PACE Trial
Joint meeting of the Trial Steering Committee and Data Monitoring and Ethics Committee

2pm to 5pm, Monday 27th September, 2004

[redacted]

1. Present

TSC members

TSC Chair	[redacted]
Independent Members	[redacted]
Observers	[redacted]
Principal Investigators	Trudie Chalder Michael Sharpe Peter White
Trial Statisticians	[redacted]
	[redacted]
Administrator to TSC	[redacted]

DMEC members

DMEC Chair	[redacted]

2. Apologies received

TSC Members	
Independent Members	[redacted]
Observers	
DMEC Members	

3. Introduction

[redacted] welcomed everyone to the meeting and clarified that the function of the meeting was to have final discussions about the trial

documentation before it is sent to MREC, after which the trial will hopefully begin.

4. New members of the TSC

All members present introduced themselves, giving their affiliation and function within the TSC.

5. Members of the DMEC

The DMEC membership was confirmed. Unfortunately only [redacted], the [redacted] was available to attend this meeting.

6. Revisions to draft agenda

It was noted that the Standardised Specialist Medical Care (SSMC) manual would also be discussed at this meeting. [redacted] also noted that two documents had been tabled for discussion at this meeting which had not been previously discussed; these were the Diagnostic Criteria and the Trial Schedule.

[redacted] also took this opportunity for thanking everyone for their time and support, and to apologise for the large volume of paperwork that accompanies this particular trial.

7. Previous minutes of TSC # 1

Only one amendment was requested to the previous minutes, to correct the spelling of [redacted].

[redacted] led with a review of the action points from the last meeting.

Summary of matters discussed:

a) <u>TSC remit</u>
The remit of the TSC was reviewed for the benefit of new members.

b) <u>Annual reports</u>
It was determined that annual reports from the TSC to the MRC should be submitted annually from the date of this meeting.

c) <u>Ancillary studies</u>
The policy on ancillary studies was confirmed by the TSC. The TMG will review applications submitted for ancillary studies, and will inform the TSC of applications accepted. The TSC request a running list of such studies, with information of how much extra burden this will place on the participants. The TSC might still choose to reject a study, and the wording of Appendix 5 should reflect this.

ACTION 1: [redacted] to complete: Amendment to be made to Appendix 5 of the protocol to reflect this decision.

d) Conflicts of interest

[redacted] confirmed that letters had been received from all TSC members confirming no one had any conflict of interest.

e) Sponsorship

Queen Mary University of London (QMUL) is confirmed as the overall Sponsor for PACE. Local sponsorship for each Centre is being arranged. [redacted] attended the TSC as an observer for QMUL.

f) Protocol

It was noted that all suggested amendments to the protocol had been made, however, discussion of the objectives and adverse events would be discussed further at this meeting.

8. Remit of the DMEC and trial stopping policy

The remit of the DMEC as laid out in MRC GCP Guidelines (1998) was reiterated, and [redacted] confirmed that PACE is working in line with this guidance. [redacted] confirmed that [redacted] is happy with this and stated that very few SAEs would be expected for this trial. Interim analyses would only be conducted if required, and in the first instance, the analysis would be a blinded analysis.

ACTION 2: The TSC request that the DMEC monitor patient safety, harm and disability for each treatment arm.

9. Schedule of approvals and start of randomisation

a) [redacted] talked through the schedule of activities to be completed before the trial may open to patient randomisation. In particular, the piloting of the manuals was discussed, with particular reference to the Adaptive Pacing Therapy (APT) manual. As this is a therapy being designed specifically for PACE that has never previously been tested in a randomised trial for patients with CFS/ME, this manual requires slightly more thorough piloting than the more established therapies. As a consequence, the manual might be altered even after the MREC submission has been made. The TSC then gave advice to the PIs, and this is summarised below:

b) [redacted] advised the PIs to make direct contact with the MREC chairman to explain this issue, and request a rapid approval process for final amendments to the manuals so that the start of trial is not subject to significant delays. For example minor amendments could be sent to the MREC for their information only.

c) [redacted] stated that new procedures would be of more concern to the MREC rather than new information on procedures already described.

