GENERAL COMMENTS

1. Section two of the report outlines the overall approach that DNV have taken. One issue not addressed is the issue of possible cumulative risk due to repeated exposure. My recollection from earlier discussions is that this is not considered to be an issue. However it will be helpful if a clear statement on this might be introduced. Specifically for patients receiving repeated transfusions, particularly of plasma derivatives, is there any risk of repeated subinfective exposures resulting in , or increasing the likelihood, of clinical disease.

2. Figure 3.3 has been designed to demonstrate that the assumptions utilised in developing the model have been adjusted to meet the rate of case accrual identified to date. This suggests that approximately 45 new cases will be identified during 1998, the actual number of cases identified in year is significantly less than this. A comment on this will be helpful.

3. The assumptions used to produce table 4.3 are outlined in appendix I. The appendix identifies the lack of firm data on transfusion epidemiology and survival. This is not however clear within the text of section four. This is a concern for a number of reasons.

- It appears that data from table 4.3 makes an important contribution to the data presented in figures 4.6 and 4.7. If this view is correct then the data, and the underlying assumption, take on a significance that was not apparent when appendix I was initially reviewed. The lack of certainty in the raw data should therefore be explicitly stated in the text of section 4. I also believe that it will be helpful for a sensitivity test on the data to be undertaken and reported within the text. Clearly concern over the validity of conclusions identified in tables 4.6 and 4.7 will be less if it can be shown that individual assumptions in table 4.3 do not significantly influence the subsequent figures.

- The patient groups identified within the tables require careful review. The appendix does not identify the source of data , these should be identified if available. My impression from the appendix is that much of the data has been developed empirically, in part utilising the SNBTS study data. Recognising the process that you have used I would suggest that the patient group headings be changed as identified below, this of course applies to table 4.5 as well.

  - Acute blood loss (including surgery)
  - Acute blood loss ,complicated
  - Massive blood transfusion
  - Chronic acquired anaemias (I suspect life expectancy is too high)
  - Bone marrow failure (I suspect that the life expectancy is too high)
  - Combined anaemia/coagulopathy (in appendix identify e.g. liver disease/DIC)
  - Congenital anaemias
  - anaemia of prematurity
  - HDN babies
  - other causes anaemia

It might be better to combine the "other causes of anaemia" and the chronic acquired anaemia categories. Whilst the anticipated level of exposure and expected survival are different there will be considerable clinical overlap between them. I suspect they could be combined with a common life expectancy of 15 years and an average exposure of 4 units per year without a requirement to remodel the data. One significant benefit of a combined approach is that it will avoid difficulties in definition of two very similar groups. personally at this stage I am personally not certain of the difference between them.

The more general nature of the groups should reduce adverse comment, particularly so if sensitivity testing (see above) demonstrates that alteration of survival or numbers for each group does not dramatically alter the conclusions.

-It will be helpful if information can be provided on how the data identified within figures 4.6 and 4.7 has been derived. How dependent on table 4.3 is this. In particular what assumptions on survival post transfusion have been used, is this based on a simple estimate of 50% for all recipients or is it derived from data for individual categories presented in table 4.3.

- On page 17 (paragraph 3) the report identifies that 6% of blood donors report a history of transfusion. This is . I am however less confident that the following sentences are correct, and concerned that the text implies that the deduced figure of 5% lends support to the accuracy of data presented in table 4.3. A significant proportion of recipients of single transfusions (new within your definition) will be elderly (see SNBTS data) or excluded by virtue of underlying disease Thus a significant proportion of the 170,000 newly exposed patients will not be available to donate. This emphasises the fragility of data in table 4.3, it will be important not to imply otherwise.

4. My understanding is that one of the key requirements identified by SEAC when the risk assessment was commissioned was to assess the possible role for leucodepletion in reducing the likelihood that transfusion will be an important vector for transmission of nvCJD. If this is the case then I believe a more detailed evaluation of the possible role for this intervention is indicated. A number of issues can be identified.

-Current technologies will consistently reduce the level of white cells by at least 3 log orders of magnitude when compared to whole blood or red cell concentrate, in the majority of instances a 4 log reduction will be achieved. This should be clearly stated. It will also be important to clearly explain, given the TSE distribution assumed for the report, the reason for the difference between reduction in white cell level and reduction in infectivity- this requires to be clearly stated . This is not also the case, and in some instances (see specific comments) I believe that incorrect statements might have been made.

