure of graft and children suffered marrow aplasia for several weeks. Both developed an erythematous skin rash and pneumonitis, and died from pneumonitis. Both had receive multiple infusions of blood products. Analysis of skin and lung at post mortem was strongly positive for HHV6 by PCR testing. There had been other reports of HHV6 related death in immuno-deficient children who had received multiple infusions of white blood cells. Thus HHV6 infection transmitted by blood products was a potential worry in patients undergoing bone marrow transplantation. Dr Cant's unit used white cell filters when giving blood products to bone marrow transplant patients, to reduce the risk of HHV6 and CMV infection, although they always used CMV negative blood so the risk of this latter infection was small. "

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

- minute 4.1 - 4.4 : arrangements for reporting transfusion events

6.1 Dr McClelland introduced this tabled paper. Most of the documents had been prepared by Dr Williamson for the steering group on reporting systems for hazards of transfusion. The initial report form was designed to be very simple, and would be followed up by a more detailed form specific to the circumstances of the case. The form did not require details of infection, as this was covered by the PHLS system.

6.2 A committee would oversee the new system, with a small executive responsible for day to day operations. It was hoped that Julia Heppenstall would join the steering group, which had no microbiologists on. Wales had been involved. It was hoped that Northern Ireland would also use the system.

6.3 Provided funding could be obtained, it was hoped that the system would become operational in April 1996. Dr McClelland and Dr Robinson were exploring ways of obtaining funding from the transfusion services.

6.4 Members supported the proposals.

6.5 The Chairman pointed out the Department would not provide protection against court sub-poena. This had only been provided exceptionally for the confidential inquiry into maternal deaths. The Chairman asked that any further comments from members be sent to Dr McClelland.

ACTION - Members to send any comments to Dr McClelland.

- minute 4.7 - 4.13: blood safety leaflet

6.6 The Chairman and members commended the leaflet. Dr Robinson said it would be officially launched on 1 February.

- minute 4.17 : optimal use of FFP

6.7 Following the last meeting Dr Rejman had advised Ministers that MSBT had not seen any need to change their previous recommendation.

6.8 Dr Robinson's hoped her article on FFP could go in the next CMO Update.

- minute 4.18 - 4.20: tissue banking review

6.9 Dr Doyle confirmed that Ministers had agreed that work on the review's recommendations could be taken forward. There were two main issues; (i) safety of tissues, (ii) setting up a supervisory or body. The former was covered by the MSBT guidance referred to under minute 6.10 below. Consultation on the tissue banking options should take place later in the year.

- minute 7.1 - 7.6 : guidance on the safety of transplantation of human tissues and organs

6.10 Dr Rejman thanked members for their final comments on the draft guidance. Ministers had now agreed to its issue. Arrangements were being made for printing, in a booklet format which should last. This would be issued as a health service guideline with no expiry date. It would be sent to health authorities and trusts, consultants in relevant specialities, and Royal Colleges as well as patient interest groups. A reference in CMO Update was planned, and it was hoped that the Colleges might mention this in their own newsletters.

6.11 The Chairman referred to draft guidelines of the Council of Europe Select Committee of Experts on the Organisational Aspects of co-operation in Organ Transplantation, on serological screening methods for the most relevant microbiological diseases of organ and tissues donors (paper MSBT 7/4). The Chairman asked if members felt that the footnote 2 on page 3 suggesting testing for anti HBc should be reflected in MSBT's guidance.

6.12 After discussion, members agreed that the note might conflict with MSBT's intention to keep practice on organs closely in line with that on blood.

- minute 8.1 - 8.3 : guidance on the collection, storage and infusion of bone marrow and stem cell

6.13 Dr Rejman thanked members for their comments following discussion at the last meeting. The sub-group would meet again on 24 January. Thereafter the draft would be sent to

all members of MSBT and to professional bodies for a limited consultation, allowing 6 weeks for comment.

- minute 11.1 - 11.2 - new hepatitis viruses

6.14 Dr Mortimer said that very little information had been published since the last meeting, although there will be a paper in Science shortly. He said that hepatitis G and hepatitis GB-C appeared to be the same agent, which affected about 1-2% of the donor population in the United States. The agent is believed to give rise to chronic infection; it appeared similar to hepatitis C. There was no serological test for it yet.

6.15 Professor Zuckerman presented details of current knowledge of hepatitis G. A significant proportion of those infected had a normal ALT. Epidemiological risk factors were similar to hepatitis B and hepatitis C. Some patients developed cirrhosis, although overall the infection is clinically mild. The antibody tests appeared unreliable, and much of the work had been done using PCR.