10. Approval of PACE protocol final version 2, revised in the light of previous TSC

[redacted] led a page-by-page review of the protocol.

a) [redacted] asked for an explanation as to why the name of the medical care treatment for the trial had now been altered to Standardised Specialist medical Care (SSMC). It was explained that the clinic doctors would be working within a remit of what advice and medications they could give. The term 'specialist' refers to the fact that the patient will be seen by a CFS specialist in the clinics.

b) [redacted] identified a discrepancy between the hypotheses stated in section 5.2.3, and those listed in 12.3.1

ACTION 3: [redacted] to complete: Protocol section 12.3.1 to be amended to reflect the hypotheses stated in section 5.2.3.

c) [redacted] asked for confirmation from the PIs that the expected recruitment graph accurately reflects likely recruitment rate. [redacted] detailed how these figures had been devised.

d) [redacted] asked for an explanation of the back loading of recruitment. [redacted] explained that this was a funding issue, and that the MRC had requested spending to be back loaded, and three centres to begin recruitment in advance of the other three centres. [redacted] explained the usefulness of this strategy in that it should enable much of the trial troubleshooting to be achieved in the first year, enabling the second round of centres to have a smoother ride.

e) [redacted] recommended that the medical exclusion criteria be detailed in the appendix of the protocol.

ACTION 4: [redacted] to complete: Medical exclusion criteria to be added to the protocol as an appendix with more detail added.

f) [redacted] explained the difficulties with selecting diagnostic criteria for CFS/ME, and explained that there has been a certain amount of pressure from the ME Association to use the Canadian criteria over those that have been selected for the study (London, Oxford and CDC). [redacted] went on to explain this stating that the criteria should be selected for their reliability, validity and feasibility. None of the available criteria can confidently be described as reliable, and therefore criteria have to be selected on the basis of validity and

feasibility. The London, Oxford and CDC criteria are feasible, the Canadian criteria are not. In terms of validity, the Oxford or CDC criteria have previously been used in research, but not the London or Canadian criteria. [redacted] also explained that direct communication had taken place between [redacted] and the authors of the Canadian criteria who confirmed that as written these are not suitable for research purposes and would require ad hoc operationalisation. This coupled with the fact that the procedures themselves can be intrusive suggests we should not use the Canadian criteria. The TSC were satisfied with this explanation.

g) [redacted] asked whether there was any reason why the three belief questions had been separated out and suggested that these might simply be listed as one item, 'Belief questionnaire' in the protocol.

ACTION 5: [redacted] to complete: The three belief questions to be described as one item throughout the protocol.

h) [redacted] asked why only two subscales of the SF36 were being used, and not the entire SF36 questionnaire. [redacted] explained that this decision had been made in order to reduce the questionnaire load to patients. Items covered by other SF36 sub-scales, were already being addressed with the use of other questionnaires, e.g. three CDC asks about five different types of pain.

i) [redacted] asked whether the questionnaires had been piloted to tests how long they would take to complete. [redacted] stated that this was still to be done as part of research nurse training, but pointed out that a number of these questions would be asked by the research nurses and not all questionnaires listed were self report. In addition, the baseline assessments are to be divided between two visits, and questionnaires will be sent to the participant's home address in advance of any research visit thus reducing the load to the patient. [redacted] reinforced this by stating that clinical experience demonstrates that this group of patients are very tolerant of testing, and visits of one to two hours were routine in normal clinical practice.

j) [redacted] recommended that the order of tests be set according to importance of data.

ACTION 6: [redacted] to complete: Case Report Form booklets to be designed with order of importance of questionnaires in mind.

k) Discussion took place about the consent and information sheet with particular reference to following patients up after they have completed the trial.

