Dear [Name],

Freedom of Information request: 2018/0131

Thank you for the Freedom of Information request you outlined in your email to Professor Fiona Watt on 30 August 2018.

Your Request:

In the request you stated:

I read with interest your letter in The Times https://mrc.ukri.org/news/browse/criticism-of-the-pace-trial/
You make four important statements. Please could you supply the evidence base for those statements in the format detailed below.

I do have the names of some of these experts but I do require a complete list

<table>
<thead>
<tr>
<th>Excerpts from your letter</th>
<th>Require the following evidence base</th>
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<tbody>
<tr>
<td>The PACE trial was funded following expert peer review.....</td>
<td>Please give me the names and qualifications of ALL the expert peer reviewers together with a copy of their reviews</td>
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<tr>
<td>...was overseen by an independent steering committee...</td>
<td>Please give me the names and qualifications of ALL the members of that independent steering committee together with a copy of the deliberations of that committee</td>
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<tr>
<td>...and its published findings have also been independently peer-reviewed</td>
<td>Please give me the names and qualifications of ALL the members of those responsible for independent peer review together with a copy of their reviews</td>
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<tr>
<td>Other research groups have drawn similar conclusions</td>
<td>Please detail ALL other research groups that you have relied upon who have drawn such similar conclusions together with references to the relevant papers</td>
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Our response:

I can confirm UK Research and Innovation does hold some information relevant to your request and have responded to your questions below:

1. Please give me the names and qualifications of ALL the expert peer reviewers together with a copy of their reviews.
Peer review is the cornerstone of the work of the UKRI as a funding organisation. All proposals submitted to UKRI councils are scrutinised by independent experts who consider the importance, scientific potential and cost-effectiveness of the research concerned. Proposals for MRC grant funding are generally assessed through a two-stage process, in the first stage external reviewers provide an expert assessment of the proposal, the second stage is the research board or panel’s assessment and funding decision. Like other UKRI councils the MRC’s peer review process is confidential to protect proposals and anonymous to support the free and frank exchange of views.

In assessing the proposals for the PACE study, reviewers participated on the basis that their comments provided advice to MRC boards (supporting their consideration to inform their decision) and only their unattributed comments would be made available (in confidence) to the applicants. These aspects of the peer review process applied in 2002 and remain unchanged, with reviewers today participating on the same basis.

UKRI is therefore withholding information relating to the names of external reviewers and their reviews under Sections 36(2)(b) and (c), 40(2) and 41 of the FOIA. An explanation of the exemptions applied is provided below.

In relation to the PACE study application, UKRI does not hold any CVs relating to the selected peer reviewers on the grant file. Therefore, no information is held on peer reviewers’ qualifications or expertise obtained at the time the PACE study proposal was reviewed.

2. Please give me the names and qualifications of ALL the members of that independent steering committee together with a copy of the deliberations of that committee.

The Trial Steering Committee (TSC) was responsible for the independent oversight of monitoring and supervising the progress of the Trial. In line with the MRC Guidelines for Good Clinical Trials (1998), the PACE study Investigators were required to provide a list of proposed TSC members as part of their application. After the proposal was awarded the TSC membership was finalised by the Investigators and the MRC, before being published in the trial protocol, which is publicly available at BioMed Central, it should be noted that the final TSC membership was different from that initially proposed in the application: [https://bmcneurol.biomedcentral.com/articles/10.1186/1471-2377-7-6 and as such we are applying Section 21 FOIA. Further information on this exemption is provided below.

In relation to the PACE study proposal UKRI does not hold any CVs or information relating to the qualifications or expertise of proposed or appointed TSC members.

The minutes of the TSC were shared with MRC research management staff in their capacity as Observers on the TSC. Copies of the TSC meeting minutes are provided in the folder entitled UKRI_2018_0131_TSC_Minutes. A small amount of information has been redacted under Section 40(2) of the Freedom of Information Act (FOIA) because it comprises the personal information of the research team and TSC members.

3. Please give me the names and qualifications of ALL the members of those responsible for independent peer review together with a copy of their reviews.

The findings of UKRI funded studies are subject to independent peer review by the journals in which the results are published; as a funder UKRI would not normally have any involvement in this process. In the case of the PACE study I can confirm that the peer review of the published findings was independent of the MRC. Therefore, no information is held by UKRI on the names and qualifications of reviewers consulted by the relevant journals and no copies are held of comments that might have been provided by the journal to the Investigators.

4. Please detail ALL other research groups that you have relied upon who have drawn similar conclusions together with references to the relevant papers.

The reference in Professor Watts’ letter was to Cochrane Reviews, which are systematic reviews of primary research in human health care and health policy and are internationally recognized as the
Three Cochrane Reviews have been undertaken in the area of CFS/ME and are available online from the Cochrane Library. The first of these was published on 19 July 2014 and covers Exercise therapy for chronic fatigue syndrome. A copy of the abstract is available at: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD003200.pub2/abstract. This review was updated on 25 April 2017 and the abstract, together with the full paper is available at: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD003200.pub7/full. The third review covers Cognitive behaviour therapy for chronic fatigue syndrome and the abstract, together with the full paper is available at: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001027.pub2/full#CD001027-abs-0001.

Exemptions from disclosure

Sir Mark Walport, UK Research and Innovation Chief Executive has considered the public interest in relation to names and comments of peer reviewers and has found that the case for withholding information relating to this information outweighed the public interest in disclosure. Despite arguments in favour of releasing this information that relate to the high level of interest in the research study, this information is withheld under Sections 36(2)(b) and (c), 40(2), 41 and 21 of the FOIA for the following reasons:

The peer reviewers who provided comments on the PACE proposal participated on the basis that their comments provided advice to MRC boards (supporting their consideration to inform their decision) and only their unattributed comments would be made available (in confidence) to the applicants. Therefore, we consider that Section 41 applies as this information was provided to the MRC by an external third party in confidence. Section 40(2) is also considered to apply as reviewers participated on the basis that they would remain anonymous, and their identity would not be disclosed to any third parties. In addition, as peer reviewers are asked to comment on the research team and the research environment they will also include comments about third parties. To release the names and comments you have requested without the permission of all of those concerned would result in a breach to the established duty of confidence and would not be fair to any individuals named.

Sections 36(2)(b) and (c) are also considered to apply as releasing reviewer names is likely to impact on the future behaviour of potential reviewers and of applicants. This would be likely to damage current UKRI peer review processes by limiting our ability to secure comments, and for those comments to be of sufficient depth to provide advice to the boards/panel which take funding decisions and to support the free and frank exchange of views essential to effective peer review.

We acknowledge that the main findings of the PACE study were published in 2011 however UKRI peer review processes operate in much the same way to those used by the MRC at the time the PACE study was awarded. In reaching this decision we have also taken account of the continuing level of interest in the PACE study and the level of debate and comment online.

As information on the finalised TSC membership is available in the published trial protocol on BioMed Central website we believe that this is reasonably accessible to you and is exempt to disclosure under Section 21(1) FOIA. This exemption is not subject to the public interest test.