I am concerned that the comparison of white cell levels refers to leucodepleted against buffy coat depleted red cells. A more appropriate comparison would be to compare against the standard product produced by centres, namely red cell concentrate. I have no objection if additional to this comparisons between two possible interventions are identified (that is universal leucodepletion versus universal buffy coat removal) The primary comparison however must relate to current standard practice.

I am concerned that the possible benefit of leucodepletion is not fairly presented. Whilst I recognise the concerns relating to membrane fragments, and also that platelets might carry the prion, I believe that a more detailed sensitivity analysis of this intervention should be undertaken. Other than the unpublished work of Brown and Rowher I am not aware of data that identifies fragments to be more than a theoretical concern.

Membrane fragments might arise in two settings, firstly as a consequence of storage and secondly consequent upon passage of blood within the filter. The plans for implementation of leucodepletion within the NBS in England will require filtration to be undertaken within 48 hours of collection. This would be a maximum limit with most blood being processed earlier than this. This approach should greatly reduce the risk of membrane fragments arising because of storage. It is also the case that the routine filters which will be applied to red cells will remove the majority of platelets, thus removing an additional source of residual PrP. In the absence of clear data that fragments do occur I believe that the report's conclusion are pessimistic, and will appreciate it if this can be reassessed.

The section on leucodepletion requires to be expanded and the conclusions reassessed. The conclusion might be rephrased as identified below.

The maximal benefit that might be achieved by leucodepletion would be a reduction in total cases attributable to transfusion by 85%. This figure is likely to be reduced significantly if membrane fragmentation occurs during early storage or as a consequence of the filtration process. Research in this area should be considered a priority for the Blood Services.

On the basis of this assessment leucodepletion will need to be shown to reduce infectivity levels in blood by more than a factor of 100 before it is likely to have a significant impact on the number of cases which will arise from this source.

I will also appreciate it if sensitivity tests can assess the impact of combining leucodepletion with removal of plasma from red cells and platelets. The use of artificial additive solutions means that this is practical, indeed the majority of red cell issued to hospitals are in this form. If the concern that leucodepletion might be ineffective relates to membrane fragments then presumably removal of plasma might impact on this.

The above issues will be important to transfusion services which will require to develop strategies for component production that will minimise any risk. Whilst I recognise that the available data might be soft it will be important to understand the potential value of various interventions.

5. The report identifies that a two log reduction in infectivity would reduce the risk from platelets and from FFP considerably. One issue that is currently the source of debate within transfusion circles relates to the most appropriate source of clinical FFP. Currently this is derived predominantly from whole blood donations. However a pooled virally inactivated preparation (600 donors)is now available produced from German volunteer donors. The relative benefits of the two preparations will be important, the FDA within the US has recently identified that the two products should be considered equivalent with respect to standard viral risks. It will be helpful if some guidance can be provided on the relative risk from the vCJD standpoint. My interpretation from the assumptions made is that , even if it is assumed that the level of risk within the UK and German donor population is the same, that the dilution associated with pooling will reduce the risk of transmission. I will appreciate guidance on this point, again it is a real dilemma for clinicians prescribing FFP.

6. The report identifies that one measure that might significantly reduce the level of transfusion mediated cases is to exclude donors who have themselves received components from donating. This intervention will have a significant impact on the ability of Blood Services to meet demand from hospitals for blood. This in itself potentially results in a risk to prospective recipients. I believe that additional information should be provided to identify the assumptions used to produce the level of benefit stated within section 5. I recognise that 6% of the donor population will give a history of transfusion, I am somewhat suprised that the benefit of excluding this group of donors will reduce the risk by 16%, or even higher. What level of prevalence of infection within the donor population is assumed here. Clearly this measure should be considered if it can be shown to be of likely benefit, the impact on availability of blood and also the impact on donors excluded because they are assumed to be at risk will need careful consideration .

7. The report contains much data, often based on relatively uncertain assumptions. Will it be possible to provide some indication of confidence limits ,at least for the most important conclusions? Data presented graphically will often appear to imply certainty, or at least accuracy. This effect will be reduced by introduction of confidence limits, or a statistical assessment. I recognise the difficulties that this assessment provides, and that the process of sensitivity testing might overcome some of these issues, but clarification on confidence levels will be helpful.