6.16 Professor Thomas said that the Science paper will confirm that the virus can be transmitted through transfusion. There is some response to Interferon, but with a high relapse rate.

6.17 The Committee agreed to return to the subject at its next meeting, when more data would be available.

ACTION - Dr Rejman to co-ordinate a paper for the next meeting, with contributions offered by Dr Mortimer, Professor Zuckerman and Professor Thomas.

7. CJD and blood transfusion

7. 1 Dr Purves reported that CPMP had discussed CJD and blood products twice in 1994. Experts on CJD attended these meetings. Initially the French had wanted to exclude a large group of donors, but had subsequently recognised this would mean destroying a large proportion of their available blood products. The CPMP expert group concluded that, there was insufficient scientific reason to withdraw blood products from the market, when a donor who had contributed to a pool subsequently developed CJD.

7.2 Following the recall of products by the FDA in 1995, CPMP looked again at the issue, and again decided against withdrawal. All Members States now shared this view. There was no evidence of CJD having been transmitted by blood products. Furthermore the FDA policy of quarantining products and possibly releasing them later if there was a supply problem was illogical. If products were withdrawn as unsafe, it was unclear how such products could be considered safe at a later date.

7.3 Political and legal considerations were thought to have been influential factors when America and Canada had taken large amounts of products off the market. Dr Perry noted that industry had been unable to estimate the likely effect on supplies of these product withdrawals.

7.4 Members were unanimous that decisions should be taken only on a scientific basis. The UK should carefully monitor what the FDA and other Member States were doing. Positive steps had been taken to involve manufacturers associations in decisions in Europe.

7.5 Dr Perry explained that EPFA had been developing a line, but this had been overtaken by CPMP's work. The EAPPI paper circulated in October 1995 had implicit dual standards. That could mean products rejected in America being used in Europe. But Dr Purves confirmed that CPMP had included a statement that such products should not be used in Europe.

7.6 The Chairman referred to letters from relatives of donors who developed CJD asking if blood products should be withdrawn. They were being informed of the CPMP guidelines. Some had asked if UK experts were agreed on this approach.

7.7 Dr Snape clarified existing practice :- while products manufactured from pools to which a donor with CJD were not being withdrawn, where the donor's CJD was identified at an early stage plasma was excluded from fractionation.

7.8 Dr Rejman warned that the Guardian planned an article on the subject. The Chairman underlined public interest in the subject. The UK should hold to the CPMP line, which was helpful. While Canada was doing a full lookback exercise, the MSBT confirmed its earlier advice that the UK should not do so.

8. Virological Screening of UK blood donations - HTLV I/II and HHV 6

8.1 MSBT had previously considered testing for HTLV I, but screening for other infections such as parvovirus was now proposed. MSBT needed to take stock of general policy on screening of donations.

8.2 Introducing paper MSBT 7/6, Dr McClelland was seeking initial reactions before progressing to more detailed work. The options were :

- selective testing (possibly only of first-time donors), for specific groups of recipients
- maintain universal screening of all donors for a specified list of conditions
- filtration or inactivation procedures to reduce the risk of infection from blood products

- reduce the number of donors whose blood goes into each patient

- more use of autologous transfusion for elective operations.

8.3 Tables 1 and 2 (based on data from Edinburgh) showed that when children under age 1 were transfused, it was highly likely that repeat transfusions would follow. Special consideration should be given to the transfusion needs of that age-group. These children were premature and were mainly in special care baby units, which ran their own blood banks. A donation from a donor, who had tested negative to a wider battery of tests over perhaps 2 or 3 years, might be divided into a number of paediatric size packs. These could be dedicated for use for a particular child.

8.4 It was hard to quantify the benefits of this approach, but the theoretical arguments were good. It would involve quite a lot of work to introduce, and additional start up costs. The question was whether such a system could be justified for this group of children alone.

8.5 Members welcomed the ideas in the paper. Whether a cut-off at age 1 as distinct from age 5 was right needed further debate.

8.6 It was noted that HHV-6 testing was not a viable option, as most donors would be positive. There was also no data to show whether filtration would eliminate HHV-6 infection, although this was likely.

8.7 The Chairman summarised members views that it was worth pursuing further the idea of a cut-off at 1 month or 1 year. Dr McClelland and Dr Robinson agreed to develop the logistics of the case further. The Chairman noted the duty of care to these young children which might be a defence to arguments about a two tier system. It might also be helpful later to obtain the views of the wider range of medical experts via the Standing Medical Advisory Committee.

8.8 The Chairman asked members views on the recommendation for screening for HTLV-I contained in the final paragraphs of the BMJ article circulated as part of paper MSBT 7/1. Reliable tests were available. Dr Robinson said that SAACTI would be considering aspects such as lack of viability and costs at their meeting next month. It was agreed therefore to defer discussion until the next meeting.