If you have any queries about this response please contact me, or if you are unhappy with the service you have received in relation to your request and wish to request a review of our decision, please write to:

Complaints Officer
UK Research and Innovation
Polaris House
North Star Avenue
Swindon
SN2 1FL

www.ukri.org

VAT number: 287461957
Please quote the reference number above in any future communications.

If you are still not content with the outcome of the review, you may apply to refer the matter to the Information Commissioner for a decision. Generally, the ICO cannot make a decision unless you have exhausted the review procedure provided by UKRI. The Information Commissioner can be contacted at:

Information Commissioner
Wycliffe House,
Water Lane
Wilmslow
Cheshire
SK9 5AF

Enquiry/Information Line: Between 9am and 5pm Monday to Friday 0303 123 1113 or 01625 545745
Further information about the Office of the Information Commissioner can be found at http://www.ico.gov.uk/

Yours sincerely,

UK Research and Innovation, Information Governance Team
Email: foi@ukri.org
The PACE Trial

First Meeting of Trial Steering Committee

Held on 22nd April 2004
at

Draft Minutes

Present:

Apologies Received:

INTRODUCTION

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 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: to invite , as an observer.
Action: 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 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: to write to all members outlining potential conflicts of interest, and invite replies.**

**MEMBERSHIP OF DATA MONITORING COMMITTEE**

It was noted that and had agreed to be members of the data monitoring committee. 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: would send on the MRC charter for DMCs to the members, once available.**

**TRIAL MANAGEMENT STRUCTURE**

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: 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 was strongly endorsed. and 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.

and 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 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, 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**

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

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: to arrange next meeting in liaison with
Action: to be sent final protocol and to decide if 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: to arrange this meeting once membership of the DMC is confirmed

24/4/04
Minutes revised 16/5/04
PACE Trial
Joint meeting of the Trial Steering Committee and Data Monitoring and Ethics Committee

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

1. Present

TSC members

TSC Chair
Independent Members

Observers

Principal Investigators  Trudie Chalder
Michael Sharpe
Peter White

Trial Statisticians

Administrator to TSC

DMEC members
DMEC Chair

2. Apologies received

TSC Members
Independent Members
Observers

DMEC Members

3. Introduction

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 [blank], the [blank] 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. [blank] 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.

[blank] 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 [blank].

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

*Summary of matters discussed:*

a) **TSC remit**
The remit of the TSC was reviewed for the benefit of new members.

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

c) **Ancillary studies**
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) 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

led a page-by-page review of the protocol.

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

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

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

d) asked for an explanation of the back loading of recruitment. 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. 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) recommended that the medical exclusion criteria be detailed in the appendix of the protocol.

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

f) 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). 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. Also explained that direct communication had taken place between 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) 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:** to complete: The three belief questions to be described as one item throughout the protocol.

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

i) asked whether the questionnaires had been piloted to test how long they would take to complete. 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. 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) recommended that the order of tests be set according to importance of data.

**ACTION 6:** 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:** 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.

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

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

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

ACTION 11: [Name] 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) asked that section 10.6 (therapeutic input) be revised.

ACTION 13: to revise the therapeutic input questions.

ACTION 14: to add in ‘analysis of deterioration of primary outcomes’ to section 12 of the protocol.

ACTION 15: 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: to replace ‘new’ with ‘increased’ in section 14.1.1

ACTION 17: to remove exercise equipment from section 14.2.

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

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

ACTION 20: 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) recommended that the publication policy (section 19) be clarified in greater detail, and that a decision should be made about authorship, and for the main publication, the TMG should consider authorship as the ‘PACE trial team’.

ACTION 21: to amend section 19 to reflect this suggestion.

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

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

ACTION 23: to ensure that ISD is also mentioned (to reflect Scottish practice) where the protocol and information currently only refer to ONS.
t) recommended re-phrasing the paragraph on alternatives for treatment in the PIS.

ACTION 24: 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: to rephrase PIS section ‘Benefits of taking part’ according to suggestion: ‘we hope that the treatment you receive will be of help to you’.

ACTION 26: to ensure that 10 year long term follow-up is included in the PIS and Consent Form.

ACTION 27: to re-word paragraph three of the GP letter according to 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: 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. asked whether this rate had been piloted, and expressed anxiety that recruitment might be impede by the anti-PACE/FINE lobbyists. and 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) asked whether there was a real danger of patients withdrawing from the trial after randomisation if they are not allocated their preferred treatment. reinforced this and stated that had seen similar happen on a previous trial. 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. 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] on whether there were items for pacing that could be included that reflect users’ views. Stated that the surveys carried by [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. particularly identified information on how to deal with a distressed patient, therapeutic alliance, warmth and empathy. 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 have already been incorporated. stated that 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

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

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

a) 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: 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) stated that 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. 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. [Name] stated that contact had already been made with [Name] 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 [Name].

**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:** to contact [Name] for a review/rewrite 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:** to send the completed CRFs to the TSC for their comments and advice before submission to MREC.

20. **Public Relations**

a) [Name] summarised the policy so far. All media enquiries should be directed to [Name] at the MRC Press Office in the first instance. [Name] 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. 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**: to email all TSC and DMEC members with contact details for and some information on how to deal with queries.

**ACTION 44**: 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 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.
1. Those present and apologies

Independent members

Other members

Observers

Apologies
2. DMEC report
The DMEC will produce a formal report. The following is based on the initial verbal feedback from the chair.

a) Definition of deterioration
The DMEC needs to have a definition of serious deterioration in order to monitor possible deleterious effects of the therapies within the trial and asked the TMG to develop one. The measures suggested as part of a definition of serious deterioration might include a combination of:

- Step test – for an objective measure
- HADS – depression
- PHQ-15 physical symptoms questionnaire – subjective measure

The normal distribution of the scores for these scales would be helpful in order to define serious deterioration. It was suggested that participant drop out rates by treatment could be a good proxy for identifying potential problems but that it would be important to consider the individual reasons for drop out and not just look at the numbers. The TSC suggested that the TMG might also consider a measure of life participation as people might be able to maintain therapy but social/work functioning might be reduced.

Further discussion led to a recommendation that a combination of both drop-out and self report by treatment should be considered. Self-rated global deterioration could be used as a possible single measure but it might be preferable to have more than one.

ACTION 1: The PIs in conjunction with the TMG to respond to the DMEC request to develop an operational definition of serious deterioration. This definition should be sent to the DMEC & TSC for comment by email rather than wait for next meeting.

b) Life participation
The DMEC noted that participation in activities is not directly measured. They accept that a new questionnaire would add to burden and suggested that the PIs identify items within other questionnaires that might be used to measure this. (This might also form part of the definition of serious deterioration – see above)

ACTION 2: PI's with help of the statisticians and DMEC, to consider how best to measure life participation.

c) Frequency of meetings
The DMEC would plan to meet annually to consider the data and preferably one month before the TSC in order to allow enough time to produce a report for consideration by the TSC.
ACTION 3: __________ to set up dates for next year’s meetings for the TSC and DMEC.

d) Recruitment of participants
The DMEC would like a recruitment report every 6 months.

ACTION 4: __________ to send the DMEC recruitment reports annually.

e) Participation in therapy
The DMEC were interested in receiving data about any lack of attendance at treatment sessions and would like to know what is happening on a per session basis. The DMEC requested annual reports on this.

