Minutes of the Microbiological Safety of Blood and Tissues for Transplantation vCJD Subgroup

Meeting 3: Friday 16 May 2003
Room 125A, Skipton House, SE1 6LH

Present:

Chair
Professor Don Jeffries (St Bartholomew's Hospital)

Members
Dr Trevor Barrowcliffe (NIBSC)
Dr Jonathan Clewley (HPA/CPHL)
Dr Roger Eglin (NBS)
Mr Peter Garwood (NBS)
Professor James Ironside (NCJDSU)
Dr Kieran Morris (NIBTS)
Dr Neil Raven (CAMR/HPA)
Mr Graham Rowe (WBS)
Dr John Saunders (DH/MRC Advisory Group)
Dr Marc Turner (SNBTS)

Officials
Dr Peter Bennett (EOR/DH)
Mrs Jill Dhell (MDA/MHRA)
Dr Philippa Edwards (CJD/DH)
Dr Rowena Jecock (CJD/DH)
Dr Denise O'Shaughnessy (Blood&HCAI/DH)
Dr John Stephenson (RD/DH)

Secretariat
Ms Sara Johnston (Blood&HCAI/DH)
Dr Linda Lazarus (Blood&HCAI/DH)
Mr Charles Lister (Blood&HCAI/DH)

Agenda item 1 Welcome and Chairman's introduction

1. The Chair opened the meeting and welcomed Professor James Ironside (National CJD Surveillance Unit) and Dr Denise O'Shaughnessy (DH) who were attending for the first time.

Agenda item 2 Apologies for absence

2. Apologies were received from Dr Moira Carter (SNBTS), Mrs Mary Holt (CJD/DH), Dr Vicki King (Blood&HCAI/DH) and Dr Philip Mortimer (HPA/CPHL).

Agenda item 3 Minutes of the last meeting

3. Comments were invited on the accuracy of the minutes. The minutes were accepted as an accurate record of the meeting subject to the following changes:
   - Members attending: Dr Morris's affiliation to be corrected to NIBTS.

- Paragraph 8: to add reference to representation of the Welsh Blood Service on KEG.
- Paragraph 10: confirmed that recombinant prion protein is most stable at low pH.

Agenda item 4 Matters arising

4. Actions from the previous meeting were reviewed and updates provided for those not listed as separate agenda items.

Agenda item 4.1 Verbal updates on actions from the last meeting

5. Action 1: Seminar on the ethical and social issues surrounding a blood test for vCJD. Holding the seminar had been agreed in principle. No date had been set, but the aim would be to hold it in the current financial year (i.e. by end of March 2004). It was hoped the seminar would reach a wide audience, including consumer and patient groups, but it would not be a public awareness campaign. Reaching a professional consensus through this forum would be valuable but was not a primary goal.

   Action 1(3): CJD Policy team to inform the group once the date has been set.

6. Action 2: Legal position on disclosure. MHRA were continuing to follow this up with lawyers.

7. Action 3: Risk assessment. NBS reported that the risk assessment had been completed and submitted to HSE and a response from the HSE was awaited. Members' attention was drawn to the extract from the Biological Agents Bulletin from December 2002 (included as an information paper) which included guidelines from the HSE on safe handling of known or suspected CJD-containing specimens. The guidance had been issued in response to concerns that patient care might be compromised if laboratories felt unable to process these samples without containment level 3 facilities.

8. Action 4: Target repeat reactive rate. NBS confirmed that a repeat reactive rate of more than 0.2%, using one or more tests, would result in unacceptable levels of blood wastage. [In practice, a repeat reactive result requires re-testing in duplicate of an initially reactive sample and for at least 2 of the 3 tests to be positive. If two tests are used, greater confidence would be placed in the result if a sample is repeatedly reactive in both assays.]

9. Action 5: Amendment to Annex II List A of the in vitro diagnostic devices directive. The subgroup's recommendation to add CJD to Annex II List A would be on the agenda for discussion at the next MSBT meeting on 10 June 2003.

10. Action 6: Clarification of the boundaries for DH involvement in NBS's evaluation work. There was a concern that if DH were closely involved with the setting of the standards that a diagnostic device would need to meet (prior to evaluating), this might constitute a technical barrier to trade. Accordingly, MHRA would be seeking legal advice and planned to meet with DH (RD) in the near future to discuss this.

11. Action 7: Standards (see also agenda item 5). Preliminary discussions had already taken place between NBS and NIBSC on preparing/supplying suitable

standards and reference reagents (currently based on brain or spleen). Collection of animal sera from the Institute for Animal Health for future evaluation was already under way and NIBSC had been in contact with the Veterinary Laboratories Agency. It was felt to be logistically difficult and probably unnecessary (because of sufficient ongoing work) to inoculate sheep with BSE solely to provide a source of sera for making reference reagents.

12. Action 8: Archive storage temperature. SNBTS would check what temperature they have used for the Scottish virology archive and report back. [After the meeting, SNBTS informed the Secretariat that samples are stored at -20°C.]

13. Action 9: Standard protocol for processing blood samples. Paper [16.05.03 – 1] was provided in fulfilment of this action.

