DRAFT

Minutes of the First Meeting of the

CJD Therapy Advisory Group

Date: Wednesday 23 October 2002.

Time: 11:00 am

Venue: Eastbourne Terrace, Paddington

Present

Chair	
Sir Michael Rawlins	National Institute for Clinical Excellence
Members	
Professor David Chadwick	Walton Centre for Neurology & Neuro-surgery, Liverpool.
Professor John Collinge	MRC Prion Unit
Professor Janet Darbyshire	MRC Clinical Trials Unit
Dr Brian Davis	Medicines Control Agency (Licensing)
Mr Lester Firkin	Human BSE Foundation.
Dr Richard Knight	National CJD Surveillance Unit
Professor Richard Lilford	Department of Public Health and Epidemiology, University of Birmingham.
Mrs Gillian Turner	CJD Support Network.
Professor Charles Warlow	Association of British Neurologists.
Officials	
Dr Mark Pitman	Medical Research Council
Dr Elaine Gadd	Department of Health
Dr John Stephenson	Department of Health
Observers	
Dr Elizabeth Mitchell	Department of Health (NI)
Mr Tim Gardner	Department of Health
Secretariat	
Dr Rowena Jecock	Department of Health
Mrs Mary Holt	Department of Health
Mr Ian Parsons	Department of Health

ITEM 1. WELCOME AND INTRODUCTIONS

1.1 The Chair thanked those present for giving their time to this Group which had been established at the request of the Chief Medical Officer, Sir Liam Donaldson, to advise UK Health Departments on potential therapies for human prion disease. Members introduced themselves around the table. Apologies had been received from Professor Trevor Jones of the Association of the British Pharmaceutical Industry, Dr Mike Simmons, observer representing the National Assembly for Wales, and from Mrs Patricia Noons, Department of Health, who was represented by Mr Clive Marritt.

ITEM 2. TERMS OF REFERENCE.

2.1 Officials briefly outlined the background to the establishment of the Group and invited members to comment of the draft terms of reference. It was in particular pointed out that the Group would advise all four UK health departments. Members discussed the need for the work of the Group to support rather than duplicate the work of other committees in the field including such groups as the Joint Funders Group, Spongiform Encephalopathy Advisory Committee, SEAC, the CSM and relevant European committees. The need to avoid overlap with various steering and expert groups linked to individual trials was also noted.

2.2 The draft terms of reference were discussed point by point. Members emphasised the need to encourage NHS involvement and participation in trials as they occurred. Members agreed that with such a small case population it was important that the CJD Therapy Advisory Group maintained an overview, to enable the maximum amount of useful data to be obtained.

2.3 With small numbers of patients and the possibility of an increasing number of potential therapies, the Group could be considered as a "clearing house" for new therapies. The need for a standardised evaluation process was discussed and the development of "markers" by which to evaluate any disease progression. Such markers would need to be simple and able to be administered locally wherever possible. Studies would also be required to see how such markers varied over the course of the disease in patients unwilling to enter trials so as to increase our knowledge of the natural history of the disease process in more detail.

2.4 Multi-national collaboration to increase the numbers of possible participants in a trial was discussed. It was generally agreed that wider networking, whilst it might be problematic, was worth pursuing. The Group were informed that UK researchers were already in constructive contact with their French and German colleagues.

2.5 In considering bullet points 2, 3 and 4 of the draft terms of reference, those present saw the identification of potential new therapeutic agents as central in countering mis-leading information that was currently available. Members

emphasised the need for a collective overview looking at trials elsewhere and the establishment of a computerised database of potential therapeutic agents and trials was suggested.

2.6 Parallels with United States collaboration over AIDS research were highlighted. It was pointed out that the European network included links with Canada. It was also noted that the National CJD Surveillance Unit had close contact with American workers.

2.7 Members were informed that extending their remit to providing advice to clinicians and researchers on technical and ethical issues relating to therapeutic clinical trials was open for discussion. Members generally agreed that they might better be able to advise on mechanisms that could stimulate maximum participation in trials. The provision of advice on therapeutics to families and potential patients was discussed. The secretariat clarified that this was not within the Group's remit, which was to advise the UK health Departments, but agreed that information, rather than advice, might usefully be made available to the public and undertook to seek the Chief Medical Officer's agreement to making a public summary of each meeting available through the DH website. It was agreed that a trial register could also be helpful to consumers and that this too, could be published on the DH website.