ACTION 5: PI's to address how participant attendance might be recorded on a session by session basis and the format of the report for DMEC.

f) Participant follow-up
The DMEC noted that it might be possible for patients to attend therapy but not attend for outcome assessment and asked whether the PIs had considered this. The PIs reported that so far there have been no cases of participants missing outcome assessments but they would monitor this carefully.

ACTION 6: PIs to monitor attendance to therapy versus attendance to follow-up visits.

g) Competing research
The DMEC and TSC would both like a summary table from the PIs at each meeting that provided an update on all other relevant ongoing and published research into CFS/ME.

ACTION 7: PI's to provide a summary report for each meeting listing all ongoing research and recent publications.

3. Agreement of agenda
The agenda for the meeting was agreed by all.

4. Previous minutes of TSC # 2
The previous minutes were agreed apart from one change to page 5 detailing the rationale for the choice of criteria for PACE.
ACTION 8: to send a revised paragraph to for incorporation into the final draft of the minutes for TSC meeting #2.

a) Indemnity
It was reported that since the last meeting it has been confirmed that the sponsor (Queen Mary University of London) is responsible for indemnity and that the MRC do not provide indemnity for studies that they fund but are not the sponsor.

b) Adverse experiences of randomisation to SSMC
The PIs reported that they are aware of two participants for whom the experience of being randomised to SSMC alone was associated with increased distress. However, the first of these participants has been seen for a follow up assessment with the research nurse and reported only transient low mood which the participant does not attribute to the randomisation. The second participant is being closely monitored with nothing to report so far. It was also noted that conversely some participants have refused PACE on the grounds that they would prefer to receive SSMC alone and did not wish to take the chance of being randomised to one of the therapies.

c) Meeting documentation
The TSC requested that at future meetings the supplementary documents are numbered according to their place on the agenda for easier reference.

ACTION 9: for future meetings, to number the papers according to their place on the Agenda.

5. Recruitment update
a) Start date of recruitment
presented a recruitment report to the TSC. It was noted that the trial was delayed in starting recruitment due to delays with the MREC approval of trial amendments. When allowing for the delay, recruitment was at 95% of target at the end of May and at slightly over 100% at the time of the TMG (31 participants recruited; target=30).

The TSC would like to review the screening and recruitment data but will remain blind to the numbers allocated to each treatment option.

b) Proposed end date for recruitment
Currently, the end date for recruitment has been revised and is two weeks later than originally proposed in the protocol to allow time to catch up on the three month delay to the start of recruitment. The TSC would like to be kept informed how feasible this end date is within the limitations of the grant and the PIs assured the TSC that this would be carefully monitored.
c) Actual recruitment versus target recruitment by centre
All the three lead centres have opened and recruited at a similar rate. The TSC request that the TMG review relative recruitment rates at each meeting and alert the TSC if there is a problem with recruitment at any centre(s).

**ACTION 10:** TMG to review data on recruitment by centre at each meeting and alert the TSC immediately if there is a problem with recruitment at any centre(s).

The TSC asked if the PIs saw any future potential problems that might threaten recruitment to the trial. The PIs have considered whether the opening of fifty new CFS centres might take patients away from PACE. However it is felt that if this happened, the TMG could explore the possibility of recruiting to the trial from these centres.

d) Acceptance rate as a proportion of those offered the trial
It was explained that at present it appears as though there is a large difference between the number of participants screened and those offered and accepting the trial. The TMG members offered the following explanations for this:

i. Screening takes place at two stages: Patients are screened at the secondary care clinic by the clinic doctors for their suitability for the PACE trial. If thought suitable they are referred to the research nurse. Secondly, referred patients are screened at the baseline 1 visit for the trial. Suitable patients are randomised at the baseline 2 visit.

ii. NHS activity complicates this diagram because it can take some time for a patient’s diagnosis to be confirmed. The CONSORT diagram presented includes all patients referred to one of the participating secondary care clinics with a suspected diagnosis of CFS/ME. Once these patients have been assessed by a clinic doctor, other reasons for their CFS may emerge (e.g. hepatitis, thyroid problems etc). In order to confirm a diagnosis it may be necessary to refer the patient for other investigations in other clinics first. The screening figures presented do not differentiate between those participants referred with a suspected diagnosis of CFS/ME and those who go on to have this diagnosis confirmed.

iii. There are a proportion of participants (17) who have been offered the trial subject to blood results being obtained to confirm diagnosis and eligibility.

iv. Therefore, the largest proportion of patients that appear as screen failures are those either definitely screened out by the clinic doctors, or those awaiting confirmation of diagnosis or those awaiting blood results. Only a very small portion of patients fail at the baseline 1 screening stage (i.e. after diagnosis and blood results are known).
The TSC were satisfied with these explanations and ask that the data on the numbers screened and who decline is given in greater detail at future meetings. The TSC also asked the TMG to monitor this.

ACTION 11: to present extra information in future reports showing the proportion of participants whose diagnosis of CFS/ME is confirmed of those referred to the clinic.

ACTION 12: to alter the word ‘refuse’ to ‘decline’ on the CONSORT diagram.

ACTION 13: to add a line in to the CONSORT diagram to show Acceptance Rates as % of Eligible.

ACTION 14: to review the group who declined in greater detail and report any problems to the TSC

e) Forecasts for recruitment
presented a revised recruitment chart for the trial to take into account the delay to starting. At this time, the target end date for recruitment has been delayed by two weeks.

f) Drop out, withdrawals and losses to follow up by month and as a proportion of those entered
Drop outs are classified as those participants who opt to withdraw from the trial or who are withdrawn from the trial by the PI/centre leader. Losses to follow-up are those participants who do not attend follow up sessions and give no reasons for their withdrawal from the trial.

There are no reported drop outs or losses to follow up at this time.

g) Serious adverse events and reactions
Additionally there have been no serious adverse events or severe reactions reported.

h) Completeness of data
The trial database is almost complete and ready to distribute to centres to begin data entry. For this reason, no data entry has yet taken place and missing data cannot be reported at this time. The TSC requested a report on completeness of data at future meetings and commented that the TMG should monitor completeness of data at every meeting.

ACTION 15: to inform the DMEC and TSC if there are any concerns regarding completeness of data.
i) Relevant published studies since last meeting (e.g. Ross-Morris and Wallman GET studies and Adolescent CBT study)

For future meetings, the DMEC and TSC would like a summary report presented which details:

- All other ongoing and published research into CFS/ME
- A summary of what (if any) impact this will have on PACE; for example, are the estimated effect sizes likely to be different to that which we expect?

It was agreed that the new papers presented to the TSC are not likely to have an impact on PACE. The PIs are aware of another trial that is closing shortly and due to be analysed in the near future.

It was noted by the TSC that rates of participants ‘lost to follow-up’ were high in the presented papers. It was felt likely that this was in part due to the use of intrusive measures such as gas analysis.

ACTION 16: PI’s to summarise all other studies going on in the area of CFS/ME which should include outcome data and the numbers of participants included. This will include the conclusions of a meta-analysis.

j) Summary of other discussions

At each future meeting, the TSC should review:

- Actual vs. target recruitment
- Acceptance rate
- Loss to follow-up
- Adherence to treatment
- Baseline data but not outcome data.
- A report on data quality (the DMEC will also review this)

ACTION 17: to present the same report to TSC as to DMEC but the data will not be presented by treatment group.

