SACTTI WORKING GROUP ON vCJD
PRION REDUCTION FILTER EFFICACY SUB GROUP MEETING
TUESDAY 20th SEPTEMBER 2005
POSTGRADUATE EDUCATION CENTRE (CRAIGMILLAR ROOM)
ROYAL INFIRMARY OF EDINBURGH

IN ATTENDANCE: Dr Mark Head
Dr Frank van Engelenberg
Dr Mark Sutton
Dr Lorna Williamson
Dr Robert Somerville
Dr Mark Glatzel
Dr Neil Raven
Dr Paul Harrison
Dr Stephen Dobra
Dr Marc Turner

APOLOGIES: Professor David Anstee
Dr Peter Bennett
Dr Chris Prowse
Dr Elizabeth Love
Dr Phil Minor

1. WELCOME

Marc Turner welcomed Drs Frank van Engelenberg, Markus Glatzel, Stephen Dobra and Robert Somerville to the group. Professor Moira Bruce, Dr Rebecca Cardigan and Dr Peter Foster have left the group.

2. MINUTES OF LAST MEETING

There were 2 minor amendments following this the minute was accepted as correct. There were no matters arising not already listed on the minute.

3. CONFLICTS OF INTEREST

No further conflicts of interest were noted.

4. REPORT FROM PRION REDUCTION WORKING GROUP

Lorna Williamson reported that progress was being made in the phase 0 (pre-clinical) evaluation of the Pall filter and phase 1 clinical studies were due to start in Ireland with 20 patients receiving a single unit of prion-reduced red cell concentrate, 20 patients 2 units and 20 patients 3 units. The intent was to establish the extent of immediate adverse effects. Two clinical safety studies were planned to commence in the New Year, the first in 300 patients undergoing complex cardiac surgery and the second involving a randomised controlled study with 150 multi-transfused haematology patients in each arm. The intent of both was to establish the incidence of adverse events including allo-immunisation rates. It is hoped that the 2 studies can be overlapped to a certain extent once sufficient initial safety data has been obtained

from the cardiac study. It is felt likely that the clinical studies will take at least 12 months to be complete *i.e.* the end of 2006 at earliest. Lorna Williamson and Marc Turner are intending to brief MSBTO at its next meeting, highlighting the timeframes involved and raising the question as to how much data MSBTO would be satisfied with before making an initial decision with regard to implementation. One proposition is that a phased implementation could be commenced once the initial data is available from the cardiac study and should be accompanied by close patient monitoring for adverse effects.

5. REVIEW OF RISK ANALYSIS

Dr Stephen Dobra spoke to the most recent draft risk analysis which is based on the infectivity model of Bob Rowher *et al.* It suggests that, under the assumptions made, at least a 3 log reduction in infectivity would be required across the prion reduction filter in a bottom/top red cell concentrate to significantly reduce transmissibility. Stephen Dobra emphasised the contingent nature of the analysis up on the assumptions made around the infectivity. Chris Prowse has raised some issues. Stephen Dobra indicated that some of these had been taken into account in a previous ESOR document which had been circulated to members of the group. Marc Turner asked him whether he could respond to Chris Prowse by e-mail in Chris's absence.

Stephen Dobra indicated the risk assessment had gone on to consider likely cost effectiveness in terms of quality adjusted life years saved. Marc Turner indicated that though this was interesting and important data it was not the remit of this group to consider the issue of cost effectiveness, but only to advise on the likely efficacy of the filters and give an opinion as to their potential impact in terms of reducing secondary vCJD transmissions.

6. REVIEW OF PALL DATA

Marc Turner indicated that since the multi-institutional confidentiality agreement had not being signed off the Pall data could not as yet be reviewed by the group. The data had been made available to the Prion Reduction Working Group (to which confidentiality agreements already apply) who had fed a number of comments back to the company. It was felt that it would be valuable to formally review the Pall data at the next meeting if possible in the presence of appropriate company representatives.

7. REVIEW OF PRDT DATA

Similarly multi-institutional confidentiality agreements had not yet been agreed with PRDT and so this data could not be shared. The group similarly indicated that they would like to review the data at the next meeting in the presence of members of PRDT.

8. INDEPENDENT EVALUATION STUDY

Marc Turner indicated there it was now an unavoidable delay in initiation of the independent evaluation study because the cost would require an OJEU advert process which takes in the order of 3 months. It was agreed therefore that the current meeting would finalise the efficacy evaluation specification and that the OJEU advert process

would then be initiated. An intermediate meeting of a subset of the group will be necessary to clarify the specification with prospective tenderers, and then a further full meeting will be required to choose a tendering organisation. Marc Turner indicated that following discussion with Drs Neil Raven and Marc Sutton it has been agreed that since HPA are likely to tender for the work they should not participate in the OJEU selection process.

There was further discussion on the optimal structure and timing of evaluation.

It was agreed that phase 1 efficacy studies should consist of 263k hamster brain in 3 formats, crude brain homogenate, microsomal fraction, and sonicated microsomal fraction spiked into red cell concentrate, each of these carried out in triplicate in a total of 9 experiments. The initial data will be on Western Blot though BioAssays will also established.

In parallel, 301V spleen homogenate will be tested in triplicate by Western Blot going on to bioassay.

The purpose of these studies is both to replicate the primary data provided by the companies and also to extend that data into an arguably clinically more relevant system.

As a phase 2 study it was agreed that it would be desirable to set up an endogenous infectivity study to establish that the filters also removed the physico-chemical prion species found in plasma. This study would need to be informed by the phase 1 experiments outlined above.

It was agreed that variables such as temperature of filtration and head height should be resolved by the companies and that the independent evaluation studies should only relate to the optimised conditions.

It was felt that GLP was not necessary in this setting and that from the point of initiation of the studies it might be possible to achieve Western blot data in approximately 6 months though the results of the bioassays could take up to 2 years to come to fruition.

With this strategy agreed, Marc Turner and Lorna Williamson will write back to SEAC and to MSBTO and UK Forum notifying them of these timeframes, and in the meantime that the OJEU advert process would be progressed. *Action: MLT + LW*

9. AOCB

There was discussion over process monitoring and the group were informed that both companies had been asked to propose surrogate markers. Suggestions at the present time included prion protein, Factor IX and pro-thrombin (Factor II). One of the challenges will be demonstrating parallelism between reduction of these factors and reduction in the infectious agent and the rationale for believing that both are being removed or absorbed using a similar mechanism.

10. DATE OF NEXT MEETING

It was agreed that the next meeting would probably need to be in mid December driven by the 2 objectives of reviewing company data in their presence and making a decision with regard to the OJEU tenders.