14. Action 10: Availability of clinical specimens. Members were advised that the National CJD Surveillance Unit (NCJDSU) has a limited range of samples from patients with various forms of CJD but that they were not the sole repository. Once a test becomes available it may be possible to collect specimens prospectively. The DH Tissue Management Group (TMG) is preparing an inventory of archived UK specimens. Part of the TMG's role will be to draw up a protocol to guide best use of this limited resource, including bona fide commercial purposes.

15. On the question of consent for commercial uses, NCJDSU have obtained ethical approval to distribute patient material to third parties for research, including commercial research, applications. This is consistent with guidance on research uses of existing stored organs and tissues set out in the DH publication 'The use of human organs and tissue: an interim statement'. Constructive discussions have also been held with patient support groups who are generally aware of the need for commercial involvement. It is important that consenting process covers commercial uses and conforms with relevant European requirements (e.g. European Convention on Human Rights and Biomedicine, Clinical Trials).

16. The subgroup was assured that the WHO standard reference materials, which are ultimately derived from human tissue, have the appropriate ethical approval for wide distribution to both commercial and non-commercial organisations for research use.

Agenda item 4.2 Action 9: NCJDSU Blood Component Separation Protocol [16.05.03 - 1]

17. A standard operating procedure (SOP) for handling blood samples had been provided in fulfilment of action 9(2). Concern was expressed that blood samples were being stored inappropriately and separated in different ways, with inadequate quality control, when sent to other laboratories. The NCJDSU protocol uses citrate as the anticoagulant because of concerns that calcium chelation (by the standard anticoagulant, EDTA) may induce conformational changes in the prion protein. Importantly, this is compatible with the WHO protocol, which also uses citrate buffer.

18. This protocol has been made available to the TMG for wider dissemination. The aim is to encourage the use of a common SOP for prospective sample collection to enhance the usefulness of those samples.

Agenda item 5 **Standards and reference reagents for detection of vCJD infectivity in blood and blood products [16.05.03 – 2]**

19. This paper provided more detail on standards and reference reagents, a topic which was raised at the second meeting of the subgroup (see paragraphs 31-32 of minutes).

20. Three types of material are currently under consideration/investigation as possible blood reference materials:
    (i) Plasma spiked with a dilution of human brain (using the WHO reagents) – this is the most useful general purpose reagent but aggregated abnormal prion in brain may have a different physical form to blood infectivity, although this need not matter (depending on assay format). High infectivity in brain means that a single organ can supply large amounts of reference material. This may be an important consideration given the current decline in vCJD cases.
    (ii) Spleen from vCJD patients (neat and/or diluted in plasma) – abnormal prion is associated with the germinal centres as in other lymphoid tissue. Levels of infectivity measured by bioassay are similar to tonsil but lower (~100-fold) than in the CNS, so more spleen may be needed. Spleen homogenates are prepared as for brain, without pre-treatment (e.g. collagenase could render spleen into cell suspension). Undiluted samples are already available through WHO channels and laboratories developing assays are being encouraged to evaluate this reagent. Diluted spleen might make a useful go/no go standard for blood services.
    (iii) Blood from infected animals (sheep, hamsters) – some small volume samples from transfusion experiments in sheep are being stored with a view to collecting larger volumes if infectivity is detected.

21. Normal prion protein (PrP) and recombinant PrP also warrant development as reference materials. As a synthetic reference material, recombinant PrP has the advantages of being non-infectious, unlimited availability (in principle) and constant composition over time (in contrast to, for example, clinically derived material). Recombinant PrP may be useful as a quantitative standard, except for assays requiring proteinase K pre-treatment as its structure differs from the native form of the protein and this gives rise to different enzyme digestion products.

22. It was reported that clinical samples provided for ERDF analysis had yielded interesting preliminary results but no further details were currently available.

    Action 2(3): NIBSC to add recombinant PrP and normal PrP to reference reagents held by the CJD Resource Centre.

    Action 3(3): NIBSC to consider collagenase treatment to render vCJD spleen into cell suspension, as an alternative to homogenisation, for preparation as a reference reagent.

23. The NBS requires 6000x1ml ampoules of standard per year for each of its current antibody tests. Estimates are needed for the amount of vCJD standard reagent likely to be needed – this may influence decisions relating to the development of blood reference materials.

    Action 4(3): NBS/NIBSC to estimate the quantity of vCJD reference material required to support routine blood donation screening.

24. It was noted that the IVD Directive requires manufacturers to use available international standards in their performance evaluation. The reagents under discussion would therefore be included amongst the manufacturer's controls or would need to be traceable to them.

Agenda item 6 **Feedback from the SEAC Epidemiology subgroup meeting on 12 May**

25. Advice had been sought from the SEAC Epidemiology subgroup on two specific issues at the request of the vCJD subgroup. Firstly, their views were sought on the size and structure of the test assessment panel and secondly, on what further epidemiological studies should be undertaken to measure the UK prevalence and gain a better understanding of the significance of reactive results once a blood screening test was in routine use.