ACTION 18: and the PIs to develop the format for this report to show to DMEC and TSC chairs for their agreement by email.

The analysis plan will be written once it is felt no further amendments to the protocol are likely. Discussions were held as to whether any formal interim analyses were planned and what might trigger a need for an additional interim analysis. The TSC proposed that a formal interim analysis will not be done unless there is a specific reason to do so. This should be stated in the DMEC charter.
ACTION 19: to ensure that the TMG, TSC and DMEC approve the Statistical Analysis Plan prior to commencing analysis to demonstrate that the plan was developed independently of the data.

ACTION 20: Whilst no formal interim analysis is planned, it was agreed that the DMEC should include in their Charter: any possible reasons why an interim analysis might be performed and what would happen in the event of an interim analysis being requested.

The TSC suggested that the TMG consider methods for keeping people interested in the trial, both participants and staff. The issue of summer and Christmas holidays was raised as time periods where the TMG could expect a slower rate of recruitment.

The TSC would also like the TMG to consider issues of staff retention/motivation:
- newsletters
- a monthly update e-mail to all trial staff
- incentives for centres to encourage healthy competition (if centres want this).

It was reported that a PACE day for staff had already been proposed for the end of August – the second wave centre staff will hopefully all be in post by this time.

ACTION 21: to continue sending monthly update emails out to all trial staff and to begin producing newsletters for the trial.

The PIs have noticed that the therapists talk across teams and that this has been both a positive and negative thing. When it affected the whole team across the country, but following this, the contingency plan put in place by the therapists to cover the absence of a therapist had a positive affect across the whole trial team.

The PIs note that the doctors are the hardest staff group to keep interested in the trial particularly where they rotate periodically. Regular team meetings for the PACE teams (including recruiting and assessing doctors) within centres are being used to keep interest and awareness of the trial high.

The TSC would like to record their congratulations to all staff that the trial is recruiting to target.

6. Contingency policy for absent therapist
a) Absence due to long term sickness, maternity leave or resignation

The PIs presented the proposed contingency policy. The background came in part to deal with a situation which arose when a therapist at [redacted] resigned but had already been considered because of holidays. The PIs explained that an amendment would be sent to MREC regarding this issue incorporating the decisions made by the TSC at this meeting.

The resignation of the [redacted] was especially difficult because of the geographical location of the centre. The PIs reported that the [redacted] GET therapist [redacted] and the [redacted] CBT therapist [redacted] had both generously offered their time to overcome this problem. The [redacted] took over the [redacted] GET caseload whilst the CBT therapist acted as therapy assistant and was learning to give GET. The participants have had all of their therapy delivered by these two therapists in combination. [redacted] has either travelled to [redacted] to give sessions with [redacted] sitting in as a physiotherapy assistant and observer, or has given telephone sessions with the participants sitting with [redacted] in the [redacted] hospital for support. As [redacted] is trained up, [redacted] will take a more supervisory role in these sessions and will lead them. The PIs reported that the participants affected have responded well to this and are happy with the arrangement.

A new GET therapist for [redacted] has recently been recruited and will be trained over the coming months.

The PIs explained the original rationale in the trial design for dividing the therapies by clinical discipline (i.e. APT delivered by an occupational therapist, CBT by a psychologist or CBT nurse specialist and GET given by a physiotherapist). This was to help ensure clear distinction between the three supplementary therapies. The TMG now feel that disciplines can cross-cover; there are some core clinical skills common to all and the therapists have no difficulty differentiating between each treatment. It was felt sensible in the long term to have cross cover because if one treatment is shown to have a greater efficacy than the others then it will avoid the issue of one clinical discipline ‘owning’ the best therapy. This will require some minor amendments to the therapy manuals which currently define the discipline delivering each therapy.

**ACTION 22:** [redacted] to include the changes to therapy manuals in the MREC amendment.

The DMEC had given consideration to the plans at their morning meeting and were happy with distant cover and cross cover, but not happy with the suggestion that a participant could be randomised to receive one therapy but be given another if the therapist was unavailable. They would prefer to suspend recruitment at the affected centre until another therapist was recruited.
The TSC would not recommending suspending recruitment to all the groups in a centre as this could affect staff morale and take the centre a long time to get back up and running to full capacity. The TSC would however consider temporary suspension of randomisation to one therapy within a centre as a preferable solution.

Spoke to the potential problems if this happened, these include: patients might agree to the trial because a particular therapy was no longer on offer and therefore there might be differences in the population recruited; and unless the minimisation algorithm is changed, not randomising to intervention X in one centre would mean that intervention X would be assigned more frequently to the other centres to preserve the overall balance of assignments between intervention groups which would have practical implications for the trial.

There was some discussion regarding the difficulty of keeping staff in post in some of the disciplines because remaining a long time in a post is contrary to normal career structure and progression. The PIs asked for TSC approval to train therapists to cross-cover following the successful implementation of this system in . The TSC endorsed the plan, believing it to reflect actual practice and supported the concept that no single discipline owns a therapy. A note of caution was made that Physiotherapists and Exercise Physiologists often have a different idea of what is meant by ‘graded’ and this may need careful monitoring.

ACTION 23: to include the cross-cover plans in the amendment to MREC.

The TSC asked whether the anti-PACE campaign has impacted on staff at all. The PIs reported that there was no evidence of this and as yet no trial staff has been directly contacted with the exception of those already known to the campaign groups (i.e. some of the PIs and one of the treatment leaders).

The TSC commented that the TMG should consider the following:

- survey of GET & CBT as considered by a small number of surveyed members (not sure what this means). It was found that patients who GET given by OT's reported more negative outcomes than GET given by other disciplines.
• Therapist cross cover will make any analysis incorporating clustering induced by a therapist effect more difficult.

b) Holiday cover arrangements
The PIs explained the contingency that the TMG are proposing for dealing with holiday cover for a therapist. It was recognised that a flexible approach should be taken. In summary, the plan is that where someone is on leave for:

- **Less than 3 weeks** the therapist will attempt to fit in the missed sessions within the five month treatment period but that no more than one session will take place in any one week. This is particularly important for GET where a high frequency of sessions might be too much of a burden to the participant.
- **3 weeks or more** someone else will conduct the missed session.

There has been discussion as to whether the covering therapist should retain a participant taken on where there is more than three weeks holiday, or whether the covering therapist may hand the participant over to the local centre therapist when they return from holiday. Flexibility is advised here with it being recognised that an increasing trial case load may make retaining a participant difficult for a covering therapist, but that it might be more disruptive to the participant to change therapist. Whatever happens should be carefully documented for each case.

The TSC raised a concern about how many sessions should be given by telephone and stated that as per protocol, this should ideally not exceed four sessions. The TSC accepted telephone sessions may be given where the participant sits with a local centre cross-cover therapist whilst receiving a telephone consultation from a distant same-discipline therapist as has been piloted in...

