The PACE Trial

First Meeting of Trial Steering Committee

Held on 22nd April 2004
at
[redacted]

Draft Minutes

Present: [redacted]

Apologies Received: [redacted]

INTRODUCTION

[redacted] welcomed everyone to the meeting and clarified that the function of the meeting was ensure that everything was in place for the beginning of the trial.

PROPOSED MEMBERSHIP OF THE TSC

The membership of the existing TSC was agreed but it was also suggested that it would be worth inviting additional members. It was suggest that [redacted] should be invited as observer, and that we should also invite an independent physiotherapist and occupational therapist to ensure that these views were represented on the committee. It was suggested that these individuals ought to be from outwith the field of CFS/ME and have experience in a complementary area such as cardiac rehabilitation or chronic pain. Endorsement of their membership by the appropriate professional bodies was desirable but we would not require that they would be regarded as representative.

Action: [redacted] ***to invite*** [redacted]***, as an observer.***
Action: [redacted] ***to suggest names of a physiotherapist and occupational therapist for approval by the TSC Chair.***

REMIT OF THE TSC

The remit of the TSC and the MRC guidance were discussed. It was noted that the TSC's terms of reference were as follows:

1. To monitor and supervise the progress of the trial towards its objectives.

2. To review relevant information from other sources (e.g. other related trials)

3. To consider the recommendations of the data monitoring committee.

4. In the light of 1, 2, and 3, to inform MRC Council and the relevant research boards on the progress of the trial.

5. To advise MRC Council on publicity in the presentation of all aspects of the trial.

To the above [redacted] suggested we add oversight of the publication and presentations plans and ancillary study policy. It was suggested that the TSC did not have to 'micro manage' this, but would like to be informed, and would also act as a court of appeal in the case of dispute that was irresolvable at the TMG level.

Action: PIs to keep TSC informed of proposed publications
Action: PIs to keep TSC informed of all TMG approved ancillary studies

Conflicts of Interest
All members of the committee present at the meeting were asked to declare any conflict of interest. No financial conflicts of interest were declared and it was agreed that no one present had any other substantial or material conflict relevant to their work on the committee.

Action: [redacted] to write to all members outlining potential conflicts of interest, and invite replies.

MEMBERSHIP OF DATA MONITORING COMMITTEE
It was noted that [redacted] and [redacted] had agreed to be members of the data monitoring committee. [redacted] was unable. It was noted that the DMC required a remit based on the MRC guidance but tailored to the individual trial. The MRC CTU was currently writing a charter for DMCs, and it was hoped this would be available for the PACE DMC. It was suggested that the DMC meet before the trial begins, possibly with the TSC.

Action: PIs to identify possible Chair.
Action: [redacted] would send on the MRC charter for DMCs to the members, once available.

TRIAL MANAGEMENT STRUCTURE
[redacted] outlined the management structure consisting of the TSC, DMC, TMG, six clinical centres, and the CTU. The target date for first randomisation is 11th October 2004.

The TSC commented on the importance of ensuring trial procedure and data quality, particularly eligibility criteria and consent, primary outcome data, and treatment received. Various strategies for checking quality were discussed, including site visits and auditing of hard copies against the electronic database.

Action: The TMG will oversee the establishment of standard operating procedures (SOPs) to check the quality of all these data.

TRIAL SPONSORSHIP

The MRC's change in policy regarding trial sponsorship was noted. The importance of ensuring indemnity was noted.

Action: The PIs would ensure that each trial centre has local sponsorship with Queen Mary taking overall sponsorship responsibility for the trial.
Action: [redacted] will invite a representative from Queen Mary to sit as an observer on the TSC.
Action: Each centre leader would ensure proper indemnity cover was available, to be checked by the PIs.
Action: All these decisions would be checked by the TSC.

PUBLIC RELATIONS STRATEGY

The need for active public relations strategy that involved the PIs, TMG, MRC, and [redacted] was strongly endorsed. [redacted] and [redacted] from the MRC attended for this part of the meeting. A discussion paper was circulated. It was agreed that the MRC wished to address PACE in the context of their general scientific programme and particularly within public education concerning clinical trials. The TSC advised that PACE should be considered in relation to other similar studies, such as the FINE study, rather than stand alone. The TSC suggested that the PR policy for potential and actual participants was particularly important. It was also agreed that there needed to be a specific working group to plan the public relation strategy and that this would have the following elements.

a) Positive public education and information about the trial.

b) Ensuring accurate information reaches the potential and actual participants who took part in the trial.

c) The correction of disinformation being circulated about the trial.

[redacted] and [redacted] were thanked for their involvement so far in answering media enquiries, parliamentary questions, and queries from private individuals. The MRC was already writing answers to frequently asked questions which could be placed on their web site. It was agreed that the principal investigators would meet with the MRC and [redacted] to develop a media strategy.

The TSC suggested that it would be willing to act as an advisory body and even an authoritative source for PR on behalf of the trial.

The issue of making the names of members of the TSC and DMC confidential was discussed, but it was thought that this could be counter-productive.

Action: PIs and the MRC will meet to agree a PR strategy and policy, as suggested above.

REVIEW OF THE PROTOCOL

A page by page review of the protocol was undertaken.