ACTION - Dr McClelland and Dr Robinson to develop a more detailed paper for the next meeting.

9. Screening for HIV-1 Antigen

9.1 Dr Rejman introduced Paper MSBT 7/3, and invited comments on whether HIV-1 antigen screening should be introduced in the UK. This had been recommended by the FDA. There had been no support from CPMP, as the low incidence of HIV in European blood donors meant that the slight shortening of the "window period" was likely to identify very few additional infected donors.

9.2 The committee agreed with CPMP that HIV-1 antigen screening did not represent a significant improvement over HIV-1 antibody screening.

10. Other EU activities relevant to the committee - viral inactivation of intra-muscular immunoglobulins

10.1 Dr Purves introduced paper MSBT 7/2. MSBT had expressed concern about the CPMP position at the last meeting. That position was that where additional valid viral inactivation steps had not been applied to intramuscular immunoglobulins, nucleic acid amplification tests for HCV RNA were required.

10.2 Dr Purves provided further background information to the CPMP decision. The 1994 German plan of action in 1994 had required action by manufacturers within an unrealistically short time-frame of 6 months. CPMP had in discussion with manufacturers sought information on why certain processing methods achieved viral inactivation, eg why had the Cohn fractionation method produce safe intramuscular, but not intravenous, immunoglobulins? Progress had been confounded by the FDA decision on PCR testing for Hepatitis C for intramuscular as well as intravenous immunoglobulins.

10.3 The UK view was that the quality of PCR testing needed to be proven before it was introduced. The UK wanted to look at this and ways of introducing additional viral inactivation steps in a controlled manner and in conjunction with manufacturers.

10.4 Paragraph 2.6 of the paper recognised that viral inactivation methods must not adversely affect overall safety of blood products.

10.5 Dr Purves clarified the penultimate sentence of paragraph 3.2 (page 5) and referred to discussions with the commercial sector so that they were fully aware of the proposed requirements.

10.6 Dr Purves drew attention to CPMP's conclusions and recommendations (page 12). The intent behind the first point was to introduce reality into the timescale for the exercise. The reference to "valid" viral inactivation steps was useful to flag up questions about whether particular processes, such as Cohn fractionation, had been validated. The third point, on C testing (HCV-RNA), indicated that testing was "requested" but was not currently mandatory. It was open to Member States

to interpret this pragmatically until an acceptable validated test method was available. CSM had considered the question of use of products from positive pools, and wanted to consider such issues on a case-by-case basis.

10.7 Although years of experience suggested that manufacture intramuscular immunoglobulins derived from the Cohn fractionation method were safe, data was still needed to demonstrate the validity of the viral inactivation. Because of concerns about the safety of using that method alone, some manufacturers additionally used the light exposure methods for intravenous immunogloulins, although these could not be used for intramuscular products. Dr Mortimer said he was not convinced that this made the product any safer. There was also a need to ensure that sufficient account was taken of other changes that had taken place over the years, for example changes to the quality of starting materials (viral load/antibody levels), and of new viruses.

10.8 Dr Snape anticipated that a requirement for PCR testing would be introduced in July. He was content with the position outlined in the paper. So as not to compromise safety, use should not be made of immunoglobulins from pools later found to be infected. Dr Perry was concerned about the use of "second class" product if this was released to meet supply problems, and also about the administration of the immunoglobulins to healthy women, if there was any doubt at all doubt about product safety. These concerns underlined the need for test methods to be fully validated and accepted by regulators and manufacturers.

10.9 Dr Snape noted that manufacturers practice had a major impact. If most carried out HCV PCR screening and publicised this, it would become necessary for competitors to follow suit.

10.10 The Chairman referred to paragraph 3.1. This pointed to the safety record of intramuscular immunoglobulins, but asked what would happen if batches released were later found to be PCR positive ? Dr Purves agreed that these products were believed to be safe, but stressed the need to validate safety. New approaches for doing so had been achieved over the last few years. A better forum been created in Europe involving the CPMP Biotechnology Working Party and manufacturers associations. He would carry MSBT's views to that forum.

10.11 Summing up, the Chairman noted that the position was now better than it might have been if invalidated tests had been introduced. Discussions between manufacturers and regulators paved the way for better outcomes. That we were applying an agreed European position would be a good defence should the UK's approach be challenged.

11. Any Other Business

The Committee agreed that parvovirus B19 should be on the agenda for the next meeting.

12. Date of next meeting

The next meeting would be held in May or early June, on a date to be arranged.

ACTION – Secretariat to arrange next meeting