**ACTION 24:** to send MREC amendment to [name] first to ensure it reflects what the TSC have agreed.

7. PACE trial ancillary studies
For future meetings the TSC would like a written summary of all proposed ancillary studies. The TSC recommend that the TMG keep a register detailing:

- Number of participants to be involved
- Any measures that will be taken that are additional to those used in PACE (presented as a chart so that additional participant load can be monitored)
- Whether the study conduct or results could have any impact upon PACE
- Arrangements for ensuring that participants are not being included in several sub-studies if this puts an excessive load on them

**ACTION 25:** PIs and [name] to maintain a register of ancillary studies and to provide a summary report for each TSC meeting.
a) PACE trial ancillary studies approved by the TMG (Genomics study, therapeutic process)

Genomics study
There are four blood samples to be taken across the 52 weeks that the participant is involved in the trial. The TMG did not think taking blood samples would be a problem and had given this study team approval to develop the protocol further. The TSC suggested that the MREC might be concerned about the extra demand on participants with multiple blood samples. The committee also had a number of other questions relating to sample size, power, whether this would require an equal number of participants from each of the four PACE treatment groups and the number of blood samples required.

ACTION 26: to collate questions from TSC to take to and the genomics study group about the proposed sub-study.

ACTION 27: to review the power and sample size for the genomics proposal and advise the TMG. The TMG then to re-consider the proposal.

ACTION 28: to seek a peer review of the genomics study from an expert in genetics.

Therapeutic Interaction
The PIs raised a few items for the TSC to consider when reviewing this proposal:
- Would this study require participants to sign a separate consent?
- The discourse analysts would need to know the outcome data of the main trial

The TSC stated that the outcome data can only be released after the main analysis has been submitted for publication. Before this a certain amount of analysis could be completed without knowledge of the outcome data.

In addition, the TSC made the following comments:
- Ethical issues - A consent form would be required to be signed by the therapists. It might be difficult to argue that the therapists wouldn’t feel coerced into giving their consent, however the fact that the actual analyses are being carried out by people not working on PACE may make it more acceptable
- TMG approval - TSC approval would be subject to TMG approval

b) PACE trial ancillary studies awaiting approval by the TMG (Experience of a trial and Two year follow-up studies)

Patient perspective
The PIs explained that the TMG raised a question about sampling which needs to be resolved. The load to the participants will be one extra interview after the 52 week assessment. The interview style is open allowing the participants to speak freely about PACE.

The main concern that the TSC had with this study was over whether there could be an interaction between this and the 2-year follow-up study. This would need to resolved before the TSC could approve it.

**ACTION 29:** The TMG were advised to reconsider this study in terms of whether it would impact on the two year follow up study [further discussion below].

2-year follow-up
This study was supported in principle. However the complexity of the proposed analysis was noted and it was suggested that the primary analysis should only be based on randomisation. The TSC suggested that a longer period of follow up should also be considered.

The PIs asked whether the TSC would be better placed to decide which sub studies are accepted because the PIs may have personal interest in one or more of the studies and should therefore not judge. The TSC would be willing to take the decision but would require more information on each proposal.

It was noted that the two year follow up study and patient perspective studies could both be carried out only if the 2 year follow-up data were collected and the patient prospective study was completed within the lifetime of the trial unless additional funding was sought. This would mean that participants recruited in the last 24 months of recruitment could not be included into the follow-up study.

The TSC also asked that the study team consider what methods they will use to keep participants under follow up after the end of their participation in the main PACE trial.

**Summary**
- TSC would like to see a report from the TMG summarising each of the proposals. They are concerned about the cumulative burden on participants.
- For each proposal, the TMG should:
  - Consider whether the sub-studies interact with each other and in what ways
  - Present a timeline showing PACE and the sub-studies
  - Include details of the sample of PACE participants to be used.
8. Any available results (pooled)
The TSC asked whether there was any information available yet regarding the distribution of the participants at baseline according to the different CFS/ME criteria. presented the information as the proportion of participants fulfilling the different criteria:

- 100% = Oxford
- 57% = London
- 76% = CDC

Additionally:
- 29% = current depressive disorder (a stratification factor)

This is based on only 30 participants and may therefore change considerably over time.

The TSC would like to know what the overlap is between the definitions at future meetings.

9. Organisational issues
Rotation of TMG meetings to include each participating centre
The PIs spoke about a recent TMG meeting which was held in and explained the value to be had from holding these meetings at each participating centre rather than basing them in one alone. Also discussed was the fact that TMGs have been opened up to local PACE staff to observe if they wish. Costs of the meetings do increase due to the extra travel involved to facilitate this happening, and whilst money for this has not been included in the original grant, the TMG believe this is valuable for building and maintaining the team. This was pointed out to the MRC staff present.

The TSC endorsed the rotation of TMGs and thought it useful to include local staff. The TSC suggested teleconferences be considered to reduce costs but if these were used to continue to have alternate meetings as face to face

Unused salary funds
The PIs asked whether it is permissible to utilise monies not spent on salaries (i.e. where there is a break between changeover of staff) for other trial purposes. The MRC confirmed that the salary costs may be vired but care should be taken in viring between staff and non staff costs as it has implications for overheads. If in doubt they should be consulted,

Second wave centres
Some issues with the institutions involved in PACE at Oxford which might delay start of this centre were discussed.

The TSC suggested that the second wave centre leaders are invited to sit in as observers to the TSC meetings. It was clarified that they may not be voting members because the formal TSC membership must have a majority (> 50%)
of independent members. It is especially important to adhere to this because of the publicity surrounding the trial. It was also noted that [ ] of the [ ] sits on both the PACE and FINE TSCs. (Cross representation of the FINE and PACE PIs on each other’s committees was also considered desirable if possible).

10. Public relations
MRC receive a lot of correspondence amounting to several letters a week regarding the PACE and FINE trials. Some of these are direct correspondence and others come as queries sent via local MP’s. The MRC Head Office offer support to all staff involved in the trial and reinforces the recommendation that if anyone should receive any correspondence they should pass this on to the MRC press office to answer.

ACTION 30: The MRC request that when time allows a PACE trial website be launched that will answer some of the common questions.

ACTION 31: The MRC recommend that an abridged version of the protocol be published soon.

ACTION 32: [ ] to speak to MRC for advice on how much of the protocol should be published.

11. ISRCTN registration
The issue was discussed as to whether or not registration with the ISRCTN is considered sufficient to enable the TMG to publish the PACE results in an International Committee of Medical Journal Editors (ICMJE) journal. The MRC stated that at present all MRC trials are registered with ISCRCTN only. It was recommended that the TMG keep an eye on this situation and consider registering with The Lancet as well.

ACTION 33: TMG to consider registering PACE with the Lancet.

12. Any other business
Definition of a new patient
The PIs raised the issues that, according to the protocol, patients are ineligible for PACE if they have received one of the trial treatments before for CFS/ME. The PIs on behalf of the TMG raised the issue of whether to define what constitutes having received Standardised Specialist Medical Care (SSMC) before. They propose that a new patient be defined as someone who has not received more than three sessions in a secondary fatigue clinic with a fatigue clinic specialist.

The TSC suggests the PIs consider this on a case-by-case basis as this was difficult to define. The TSC recommend the PIs establish whether each new patient has received a treatment close to SSMC in the past and to establish a
time frame within which change, as a result of a treatment, would have been expected.