The Major points were as follows:

1. It was noted that the MRC will no longer be the sponsor of the trial, and that this needed to be clarified. It was likely that the trial sponsor would be Queen Mary's College with functions delegated to the other centres. It is noted that research governance (but not sponsorship rules) is a devolved function regarding the Scottish centre.
   Action: PIs and centre leaders

2. There was a discussion about the trial aims and the extent to which it would be able to determine the predictive value of specific CFS/ME diagnostic criteria. It was suggested that we stratify by type of diagnosis if we wished to do this. This will need to be discussed with the trial statistician.
   Action: TMG agenda item

3. It was agreed that a detailed screening Standard Operating Procedure (SOP) was required in the appendix. In particular a policy for screening for coeliac disease was required.
   Action: TMG agenda item

4. The recruitment estimates were noted and these need to be reviewed. It was particularly noted that it may be worth training the clinicians who would be recruiting patients into the trial in recruitment strategies and procedures.
   Action: Protocol change and TMG agenda item

5. The issue of blindness to treatment allocation was discussed. It was agreed after discussion that in practice it was not possible to keep the research nurses truly blind to treatment allocation, and therefore it was recommended not to attempt this. It was noted that there was no plan to keep the doctors giving usual specialist care (USC) blind to treatment allocation.
   Action: Protocol change and TMG agenda item

6. Because of this it was argued that consideration should be given to an independent "objective" examination of outcome for example by video or audio-taping interviews. However, as the outcomes are self rated it was unclear that this would add additional data in particular, as there were already walking and fitness tests. This matter was left for further consideration by the principal investigators.
   Action: TMG agenda item

7. The outcome measures were discussed. It was noted that they may need to be an adjustment of the threshold needed for entry to ensure improvements were more than trivial. For instance a participant with a Chalder score of 4 would enter the trial and be judged improved with an outcome score of 3. The TSC suggested one solution would be that the entry criteria for the Chalder scale score should be 6 or above, so that a 50% reduction would be consistent with an outcome score of 3. A similar adjustment should be made for the SF-36 physical function sub-scale. It was also suggested that as well as measuring the proportions of participants who

improved in fatigue and functioning separately, we ought to also look at the proportions who improve on both.
Action: Protocol change and TMG agenda item

8. The need to review the content of therapy sessions was discussed and it was noted that we did not need a sample from every patient but merely from every therapist, in order to judge therapy discrimination.
Action: Protocol change and TMG agenda item

9. It was noted that when monitoring quality control of therapy and data that it would worth being flexible, scrutinising more intensively at early stages in the trial.
Action: PIs and Trial Manager

10. It was noted that severe adverse events (SAEs) (e.g. a patient having a stroke) was not necessarily a severe adverse reaction (SARs) to treatment. Therefore, the procedure for notifying every one of severe adverse reactions did not apply to all severe adverse events. It was also noted that SARs need to be operationalised into mild, moderate and severe. Finally, it was important to discriminate SARs of the supplementary therapies from SARs to USC. The definition of SARs in this trial is complex and requires further consideration
Action: Protocol change and TMG agenda item
Action: Agenda item for next TSC

11. The data monitoring committee safety role would require it to monitor for deterioration of participants in a particular group, as judged by outcome data. It was noted that there needs to be agreement between the PIs, the Chair of the TSC, and the DMC about under which circumstances the trial might be stopped.
Action: PIs, [redacted] and DMC to meet in September
Action: PIs to include in DMC remit

12. It was noted that if patients were found to have significant psychiatric disorder requiring treatment (e.g. major depressive disorder) as a consequence of the psychiatric interview at the beginning of the trial, it would be desirable and ethically necessary to inform the doctor providing USC.
Action: SOP for Research Nurse to be written by PIs and trial manager

13. SUSMC needs describing in more detail (Since SUSMC will not be standardised, SUSMC should really be Usual Specialist Care (USC))
Action: TMG agenda item

<u>A number of minor comments were made on the protocol which will be amended accordingly. These included:</u>

1. Making the abstract understandable by a lay audience
2. Making the aim of the trial explicitly to : " improve informed choice for patients by increasing evidence about treatments"
3. Consider training participant recruiters
4. Measure the plausibility of therapy for the participant after the first session

5. Ask the therapist to rate the response to treatment (Added note: This is something we could ask the USC doctor to do.)
6. Add the fact that three centres will start recruitment in year 1 and three in year 2.
7. The CRF needs to be in the appendix
8. Measure the likely power of the trial to find statistically significant differences in the walking test as an objective outcome measure

THERAPY MANUALS

The therapy manuals were tabled, but there was insufficient time to discuss them. It was agreed that members and observers with comments should pass them on to the principal investigators.

Action: All and PIs

NEXT MEETING OF THE TSC

It was agreed that the final protocol can be signed off by the chairman of the TSC unless issues arise that require a further meeting. It is anticipated that the TSC would need to meet every six to twelve months throughout the trial but would only need to meet again before patient recruitment started (estimated in October 2004) should there be difficulty in resolving any of the above issues.

Action: [redacted] to arrange next meeting in liaison with [redacted]

Action: [redacted] to be sent final protocol and to decide if [redacted] can sign off as above

FIRST MEETING OF THE DMC

This will be held in September, attended by the Chair of the TSC, the trial statistician, the trial manager and the three PIs.

Action: [redacted] to arrange this meeting once membership of the DMC is confirmed

[redacted] 24/4/04

Minutes revised 16/5/04