ACTION: DH

1. Terms of Reference to be redrafted in light of comments made

2. CMO's views to be sought on making a public summary of each meeting of this Group available via the Department of Health web-site

ITEM 3. UPDATE ON UK QUINACRINE TRIAL

3.1 Members were provided with background to this item. It was noted that in September 2001 the Chief Medical Officer had announced his request that the MRC fast track the design of a clinical trial to evaluate the effectiveness of the anti-malarial agent quinacrine (Mepacrine) as a potential treatment for CJD. Members were informed that the Department of Health had now agreed in principle to fund a trial of quinacrine, and that an announcement would be made when the trial was ready to recruit. The establishment of an infrastructure for CJD trials in general was seen as vitally important as new candidate therapies are identified and will need to be assessed.

3.2 Members were presented with a summary of the outcomes of the MRC Consumer Day, 26 July 2002, and received a presentation on the MRC quinacrine trial and protocol design.

3.3 The Quinacrine trial design was in three parts and included an option for patients who, whilst unwilling to participate in either of the two treatment groups, were willing to participate in a study of the natural history of the disease process. Members were informed that for statistical reasons it would be necessary to study some ninety patients within the randomised group.

This was considered achievable, given that a high proportion of this group would be expected to have the more common forms of the disease.

3.4 There was some discussion on how this Group would interact with individual trial steering committees. It was agreed that the Trial Steering Committee for the quinacrine trial might take on a wider role in steering other trials as other potential therapies for CJD emerged, following the model already used for cancer trials, for example. The CJD Therapy Advisory Group might be able to advise the Trial Steering Committee, but care was needed to ensure that the Therapy Advisory Group did not intrude into areas that were rightly the responsibility of the Trial Steering Committees.

3.5 It was noted that as the MRC and DH were likely to be the main sponsors of trials a single Trial Steering Committee would be possible. Should industry decide to sponsor trials, it may be more difficult to operate a single Trial Steering Committee. The MCA representative pointed out that the MCA had regulatory responsibility for clinical trials and it was agreed that the Therapy Advisory Group needed to have a clear understanding of MCA's responsibilities to ensure no misunderstandings arose.

ACTION: DH Secretariat and MCA

3.6 Members noted that randomisation would be undertaken by a telephone service-computer generated process, and that the age cut-off for participation in the trial would be twelve years and above, as twelve was currently the youngest age at disease onset.

3.7 Officials emphasised the need to stimulate interest and to publicise the trial once it was ready to start recruiting. Members agreed that simplicity in trial design would be key in getting a high level of recruitment along with the need for trials to be seen as a nationally-collaborated effort.

ITEM 4. CURRENT POSITION ON PENTOSAN POLYSULPHATE.

4.1 This item was on the agenda at the request of the CMO (England) following an individual case where the family of a patient was attempting to have the patient treated by intra-ventricular infusion with pentosan. DH had been made aware of new pre-publication data on possible use of pentosan as a therapeutic, and was seeking advice from this group, and from the CSM. SEAC and the CSM had last reviewed the available information in Spring 2001. The decision whether or not to treat in the case mentioned must remain with the local clinicians. It was not within the remit of the Group to advise on individual cases.

4.2 Department officials pointed out that when SEAC had last considered the subject of pentosan in April 2001, the committee had recommended further research, which is now being funded by the Department.

4.3 Members considered pentosan to be just one of a group of compounds that had been shown to have some effect on incubation period, but that in spite of

available reports to the contrary, there was no proven evidence of a therapeutic effect.

4.4 Concerns over the use of pentosan in human disease were raised, given its anti-coagulant properties and the unknown risk of consequences such as intractable pain should such an agent be introduced directly into the ventricles of the brain.