**ACTION 34:** PIs to consider this matter further and provide an operationalised definition.

**13. Date of next meeting**
The TSC would like to meet again after six months and once the second wave centres have opened to recruitment. Two dates have been suggested of the 23rd or 24th January.

**ACTION 35:** to offer both dates to TSC members who were unable to attend this meeting and confirm the availability of all other members.

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**13.07.2005**

### Summary of ACTION Points

**DMEC**
**ACTION 20:** Whilst no formal interim analysis is planned, it was agreed that the DMEC should include in their Charter: any possible reasons why an interim analysis might be performed and what would happen in the event of an interim analysis being requested.

**PIs/TMG**
**ACTION 1:** The PIs in conjunction with the statisticians to respond to the DMEC request to develop an operational definition of serious deterioration. This definition should be sent to the DMEC & TSC for comment by email rather than wait for next meeting.

**ACTION 2:** PIs to consider how best to measure life participation.

**ACTION 5:** PIs to address how participant attendance might be recorded on a session by session basis and the format of the report for DMEC.

**ACTION 6:** PIs to monitor attendance to therapy versus attendance to follow-up visits.

**ACTION 7:** PIs to provide a summary report for each meeting listing all ongoing research and recent publications.
ACTION 8: to send a revised paragraph to for incorporation into the final draft of the minutes for TSC meeting #2.

ACTION 10: TMG to review data on recruitment by centre at each meeting and alert the TSC immediately if there is a problem with recruitment at any centre(s).

ACTION 14: to review the group who declined in greater detail and report any problems to the TSC.

ACTION 16: PI’s to summarise all other studies going on in the area of CFS/ME which should include outcome data and the numbers of participants included. This will include the conclusions of a meta-analysis.

ACTION 18: and the PIs to develop the format for this report to show to DMEC and TSC chairs for their agreement by email.

ACTION 25: PIs and to maintain a register of ancillary studies and to provide a summary report for each TSC meeting.

ACTION 28: to seek a peer review of the genomics study from an expert in genetics.

ACTION 29: The TMG were advised to reconsider this study in terms of whether it would impact on the two year follow up study [further discussion below].

ACTION 30: The MRC request that when time allows a PACE trial website be launched that will answer some of the common questions.

ACTION 31: The MRC recommend that an abridged version of the protocol be published soon.

ACTION 33: TMG to consider registering PACE with the Lancet.

ACTION 34: PIs to consider this matter further and provide an operationalised definition.

ACTION 3: to set up dates for next year’s meetings for the TSC and DMEC.

ACTION 4: to send the DMEC recruitment reports annually.
ACTION 9: for future meetings, to number the papers according to their place on the Agenda.

ACTION 18: and the PIs to develop the format for this report to show to DMEC and TSC chairs for their agreement by email.

ACTION 21: to continue sending monthly update emails out to all trial staff and to begin producing newsletters for the trial.

ACTION 22: to include the changes to therapy manuals in the MREC amendment.

ACTION 23: to include the cross-cover plans in the amendment to MREC

ACTION 24: to send MREC amendment to first to ensure it reflects what the TSC have agreed.

ACTION 25: PIs and to maintain a register of ancillary studies and to provide a summary report for each TSC meeting.

ACTION 26: to collate questions from TSC to take to and the genomics study group about the proposed sub-study.

ACTION 32: to speak to MRC for advice on how much of the protocol should be published.

ACTION 34: PIs to consider this matter further and provide an operationalised definition.

ACTION 35: to offer both dates to TSC members who were unable to attend this meeting and confirm the availability of all other members.

ACTION 1: The PIs in conjunction with to respond to the DMEC request to develop an operational definition of serious deterioration. This definition should be sent to the DMEC & TSC for comment by email rather than wait for next meeting.

ACTION 2: PI's with help of the statisticians and DMEC, to consider how best to measure life participation.

ACTION 4: to send the DMEC recruitment reports annually.
ACTION 11: to present extra information in future reports showing the proportion of participants whose diagnosis of CFS/ME is confirmed of those referred to the clinic.

ACTION 12: to alter the word ‘refuse’ to ‘decline’ on the CONSORT diagram.

ACTION 13: to add a line in to the CONSORT diagram to show Acceptance Rates as % of Eligible.

ACTION 14: to review the group who declined in greater detail and report any problems to the TSC.

ACTION 15: to inform the DMEC and TSC if there are any concerns regarding completeness of data.

ACTION 17: to present the same report to TSC as to DMEC but the data will not be presented by treatment group.

ACTION 18: and the PIs to develop the format for this report to show to DMEC and TSC chairs for their agreement by email.

ACTION 19: to ensure that the TMG, TSC and DMEC approve the Statistical Analysis Plan prior to commencing analysis to demonstrate that the plan was developed independently of the data.

ACTION 1: The PIs in conjunction with to respond to the DMEC request to develop an operational definition of serious deterioration. This definition should be sent to the DMEC & TSC for comment by email rather than wait for next meeting.

ACTION 2: PI’s with help of the statisticians and DMEC, to consider how best to measure life participation.

ACTION 27: to review the power and sample size for the genomics proposal and advise the TMG. The TMG then to re-consider the proposal.
1. Those present

Members

Observers

Other members

2. Apologies

3. Welcome of new members

The PACE TSC would like to send their thanks to [redacted] on behalf of the whole trial team for [redacted] contribution to the trial.
4. Previous minutes of TSC #3 (document 1)

Cover for an absent therapist by a therapist of another centre or another discipline

PIs reported back on the success of the staff cover solution agreed at the last TSC meeting. This solution was two fold:

1. To allow therapists from other centres to cover for absent colleagues of the same discipline;
2. To train up therapists to cover more than one PACE trial treatment in order to enable them to cover for absent therapists at the same centre.

The PIs reported that this had been a successful solution for many reasons:

1. Randomisation did not need to be halted at any centre where a therapist has been absent for any length of time
2. PIs have noticed an added benefit of helping the therapists understand and respect the other therapies administered by their colleagues

The only potential complication of this contingency plan is that there may be clustering effects caused by one therapist covering more than one therapy or more than one centre, which may complicate the analysis. However, it was noted that this contingency plan is still considered the least disabling option to the trial as a whole.

DMEC reports

Amendment to Action Point 4, TSC minutes meeting #3: DMEC reports will be six-monthly not annually as recorded.

ISRCTN

The issue of whether ISRCTN registration was considered acceptable to allow trial reports to be accepted for publication by journals has now been resolved. The journals have accepted the ISRCTN as an independent clinical trials register.

5. Recruitment update

Revised recruitment targets

The recruitment targets for the trial have been revised to allow for the fact that the second wave centres will not start recruiting before March 2006.

TSC report discussed

The TSC report was discussed in detail and it was noted that according to revised figures, the trial was recruiting at 81% of target at 1st December 2005. The TSC congratulated the trial team on this achievement.

6. Recruitment issues for consideration by the TSC

Discussion of proposed changes to the trial eligibility criteria
Review of the CONSORT statements demonstrates that a number of patients have been excluded on the basis of SF-36 scores being too high (n = 36) to enter the trial or for having received a trial treatment before (n = 29).