ACTION 7: [redacted] to complete: Item 10 on the consent form to be split into two parts; patients should give explicit consent to allow

their records to be followed up for ten years after the end of the trial, and separately, that ONS (England) and ISD (Scotland) may be used to find the patient if they are lost to follow-up. This information should be mirrored in the participant information Sheet.

l) Section 8 was discussed and recommendations for re-wording this section made.

ACTION 8: [redacted] to re-write section 8 as per TSC recommendation.

m) [redacted] led discussion on the outcomes, and the TMG's struggle to find an objective outcome measure as requested by the TSC at their last meeting, particularly as CFS/ME is a subjective condition. It is proposed that the protocol does not alter from the three primary objectives already set.

n) [redacted] recommended that an extra measure be added for participation in life, and that the ICF scales be explored.

ACTION 9: [redacted] to investigate the use of a five point measure of Work and Social Adjustment Scale (Marks et al) used previously in research.

ACTION 10: [redacted] to contact [redacted] to ask for other recommended measures.

o) [redacted] [redacted] led discussion about how to define 'improvement'. [redacted] stated that in order to identify 'damage' by any treatment arm, it would be important to know how patients receiving no treatment would be expected to progress. The question was asked 'how soon will you know if a participant is getting worse?' to which [redacted] responded that previous research has shown that it cannot be determined if people are getting better until at least six months after the end of therapy (i.e. a year after therapy has begun). CBT and GET may both make a patient worse before they begin to improve. [redacted] clarified that there is a difference between transient and persistent deterioration. It was felt important that the DMEC be aware of this short term differential effect.

ACTION 11: [redacted] [redacted] to add into section 10.3 (monitoring adverse outcomes) a defined drop in SF36 score.

ACTION 12: DMEC: An explicit definition of deterioration should be produced before the first review by the DMEC next year. At six months and one year after the trial opens for randomisation, the DMEC (and statisticians) will review SAEs, CGI and SF36 scores to see if there is a normal distribution. In addition, previous trials will be reviewed to aid categorisation of deterioration.

p) [redacted] asked that section 10.6 (therapeutic input) be revised.

ACTION 13: [redacted] to revise the therapeutic input questions.

ACTION 14: [redacted] to add in 'analysis of deterioration of primary outcomes' to section 12 of the protocol.

ACTION 15: [redacted] to amend section 13.2 (regarding the use of NHS number) to be relevant to the Edinburgh centre.

q) Section 14 on adverse events was carefully reviewed as this has undergone substantial revision since the last TSC meeting. It was felt that a 'new' disability might be irrelevant in the context of PACE.

ACTION 16: [redacted] to replace 'new' with 'increased' in section 14.1.1

ACTION 17: [redacted] to remove exercise equipment from section 14.2.

ACTION 18: [redacted] to reference MRC GCP Guidelines (1998) in section 17, and to add in information on indemnity as provided through NHS R&D.

ACTION 19: [redacted] to check under the new MRC sponsorship agreement what indemnity the MRC offer.

ACTION 20: [redacted] to make minor amendments to section 18 as discussed (removal of word 'annually', clarify that 'significant and consistent deterioration will be quantified at the first meeting of the DMEC').

r) [redacted] recommended that the publication policy (section 19) be clarified in greater detail, and that a decision should be made about order of authorship, and for the main publication, the TMG should consider authorship as the 'PACE trial team'.

ACTION 21: [redacted] to amend section 19 to reflect this suggestion.

s) [redacted] noted that the term CFS/ME has not been used consistently and is absent from the trial title.

ACTION 22: [redacted] to amend the protocol and affiliated paperwork to ensure that CFS/ME is used consistently.

ACTION 23: [redacted] to ensure that ISD is also mentioned (to reflect Scottish practice) where the protocol and information currently only refer to ONS.

t) [redacted] [redacted] recommended re-phrasing the paragraph on alternatives for treatment in the PIS.

ACTION 24: [redacted] to rephrase the paragraph on alternatives for treatment in the PIS 'Depending on where you are, the following treatments may or may not be available'.