4.5 Members considered a pre-publication paper kindly supplied in confidence by a Japanese research team. It was noted that no clinical parameters were described in the paper to support the claim that pentosan is effective during the clinical course of disease. If the described effect of the drug was occurring following the onset of abnormal prion protein deposition in the brain rather than subsequent to the onset of clinical symptoms, then this just confirmed an effect during the incubation period. Members considered that the study might not be quite as promising as the authors would suggest. It was also agreed that experiments involving mice and dogs might not be a good model of treatment in humans. It was further highlighted that the safety data as presented in the paper summary fell short of the toxicological data needed on which to base a treatment regime in man.

4.6 It was noted that in the case of any disease, if there is a potential treatment available and a clinician is willing to perform the procedure, then treatment could go ahead. Officials reminded members that there was no reason why this should not be the case for CJD, but that treatment decisions are a clinical

responsibility. Families seeking information often turned to the internet which, whilst it may be a source of good information, also contained a great deal of misleading material. The Group felt that making the considered view of expert committees available would help to introduce a more balanced picture.

4.7 Some discussion followed on the rights and interests of the patients and it was agreed that extending survival might not be the only consideration. Members noted that this was not a new situation in medicine.

4.8 It was proposed that a small working group on pentosan be formed to consider the matter in greater depth and report back to the main group. The Group was informed that a CSM committee was to give an opinion on pentosan shortly.

4.9 The CSM were to look at human safety issues and could provide a toxicological opinion.

4.10 The Group concluded that the intra-cranial infusion of pentosan could not currently be regarded as a viable treatment in man but that the indications of an effect were sufficiently interesting to warrant further experimental study using animal models and dose finding studies. Some members were of the opinion that a lack of hard data should not necessarily stand in the way of treatment in individual cases. Members noted that to undertake intra-ventricular infusion for a CJD patient would require some £20-30,000 worth of surgical instruments be subsequently destroyed or written off as no longer accessible to other patients.

4.11 Members were mindful of media interest in the subject and proposed that advice be presented as coming from the Group as a whole and not from individual experts within the group

4.12 The formation of a small *ad hoc* group to look at pentosan in more detail and report back to the main Group was agreed. Membership could be drawn from within the current group plus possibly other experts. It was also proposed that a representative from one of the voluntary organisations should be included in the *ad-hoc* group to give the family member perspective. Families in such circumstances might well regard toxicological data as irrelevant even if it did result in a fatal outcome. The Group was also informed of a "rumour" of further data on the intra-cranial use of pentosan becoming available in the near future which would raise its profile further.

4.13 It was accepted that health professionals might be more risk averse than family members in the case of potential therapies.

ITEM 5. CURRENT RESEARCH

5.1 A summary of TSE-Related Research between April 2001 and March 2002, was presented by the DH, including an overview of current DH funded/ commissioned work on the development and assessment of therapeutic drugs for CJD/vCJD. Members were informed that a Department and MRC jointly

monitored UK research and a European Joint Funders Group was to be established in the near future

SOURCES OF DATA.

6.1 Horizon scanning was at present highly dependent upon researchers in the field, Officials would be grateful to be informed of any possible sources of data that the Group might like to be collected on their behalf. Members stated that the involvement of the ABPI, CSM and NIBSC would be helpful in this respect. The secretariat will endeavour to obtain material wherever possible, but members may have access to particular sources, which they were asked to search on behalf of the Group.

ACTION: DH

ITEM 7. FUTURE WORK OF THE GROUP

7.1 The Chair proposed the formation of two small working parties, one which he would chair, would look at new therapies, such as pentosan, which he would chair, whilst a second to be chaired by Professor Darbyshire, would consider what 'tools' CJD triallists might need in future.

ACTION: Professor Rawlins and Professor Darbyshire

7.2 Members thought that work on other diseases might have a bearing on CJD research. They also questioned what might happen if three or four potential therapies appeared around the same time. In response to the latter question the

Chair reported that it would be the job of the group to assess relative merits and rank the new treatments.

ITEM 8. DATE OF NEXT MEETING

8.1 It was suggested that the Group should meet every four months and a second meeting be held January or February 2003 was proposed. The secretariat will seek suitable dates.

ACTION: DH