The PIs noted that a substantial proportion of these patients met eligibility criteria for the trial in all other ways and that they were treated in the secondary care clinics as per normal practice. The TMG would therefore like to alter the eligibility criteria for the trial in two ways in order to both increase recruitment to the trial and to allow a greater representative sample of CFS/ME patients who are otherwise treated in secondary care to be offered the trial.

The PIs noted that the TSC had originally reduced the SF-36 cut off score from 70 to 60 in order to ensure that more disabled patients were entered into the trial. Centres’ experiences of running the trial so far are that the SF-36 is measuring subjective and not objective disability so this original concern was not now considered to be an issue. The SF-36 is a self report measure and patients’ perception of their physical function is assessed with this scale. There have been many incidents of patients objectively appearing as very disabled (using wheelchairs or mobility cars) scoring as too well on the SF-36 and thus being excluded from the trial. By contrast, many objectively fit and able patients who are still able to work and run the family home are presenting with low scores on the SF-36 and entering the trial.

Proposed changes to eligibility:

1. **Increase the threshold for exclusion by SF36 physical function sub-scale from its current level of 60 by one incremental point to 65.**

   At present, there are two ways of assessing recovery for the trial:
   
   i. To increase score on the SF-36 to a score of 70 or above, or
   
   ii. To demonstrate a 50% improvement on SF-36 score from baseline.

   The outcome score would therefore also be altered in the protocol from 70 to 75 to maintain a difference of two incremental points between entry criterion and a positive outcome on the SF-36 scale. An outcome score of 75 would be comparable with the FINE trial which uses a cut off score of 75 (the FINE trial eligibility cut off score for the SF-35 is 70).

   Of patients excluded so far, at least six have been identified as having been excluded for an SF-36 score of 65 and it possible that several more for whom we do not have SF-36 scores recorded in the trial data, may also have met criteria.

   The trial statisticians report that this change would have no impact on the analysis.

   The TSC supported this change.
ACTION 1: Trial manager/PIs to submit the proposed change to the eligibility criteria from a score of 60 to 65 on the SF-36 to the MREC for approval.

Action 2: Trial manager/PIs to submit a change from 70 to 75 on SF36 physical function subscale outcome criterion to the MREC for approval.

2. Exclude patients who have received a trial treatment at another PACE centre only (rather than anywhere).

At present, patients are excluded who have received any CFS.ME treatment similar to that in the trial (e.g. have seen a CFS specialist three times or more) although very often PIs do not believe that advice and treatment given will be similar to that offered in PACE. Similarly the PIs do not believe that therapy received at other non-PACE centres is similar to trial treatments. The TMG believe that this change will ensure that only patients who have received a treatment very similar to a PACE treatments before would be excluded. Between 10 and 19 otherwise eligible patients have been excluded from the trial so far for having received CFS treatment at non-PACE centres.

A discussion was held as to whether it would be better to remove this eligibility criteria entirely; however two main concerns were identified:

a. Firstly, this could result in treatment resistant patients entering the trial. This would effectively alter the trial question.

b. Patients might be tempted to agree to the trial in the hope that they would be randomised to a treatment that they had not previously tried. There is the risk that the drop out rate might be higher in those randomised to a treatment they had previously received.

ACTION 3: Trial manager/PIs to submit the proposed change to the eligibility criteria to only exclude patients who have received a trial treatment before at a PACE recruiting hospital (rather than at any hospital).

Recruitment strategies
In Edinburgh, the main barrier to recruitment identified was the assessment capacity of clinic doctors. An extra doctor has been brought in to help this situation. It was explained that clinic doctors are the only staff involved in PACE who do not either directly or indirectly receive any payment for their work. Assessments and explanations for the trial take extra time, and giving SSMC treatment represents a large extra burden to doctors that is in some centres extra to usual practice. Centres are investigating whether the subvention funds meant for medical care which are paid directly to the CFS services (at £160 per patient) could be used to hire doctors directly.

Doubling up centre recruitment
The study has been designed to enable three centres to receive extra money in the final year of recruitment to enable them to double their recruitment rate
from 33 to 67 per year. The TMG had discussed strategies for increasing recruitment sooner than the last 12 months, such as asking one centre to double its recruitment now for two years. Kings were asked to consider this, based on the fact that King's are seeing more patients than any other centre at present. Kings consider that a more realistic recruitment might be 1.5 or one and two thirds of current target. The TMG believe that it would be wise to maximise on this situation sooner rather than later and propose that funds increase to King's by 50 – 66% to allow greater recruitment.

TSC agree that we should start increasing recruitment as early as possible and would encourage using the funds flexibly.

**ACTION 4:** To write a letter to [insert name] at MRC Head Office to investigate whether the MRC would support releasing monies earlier than the last year of recruitment to boost recruitment at centres seeing many more patients than other centres.

**ACTION 5:** Trial manager to submit an amendment to MREC to re-word the protocol to allow for this possible alteration.

**Assessment of patients for PACE from non-PACE sources**

The PIs explained that some clinic doctors assess patients for CFS/ME outside of the secondary care clinics as part of their routine job. PACE clinic doctors who work at satellite centres (i.e. in Essex and Sussex) could refer patients to a PACE centre if they met criteria and were willing to travel to a hospital. If the patient accepted the referral but ultimately declined to take part in the trial, the centre would still be committed to offer treatment to the patient in the usual way.

The TSC support this suggestion but offer a note of caution that centres should be sure that patients recruited from further afield would still adhere to treatment and follow up.

**7. Drop out, withdrawals and losses to follow up by month and as a proportion of those entered**

**Drop outs**

There has been one recorded drop out (withdrawal of consent) from the trial at 12 weeks. The patient had seen the SSMC doctors before entering the trial and was disappointed to have been randomised to receive SSMC alone. The centre made every reasonable effort to keep the participant on board but the patient ultimately decided against any further participation.

The PIs reported that two other participants had been disappointed to be randomised to SSMC alone. It has been very important to provide the SSMC doctors with a lot of support, advice and feedback to avoid this happening on a regular basis.
8. Completeness of database entry
The trial database has gone through various revisions (currently at version 6) and it is believed only one more version will need to be released. At present the database is being revised to remove programming bugs. Once this process is completed the remaining data will be entered and the data checking process will begin.

Approximately two thirds of the data collected has been entered on to the database. It is hoped that the final database will be released in Feb/March and that data checking will begin after this time. It is envisaged that this data will be available for the DMEC meeting in the summer.

The TSC offered their support to secure any help needed to ensure that this is achieved.

9. Start of second wave centres – progress reports
Barts II – All staff recruited apart from a physiotherapist. This post has been advertised several times but it has proven difficult to recruit to a part time (0.6) therapy post in London. Agenda for Change has confounded this problem considerably as it has not been possible to state what the grade or salary will be. The contingency plans, particularly for more flexibility about the discipline of therapists agreed at the last TSC meeting have helped in this considerably: An exercise physiologist has been recruited to the Royal Free Hospital and the other London therapists have kindly agreed to cover Barts II whilst the post remains vacant. This problem will therefore, not slow the centre recruiting.

Oxford – Have recruited all staff with the exception of the data manager. This post is not critical to recruitment and will not delay this centre starting.