ACTION 25: [redacted] to rephrase PIS section 'Benefits of taking part' according to [redacted] suggestion: 'we hope that the treatment you receive will be of help to you'.

ACTION 26: [redacted] to ensure that [redacted]'s suggestion to ensure that 10 year long term follow-up is included in the PIS and Consent Form.

ACTION 27: [redacted] to re-word paragraph three of the GP letter according to [redacted] recommendation.

u) The PIs were asked why the trial was only open to patients able to speak and read English. It was explained that it would be too costly to train up and employ non-English speaking therapists for what was likely to be a very tiny minority of potential participants. The therapies could not be assured if delivered through an interpreter. As the primary outcomes are self-report measures, and many of the scales to be used have not been validated for use in other languages, it would be very difficult to fairly represent non-English speakers. The TSC were satisfied with this explanation but asked that this be clarified in the protocol.

ACTION 28: [redacted] to add a line to the protocol to explain this.

11. Participant recruitment targets

a) The TSC stated that they were happy with the proposed recruitment rate. [redacted] asked whether this rate had been piloted, and expressed anxiety that recruitment might be impede by the anti-PACE/FINE lobbyists. [redacted] and [redacted] [redacted] explained how this rate and been derived, and stated that lobby groups had not previously affected recruitment in trials of GET, which is the most controversial of the therapies to be tested.

b) [redacted] asked whether there was a real danger of patients withdrawing from the trial after randomisation if they are not allocated their preferred treatment. [redacted] reinforced this and stated that [redacted] had seen similar happen on a previous trial. [redacted] stated that the two stage consent process was designed to minimise this and that the research nurses would be trained to try to prevent this occurring. [redacted] stated this problem might be seen as a

centre effect, with patients wanting CBT if they are being seen at King's, or GET if they go to Barts.

ACTION 29: [redacted] should carry out careful checks for duplicated participants. This should be added into the trial SOP.

12. Medical Screening Standard Operating Procedure (SOP)

a) [redacted] noted that there were three changes already planned for this document:

i. 'Physician' should read 'doctor'
ii. Under medical history, patients with hyperventilation or somatization disorder would not be excluded.
iii. The exclusions would be added.

The TSC were happy with this document, with the addition of more detail to be added (see above).

ACTION 30: [redacted] to re-word the Medical Screening Standard Operating Procedure according to [redacted]'s recommendations.

13. Approval of revised Adaptive Pacing Therapy (APT) therapist manual and participant manuals and hand-outs

a) [redacted] expressed concern that the APT manual appeared to be considerably smaller than those for CBT and GET. Recommendations including copying the format of the GET manual for information on engaging the patient, the initial assessment and troubleshooting such as 'what to do if your therapist is on holiday'. It was stated that APT should have equal face validity to the other therapies, and that because this was a new treatment and one advocated by the patient groups, it was important to make this treatment of equal quality. was asked[redacted]t on whether there were items for pacing that could be included that reflect users' views. stated that the surveys carrie[redacted] [redacted] produced a wealth of complex answers and that these could not be easily included.

b) [redacted] also expressed concern that the cognitive component of APT is not significantly different from CBT at session 3. [redacted] noted that the GET manual included a section on 'how to be sure that you are giving GET and not CBT' and again reiterated that this type of advice should be common to all four manuals.

ACTION 31: [redacted] to lead [redacted] in making the recommended alterations to the APT manual.

ACTION 32: [redacted] should also contact [redacted] directly for further advice.

14. Approval of revised Cognitive Behaviour Therapy (CBT) therapist manual and participant manuals and hand-outs

a) As recommended for APT, general information should be included across all the manuals. Generalisable information should also be identified from the CBT manual and copied into those for the other therapies. [redacted] particularly identified information on how to deal with a distressed patient, therapeutic alliance, warmth and empathy. [redacted] asked whether the physiological model of CFS/ME in the CBT manual could also be generalised across all the manuals.

b) It was noted that the recommendations for the CBT manual advised by [redacted] have already been incorporated. [redacted] stated that [redacted] was very impressed with this manual.