26. In discussing the suitability of US donors as the most appropriate control group, the issue of chronic wasting disease was raised. (This was addressed by the subgroup previously.) US donors who lived in UK/Europe during the height of the BSE epidemic are already deferred but excluding visitors to the UK/Europe in the 1980s was also suggested. Sourcing the control panels from India or Australia was proposed, but issues of adequate process control and distance, respectively, ruled these out as viable alternatives. Furthermore, US plasma is soon to be imported as a vCJD risk reduction measure.

27. The Epidemiology subgroup agreed that the UK and US donor groups should be matched for age-band and gender. Matching for ethnicity was desirable but not feasible. It should, however, be recorded in case of racial differences in surrogate markers. Genotype analysis was also suggested as was collecting donations from life-long vegetarians only (control panel) or recording dietary histories. Although of potential interest for interpretation of results, these were dismissed as impracticable.

28. The Epidemiology subgroup provided no clear advice on any additional studies to be done. NBS confirmed that, as for other markers, any donors with reactive results in a vCJD screen would be followed up and a lookback conducted (if a repeat donor).

Agenda item 7 **Draft contingency plan for the introduction of a blood screening test for vCJD [16.05.03 - 3]**

29. A draft contingency plan [paper 16.05.03 - 3] had been drafted by the Secretariat for discussion and to agree the way forward for presentation to MSBT. The central requirement was a protocol for establishing a Test Assessment Panel (TAP) with consideration of the infrastructure needed, consent requirements and associated research needs.

30. NBS stressed the need to establish the infrastructure for collecting and storing the TAP as soon as possible because of lengthy lead times on acquiring laboratory space and equipment and recruiting staff and the need to develop IT systems for storage and retrieval of replicates. From a risk management standpoint, NBS argued that it would be prudent to collect the sample panel prior to a test becoming available, despite considerable uncertainty about the final format of potential assays. Previous estimates were that 20-30 donations could be processed for the panel per day, but if the options appraisal (see below)

favours fewer components, the daily throughput could be higher. NBS needed to be taking all reasonable steps (based on the best available evidence) to ensure that a suitable test could be implemented promptly. The TAP would therefore need to be flexible enough to adapt to the most likely test formats and the plan might need to be modified in light of new evidence. Urine tests are known to be in development, but the Blood Services explained that it would be impractical to collect urine at donor sessions under conditions that would comply with GMP.

31. Two key issues to resolve were which blood elements to store and whether to store replicates. The proposal to store 48 replicates (a number chosen for handling convenience) was accepted on the basis that replicated samples would be more powerful for generating comparative specificity data. On the question of which blood components to collect, the subgroup agreed that it was important to keep more than one component and asked that an options appraisal be conducted to inform this decision.

    Action 5(3): NBS/SNBTS to perform an options appraisal of the range of possible blood components to collect for the panel to inform the plan.

32. In discussing the details of the plan, a number of interesting points were made including:
    - the potential risk in investing in new buildings and facilities to prepare for a test that may not be considered significant in 5 years time (declining epidemic [see AOB]);
    - it was suggested that the composition of the panel might guide what manufacturers choose to develop as assays but in reality, the blood service will have to adapt to whatever test comes along;
    - compared with the costs of other vCJD risk reduction strategies, such as leucodepletion and importing US plasma (both introduced as precautionary measures), the costs associated with the TAP proposal are relatively modest;
    - access to the TAP samples would be restricted to testing commercially available systems or those very close to being marketed (a steering group will set the criteria to be met); NIBSC's CJD resource centre would provide standards for commercial/research use;
    - for the benefit of the other UK Blood Services, NBS were asked to specify the number of units they would expect each blood service to contribute to the TAP to make it representative of the UK's *donor* population (rather than the UK population);
    - it was questioned whether a duty of care would arise if reactive samples are found in the TAP of 5000 donors. It was agreed that irreversible anonymisation negates the duty of care and this is ethically acceptable if the terms of consent clearly state that individual results would not be available to feedback to donors. The experimental nature of the test makes interpretation of results difficult. However, in the event that a donor wished to determine the results of their test then they could request an individual named test with appropriate counselling.
    - it was pointed out that the central office for MRECs ordinarily assigns a proposal to the region of the principal investigator; however, if a proposal is presented as a continuation or extension of one that was previously considered (i.e. a precedent exists), the office would select the same MREC as considered the original application to benefit from its knowledge of the issues.

Action 6(3): **Secretariat** to revise the workplan to include a timescale for implementation, and circulate to Members for comment.

Action 7(3): **NBS** to provide detailed costed options based on the revised workplan to DH for consideration.

Agenda item 8 **Next steps**

33. The revised contingency plan would be presented to MSBT at the meeting on 10 June 2003.

Agenda item 9 **Any other business**

34. After the conclusion of business, the Secretariat was alerted to an upcoming paper in BMC Infectious Diseases by Ghani *et al.*, 'Updated projections of future vCJD deaths in the UK', which suggests that the primary epidemic in the known susceptible genotype in the UK is in the decline. The Secretariat offered to circulate a link to the paper or a pdf with the minutes.

Action Points

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