8 . Appendix 3 attempts to put the risk of acquiring vCJD in context. This is eminently sensible. The appendix clearly differentiates acquisition of infection from development of clinical disease. This distinction is less clear in section 4.9, this should be corrected. I will also appreciate it if the source of the 450 deaths from leukaemia in patients under 45 is identified. How well does this figure sit with the data presented within table 4.3?

9. The conclusions identified within the report are likely to have a significant adverse impact on confidence in the safety of blood available for transfusion within the UK. I recognise that the purpose of the risk assessment is to provide a realistic assessment of the risk. I do however believe it will be

important that the conclusion are presented in a manner which will assist the Blood Services to handle the public concerns that will arise.

Conclusion 7 which addresses the potential value that leucodepletion might provide will need to be reviewed in the context of the issues identified above.

I will prefer it if conclusion 9 is split into two. The first identifying the issue of reduction in exposure to allogeneic blood. The issue of the suitability of previous recipients as donors deserves a separate paragraph and I believe that the balance of benefit against possible non-availability of blood components should be clearly stated.

SPECIFIC COMMENTS

Section 1 Management summary (page1)

1. Conclusion 7 . change to ...any reduction in the use of allogeneic blood will give....

2. Conclusion 7. ... This latter measure need only be applied to recipients of blood components, not plasma derivatives. This needs to be balanced against the effect this would have on the availability of blood to patients.

Section 2 Overall approach

1. page 3 section 2.5 additional sentence

Comprehensive information on the epidemiology of recipients of UK blood components is not available. The data utilised within this study is based on an extrapolation of data derived from a number of sources, thus introducing a further area of uncertainty and possible error. The availability of accurate data in this area would facilitate future analysis as the impact of any epidemic becomes clearer. This should be considered as a priority area for research for UKBTSs.

2. 6 section 3.3.1 paragraph 2.

....total infectious animals eaten, advanced infections eaten and the number of cases of BSE identified in cattle

Section 3 Infection from food

No comments

Section 4 risk from vCJD due to blood

1. page 11 section 4.2 paragraph 2

However there have been 4 experiments in which infectivity was detected in the recipient animal (mouse, hamster or guinea pig). All 4 cases involved intracerebral inoculation, no published reports of transmission following intravenous inoculation have been identified.

Other experiments using TSE models in laboratory animals have detected infectivity in blood, all reported cases followed intracerebral ,as opposed to parental , inoculation.

Section 4.2 additional paragraph.

These studies did not investigate the potential impact of leucodepletion and hence cannot assist with the assessment of the potential value of this intervention.

2. page 13 section 4.4.2 paragraph 1

The first stage of processing plasma into blood products involves cryoprecipitation followed by ethanol fractionation.

3. page 13 section 4.4.2 paragraph 3

Estimates of infectivity for various plasma derivatives ... delete blood products

4. page 15 section 4.5 assumption 6.

I find this section confusing, and am not certain what the two stated assumption mean. In particular where the sensitivity test is identified as reducing infection by 3 orders of magnitude (based on white cell content) should not a 3 log reduction in magnitude be modelled.

5. Page 15 section 4.6 table 4.2

The platelet data should be identified to refer to adult therapeutic doses. The statement dose is not sufficiently specific and will add confusion. This applies to table 4.3 also.

A similar change will be required for the identical tables within appendix I

6. Page 20 section 4.8 final sentence.

Change to;

On the basis of the assumptions utilised within the model it is clear that infectivity in blood might make a significant contribution to the overall epidemic within the UK. It must again be emphasised that , given the uncertainty surrounding many of the assumptions, that the percentage increase in cases over those attributable to food is likely to be more reliable than the absolute number of cases.

7. page 22 section 4.9 paragraph 4

..probability of HIV infection through blood components ..... delete products

8. page 22 section 4.9 paragraph 5

change final sentence to ;

Hence it remains the case , despite the risk of developing vCJD by transfusion identified within this model, that for those patients for whom definite clinical need for transfusion can be identified ,and where alternative therapies are not an option, that the balance of risk continues to favour transfusion.

Section 5 Measures to reduce the risk of infection from blood

1. Page 24 section 5.1

Line 3. Change thyroid to tonsil

2. Page 24 section 5.2

The first sentence should be altered to read:

In May 1998 following a review by the committee for Safety of Medicines the secretary of State for Health decided that , since the theoretical risk that nvCJD could be transmitted by blood products cannot be discounted, that UK plasma should no longer be used for the manufacture of pooled plasma derivatives.