15. Approval of revised Graded Exercise Therapy (GET) therapist manual and participant manuals and hand-outs

a) The GET manual was passed with only minor alterations suggested by [redacted]

ACTION 33: [redacted] to pass on the recommended alterations for the GET manual to [redacted]

16. Approval of the Standardised Specialist Medical Care (SSMC) doctor's manual

a) [redacted] stated that one alteration was to be made to this manual to state that every randomised patient should be seen by their SSMC doctor within two weeks. This was to help ensure that the SSMC arm was not interpreted by the participants as the 'go away' arm. The TSC approved this manual.

ACTION 34: [redacted] to ensure that the SSMC manual is modified to include a first participant appointment within two weeks of randomisation. (NB the TMG later revised this to one month in order to reduce the number of visits required by participants in the first two weeks of the trial.)

17. Approval of Patient Clinic Leaflet

a) [redacted] stated that [redacted] thought this document was excellent. Minor amendments were recommended:
   i. 'specialist medical care' should be altered to 'routine medical care',
   ii. Error in the title should be corrected
   iii. [redacted] recommended that the word holistic be carefully considered and changed if necessary

iv. The penultimate paragraph should be placed earlier in the document.

ACTION 35: PIs should alter the PCL as advised.

ACTION 36: PIs to ensure that the Patient Clinic Leaflet (PCL) explicitly states the different theoretical models of CFS/ME in relation to the four treatment approaches.

18. Summary of changes generalisable to all manuals

a) The question was asked as to whether the TMG had considered passing any documentation to a writing expert to ensure readability for a lay audience. [redacted] stated that contact had already been made with [redacted] who has been contracted to carry out this work for other MRC Trials. This was to be pursued after the meeting.

ACTION 37: The PIs in conjunction with the treatment leads should ensure that generalisable information is consistent across all four therapist manuals. A note of caution is advised to ensure that in synchronising the manuals, the therapies do not become too similar.

ACTION 38: Treatment leaders should ensure that the finalised manuals are sent to the TSC experts for final approval as advised by [redacted]

ACTION 39: All documents should be checked to ensure that there is no tautology with the use of PIN (i.e. should always read PIN and never PIN number).

ACTION 40: [redacted] to contact [redacted] for a review/re-write of the PCL, PIS and Consent Form.

19. Case Report Form (CRF)

a) A draft earlier version of the CRF was presented and it was explained that the final version was still in development.

ACTION 41: [redacted] to send the completed CRFs to the TSC for their comments and advice before submission to MREC.

20. Public Relations

a) [redacted] summarised the policy so far. All media enquiries should be directed to [redacted] at the MRC Press Office in the first instance. [redacted] will contact the PIs for agreement before releasing any statement. It was noted that a policy statement and PACE/FINE Q&A page already exists. The PIs will also be writing to the MREC and LRECs to make them aware of the campaign to stop the trial. All were agreed that the names of the TSC and DMEC could be published to

retain transparency, but confirmation was still required from the two DMEC members. The question was asked as to how to deal with any emails or hateful correspondence received. It was agreed that these should not be directly responded to, but should be retained as evidence for the future should it be needed. [redacted] urged a note of caution that nothing negative should be written or emailed about the lobbyists as this could be libellous.

ACTION 42: PIs to write to the MREC and LRECs with details of the MEA campaign to stop PACE and FINE.

ACTION 43: [redacted] to email all TSC and DMEC members with contact details for [redacted] and some information on how to deal with queries.

ACTION 44: [redacted] to contact the two other members of this committee to confirm that they are happy for their names to be published.

ACTION 45: Any lobbyist mail to be forwarded to [redacted] for storage.

21. Next meeting and frequency of meetings of TSC

a) The next TSC meeting will take place on April 28th or six months after recruitment begins if the trial is delayed for any reason.

22. Next meeting and frequency of meetings of DMEC

a) The first DMEC meeting will take place approximately one month in advance of the next TSC meeting.