PACE trial
Minutes of Trial Management Group
Friday 7th May 2004, 2pm
[redacted]

TMG Meeting No. 7

1. **Present:** [redacted]

2. **Apologies were received from:** [redacted]

3. **Minutes of the last meeting were checked.** [redacted] pointed out that [redacted] did attend the last meeting. The Minutes were adjusted accordingly.

4. **Welcome** to [redacted] the new trial manager.

5. [redacted] reminded the team that the **Caldicott Guardian**, the R&D officer and the Data Protection Officer in each centre needed to be informed of the study and provided with a protocol.
   ACTION: Centre Leaders to contact personnel appropriately.

6. **Participant criteria for CFS/ME.** [redacted] circulated the Canadian criteria, the London criteria, the Fukuda criteria and the Melvin Ramsay criteria. We have agreed to use the Fukuda criteria and the London criteria but we have decided not to use the Canadian criteria, as it is impractical at this stage to measure. These are in addition to the Oxford Criteria, which are the entry criteria.

7. [redacted] circulated the new **Australian RCT** (Wallman et al, 2004) of graded exercise/pacing. [redacted] pointed out that the analysis was poorly reported, and that baseline measurements appeared to be made after randomisation. It was agreed that the results did not influence our equipoise.

8. **Award letter.** [redacted] confirmed that the MRC award letter had been received. All the centre leaders had received a copy aside from [redacted].
   ACTION: [redacted] agreed to send [redacted] a copy.

9. **Grant activation.** It was agreed that the grant should be activated from June 14th. Travel expenses to TMG should be claimed via local centres.

10. **NHS Support Costs**.
    ACTION: [redacted] to liase and sort out.

11. **Therapy Manuals:** [redacted] and [redacted] have yet to finalise the GET manual following feedback from the TSC.
    ACTION: [redacted] to circulate once corrections have been made.

12. **Analysis Strategy**. [redacted] stated that at this stage a detailed analysis strategy was not required. It should be developed once the trial had been running for about 6 months, and was stable. The primary outcomes will be compared using an intention to treat analysis.

13. **Protocol Deviation**. There was some discussion about what constitutes a protocol deviation. A SOP will need to be written to cover protocol deviations and obviously will need to be added to as the trial proceeds.

14. **TSC Draft Minutes.** These had been circulated. [redacted] has agreed to be an observer on the TSC. The TSC suggested a physiotherapist and occupational therapist should be invited onto the TSC. [redacted] has agreed to join the TSC. The TSC agreed to overview publications and presentations.

15. It was agreed that the **first main paper** would be presented to a joint meeting of the TSC and DMC.

16. [redacted] felt unable to commit to **chairing the DMC** as [redacted] Various people were suggested, including [redacted] in Bristol.
    ACTION: [redacted] to approach.

17. **Indemnity cover** was discussed.
    ACTION: Centre leaders to check indemnity cover locally.

18. Data Monitoring Committee. The first meeting of the DMC will be held in September (date to be agreed).

Protocol

19 a **<u>Sponsorship</u>.** The MRC are no longer taking on responsibility for sponsorship. Each centre will need to establish local sponsorship responsibility, although Bart's will be the lead sponsor for the trial.

b. **Diagnostic Criteria.** We considered the advantages and disadvantages of stratifying at the randomisation stage. However, [redacted] pointed out that it is also possible to covary in the analysis. We are currently stratifying by centre. [redacted] suggested that we use minimisation for London, and Fukuda Criteria. This would ensure that the four treatment arms would be balanced across each criteria. This "minimisation process" is not "deterministic".
   Action: [redacted] agreed to explain the minimisation procedure at the next ordinary meeting of the TMG.

c. **Medical screening was discussed**. [redacted] offered to draft a SOP and then circulate. [redacted] and [redacted] will obviously comment on the first draft, [redacted] proposed a face to face meeting to agree what constituted medical screening. This will be discussed at the extraordinary

TMG meeting on 14th June. It was generally agreed that treating medical doctors would need training on how to recruit patients into the trial.

ACTION: [redacted] to write SOP.

ACTION: Training programme for doctors to be written.

d. **Blinding of Research Nurses**. Everyone agreed that it is impossible to make research nurses blind to outcome, so therefore it was agreed that this would not be attempted.

e. **Independent Ratings.** We agreed to ask therapists to rate outcome independently of patients self report. It was agreed that the RNs should be trained in what to say and what not to say in supervising patients when completing self-report questionnaires. We discussed the possibility of the RNs recording their assessments – at least the psychaitric interview It was agreed that primary outcome measures could be gathered over the phone and if necessary patients could be visited in order to ensure complete data is collected.

f. It was agreed that **doctors would not be blind** to what treatment the patient was receiving.

g. Objective Measures of outcome. We had much discussion about various potential objective measures of outcome, including a six-minute walking test where the patient is timed using a stopwatch and the distance walked is recorded. The possibilities of using actigraphy and the step test for fitness were also discussed. We agreed that we would pilot the use of actigraphy, the step test and the six minute walking test in the first three centres. We had some discussion about whether an objective measure was to be a primary outcome. We had some discussion about the power of the trial to detect clinically significant differences between groups using the six-minute walking test.