3. Page 25 section 5.4 Conclusion.

An additional sentence should be added .

The benefit of this intervention will need to be carefully balanced against the effect it would have on the availability of blood components to patients.

Appendix 1

1. page I.5 paragraph 3

Line 8 should read 40-50 not 50-50

2. page I.6 . The table shows an apparent increase in donation rate for individuals aged 65. Whilst 65 is the normal age for retirement from donation a significant proportion of donors are allowed to continue up to their 70th birthday. I suspect that the data provided to you included donations 65-69 , and not 65 as assumed. I suspect that this explains the apparent increased rate of donation at age 65, i.e. it is an artefact . this should be corrected, including the figure on page I.6.

3. page I.7 section I.3.5

Suggest replace para 2 with

Donors undergo a health assessment and simple check for anaemia. Approximately 7-10% of donors attending will not be bled on the basis of these measures. All donations are screened during processing for evidence of infection with HIV, hepatitis B and C, and syphilis. A small proportion of donations will be discarded on the results of this testing ,and more donations will be lost during component production. Overall, about 98% of completed donations will result in usable blood components (based on experience at the Manchester Blood Centre).

4. page I.10 section I.4.4.3 para 2

This should read ..... 240ml of red cells, 13ml of buffy coat and 100ml of SAG-M.

5. page I.12 section I.4.5.3 para 5 final line.

This should read .... with many of the Cobe procedures yielding double doses

6. page I.21section I.6.5

The statements relating to platelet transfusion are incorrect and do not conform to the revised appendix I provided to DNV. The following points need to be made

- Para 3. ..... Using the SNBTS average of 3 therapeutic doses per patient suggests that 71,000 patients receive platelet transfusion each year.

-Para 4 A rounded figure of 70,000 patients receiving platelet transfusions each year is used, with an average of 3 therapeutic doses being transfused to each patient. Within the NBS each therapeutic dose will comprise 4 individual donation exposures.

It is possible that the above interpretation of the data will alter your calculations.

7. page I.21 section I.6.6

Bullet point 3 of list should read

.. Correction of coagulation disorders associated with massive blood transfusion.

8. Section I.7 page I.26 onwards.

The patient category titles should be adjusted to reflect my recommendations on table 4.3 in the general comments section above.

9. page I.27 section I.7.3

I believe that the bullet point descriptions of individual categories will be acceptable if the new titles are included for the first 3 categories. I suggest the following for the 4th category i.e. congenital anaemias.

Congenital anaemias, representing the range of inherited blood disorders leading to anaemia. In the absence of any data these are assumed to account for 5% of patients with chronic anaemia, i.e. 7,000. This category will included patients with thalassaemia major who might require regular transfusions every 4 weeks and also patients with sickle cell disorders where the requirement for transfusion will be less frequent and more variable. On average it is assumed that patients receive 5 red cell units per year. the average life expectancy is assumed to be approximately.

10. page I.28 section I.7.5 final paragraph.

Suggest change text to

Recommendations for the use of anti-D immunoglobulin have recently been reviewed. These identify that implementation of routine antenatal propylaxis will reduce the rate of sensitisation, the recommended dose schedule involves two 500iu doses during the final trimester of pregnancy. Implementation of this will result in exposure of an extra 15,000 women (and their foetuses) per year in England and Wales.

11. page I.29 section I.7.6 para 4 final sentence.

Suggest change to

Platelet transfusions are usually administered to patients also receiving red cells. For the purpose of this study it is assumed that 70,000 patients receive platelet transfusions each year within England and Wales (see Section I.6.5)

Bullet 1 .... Final sentence change to These are covered under bone marrow failure above (section I.7.3)

12. page I.30 section I.7.7 sentence 2

Suggest change to

In the absence of data on numbers of patients, these are covered under acute blood loss and combined anaemia/coagulation disorder (section I.7.3)

13. page I.30 section I.7.8

If retained as a separate category then the title should be changed to Other causes of anaemia
Suggest change text to

The remaining 25% of red cell transfusions will be given to patients with a wide variety of medical conditions. An average of 2 units per patient is transfused, with average remaining life expectancy of 15 years.

14. page I.31 section 1.7.13

The table and the text within this section will need to be altered to reflect the general and specific comments already identifed.

Peter Flanagan
May 1998