ACTION: [redacted] to send [redacted] raw data of Oxford Trial in which [redacted] used the six minute walking test.

ACTION: [redacted] to check with [redacted]

g. **Secondary Outcomes.** We agreed that improvement in employment status is important as a secondary outcome. Voluntary work and productivity should be addressed in the CSRI. It was agreed that both the therapist and the USC doctor should rate outcome at one year follow-up, using a CGI

h. **Fatigue Questionnaire.** The TSC felt that we should increase the floor of fatigue at entry to the trial. This was to ensure that the outcome in terms of reduction in fatigue is convincing. Given that a median score of 10 or 11 is found in clinical trials, we agreed that patients would have to score at least six on the Chalder fatigue questionnaire to enter the trial, and a 50% reduction or a score of 3 or below would be regarded as a positive outcome.

i. **The SF-36 Physical Functioning Sub Score.** This scale is rated on a 0-100, 100 representing perfect and healthy functioning. The healthy adult working population score a mean of 90 with a standard deviation of 15. Those who have a chronic disease or depressive illness score 70 with a standard deviation of 20. After much discussion we agreed that patients would need to score 60 or below to enter the trial and a score of 70 or more would constitute a positive outcome. It was agreed that we would use the proportion of participants who had a positive outcome in both their fatigue and physical functioning score as another primary outcome measure. We would then be able to determine the percentage of people who improve on both measures.

j. **Conditions Under Which the Trial Should be Stopped**. Given the trend of anti-exercise there was some concern that the trial would be sabotaged in some way. However, on balance people felt that this was not likely to happen very often. It was agreed that we should propose stopping rules to the DMC and TSC.

ACTION: [redacted] to write a draft for the next ordinary meeting of the TMG

k. **Audio Recording of Therapy Sessions.** Although all sessions will be audio recorded only a sample will be analysed. It was agreed that recordings should be rated early on in the process for supervision purposes. However, in addition to supervision the recordings will need to be rated by independent raters. We proposed to use digital recorders.

ACTION: [redacted] to find out how much raters will be paid.

ACTION: [redacted] to check money available for tape analysis so that we can calculate how many records can be analysed

m. **Recording of USC**. This should be an agenda item for the next TMG.

n. Adverse reactions and events. It was agreed that a policy is needed on adverse reactions and events. We need to clarify whether the situation is an event and/or a reaction and whether it is treatment related or not. This will be discussed at the USC meeting on 14th June.

ACTION: [redacted] to approach [redacted] to ask [redacted] opinion about what constitutes a reaction or an event. For example, parasuicide may be categorised as an event as apposed to a reaction. It was agreed that this was also a DMC issue to be discussed by the team.

o. It was agreed that **major depressive disorder** was not an exclusion criteria but should be recorded – and may need to be included in the minimization.

p. Expectation of treatment outcome. We agreed to measure the plausibility of therapy on a 0-100 continuum. We have done this in previous trials at the end of the assessment session and after the rational has been delivered.

ACTION: [redacted] to circulate example.

20. **The CRSI**. [redacted] to circulate when completed.

22.**Public Relations**. An MRC meeting with the PIs raised a number of issues. The MRC agreed to put frequently asked questions on their web-site. It was also agreed that there would be links between the trial web-site when created and the MRC website. We had some discussion about how to respond to enquiries about the trial locally. [redacted] has met with some of the local groups with no adverse effects. [redacted] has since had a meeting with the Camberwell group. It was agreed that a set of slides would be kept with [redacted] describing the trial.

ACTION: [redacted] to swap the slides that they already have and to create a new presentation.

23. **Training Programmes for Research Staff.** It was agreed that the research assistants and the database managers would need training. In particular they would need training in the use of the CIDI.

24. **Ancillary Studies.** A protocol for ancillary studies has been written and was approved.

25. **Centre Reports. Kings:** King's have had 3 OT's apply for their OT job and to date no physiotherapists. **Royal Free:** [redacted] reported that they had been given some space for the CFS service. **Oxford:** [redacted] reported that local ethical approval was being sort. **Edinburgh:** [redacted] reported that the LREC was being processed.

26. **Teleconferencing.** We agreed to pilot the use of teleconferencing.

27. **The dates of the next meetings were agreed**. Thursday 8th July at 2-5pm, Wednesday 15th September at 2-5pm, Thursday 4th November at 2-5pm, and Friday 10th December (2-5pm) [redacted]

[redacted]