Royal Free – Have recruited all apart from a Research Nurse/Assistant; interviews will take place in two weeks time. This post has been difficult to fill and has now reached the fourth round of advertisements and applications.

10. Relevant published studies since last meeting
A summary of relevant papers was provided. The TSC agreed that the evidence indicated that (a) there was no good evidence that any PACE treatment should be stopped because of possible harm, and (b) no good evidence that the trial should be stopped because either a PACE treatment of a non PACE treatment had been shown to be markedly effective.

11. PACE trial ancillary studies approved by the TMG
The TSC reviewed these studies to ensure that they are useful and do not jeopardize the main trial, and also to ensure that the most is made of the trial data.
a) Genomics study
This has been submitted for funding at the MRC and the PIs will be informed by 27/01/06 if this proposal is going to the Board for consideration.

An independent review was obtained as per the TSCs request at the last meeting. In summary:

is supportive of the study and believes it will be a benefit to the main trial.

was concerned about the lack of a healthy control group and whether there would be adequate power for the study. confirmed that the extra blood tests would be necessary, but the TSC noted that these had been reduced from 4 to 2.

In answer to the former issues, there are banks of blood specimens from healthy controls that we can use:

– for SNPs, age and gender are not important, only ethnicity;
– on genomic expression age and gender can have an influence and matched healthy controls would be needed.

The TSC agreed that plans for this proposed study proceed.

b) Therapeutic process
The study proposal was submitted to the Scottish CSO for funding. Whilst they liked the study, they decided against funding it. The ESRC are now being approached for funding.

The PIs sought TSC permission to adding an additional consent now for participants and therapists ahead of getting funding to allow the data to be analyzed when funding was available. The TSC were agreeable to this and supported the proposal.

ACTION 6: Trial manager to submit an amendment to MREC to consent participants and therapists to allow for their recordings of therapy sessions to be used for the therapeutic process ancillary study.

c) Two year follow-up study
This proposal has not yet been submitted for funding as the TMG decided it was important to first be able to demonstrate an ability to recruit to the main trial.

In addition to the written information supplied to the TSC for this meeting, it was noted that participants would be asked at two years for details of any other treatments that they had received since exiting the main trial at 52 weeks.
The TSC agreed to a two year follow up period in the first instance, but would support follow up for as long as possible.

d) Experience of participating in a trial
At the previous meeting, the TSC asked the TMG to consider whether this ancillary study would interfere with the two year follow up study. The PIs reported that the TMG are content that this would not interfere with either the main trial or two year follow up study.

This study already has funding pledged from the Maudsley R&D and would recruit 60 participants from King’s. The TSC feel that this research could support the main trial as it would demonstrate that the TMG are interested in gauging user experiences, both positive and negative. The TSC would support the recommendation that the interview includes questions on any negative experiences as well as positive.

It was noted that similar research is to be carried out alongside the FINE trial.

Summary
The TSC agreed that these studies will all add value and not jeopardise the main trial. In addition it is believed that the proposed research will help future trials.

12. Public relations
Update of issues
- The MRC report that there is still a steady stream of enquiries relating to PACE and FINE. It is noted that for the most part, the same few questions are being asked.

- has initiated a working party to look into whether enough research is being carried out into the ‘physical’ aspects of CFS/ME. The MRC are monitoring the progress of this.

- There has been a raft of emails to staff at one centre asking for information on the trial. As a FoI request, the PIS and PCL have been supplied to this person.

- At the same centre, the MEA have been asking individual participants to comment on their experiences in the trial.

13. Operationalised definition of serious deterioration (SAE) of CFS/ME
PIs discussed the proposed definition of serious deterioration. These were:
A significant deterioration is defined as a categorical change in one or more of the following measures within the 52 weeks after randomisation:

- SF36 physical function sub-scale diminishing by 20 or more points between any two adjacent assessment interviews
- A self-rated CGI change score of 6 or 7 ("much worse" and "very much worse") at any assessment interview
- A drop-out from treatment due to a participant's reported worsening of their condition, which is attributed to treatment received, at any stage of active treatment (between the first and last (booster) sessions)
- A serious adverse reaction, as defined in the protocol

If one treatment arm of the trial is associated with 20 per cent of participants deteriorating as defined above, despite review and revision of the treatment and after further monitoring, then the DMEC should consider stopping that arm.

Two main issues have been identified:
1. What constitutes serious deterioration for a participant?
2. How does the proportion of participants with this level of deterioration compare with other treatment groups?

Consideration was given to only counting a serious deterioration when two criteria were met. The TSC recommended that various other possibilities be explored in fine tuning this definition and recommended further work in liaison with the DMEC in reaching a final definition. The importance of differentiating between adverse events and adverse reactions was highlighted. Furthermore, the importance of clarifying relatedness to treatments was noted.

The TSC recommended that the TMG consider the balance between deterioration and benefit and not simply rely on a defined drop of 20 points on the SF-36 physical function score or 20% having serious deterioration. For example, the TSC ask the TMG to discuss what would happen if 20% in a treatment group deteriorated, but 60% improved. The danger of an absolute definition is that it might lead to closing an arm unnecessarily. Assessing relative differences were thought to be a better way of defining deterioration.

The TSC would like to discuss this at the next meeting once the TMG have discussed it further and consulted the DMEC on these issues.

**Action 7: PIs to discuss the definition of deterioration with the DMEC.**

**14. Measurement of life participation**
At the last meeting, the DMEC requested assurance that the TMG are considering life participation in the participant population.
The TSC agreed with the proposal that the WSAS considered alongside the CSRI are suitable measures of life participation.

15. Report on PACE National Team Day
The PIs reported that this day was successful and a second PACE trial team day will be held in the summer of 2006. The day included time for staff to feedback things that they liked and disliked about the trial and these are going to be addressed by the TMG at the next meeting (8th February 2006).

The PIs recognise that more is required to keep the clinic doctors engaged with the trial. The TSC suggest using other events (such as conferences) that the doctors might attend, to tie in with some PACE activities, such as a dinner.

The next PACE trial day for staff will be on 16th June 2006.

16. Any other issues
FINE trial update from

The FINE trial is based in primary care comparing three rehabilitative treatments delivered by general nurses (adult speciality) who deliver the treatments in the participant’s own home. The nurses have received six months specialist training in the treatments and receive ongoing supervision. The trial is currently recruiting from approximately 50 PCTs and 101 participants have been randomised so far out of 182 referrals (some of whom have turned out not to be suitable). There has been a 13% drop out from treatment, which was considerably less than the expected rate, but no losses to follow up so far. Referrals have been received from 66 individual GPs.

There are several ancillary studies associated with the trial:
- A qualitative study with GPs.
- A study of therapists’ experiences of training and supervision.
- A qualitative study of participants’ experiences of taking part in the trial.
- A study of the processes of change.

The TSC were interested in this update and request further follow ups at future meetings.

[ ] will sit in as an observer to the next FINE TSC.

Conflict of interest
It was noted that [Name] has been paid by the MRC for profits made from technology developed some time ago. The TSC did not consider that this would unduly influence [Name] independence as a member.

Thanks to the TSC
The PIs have found the TSC meetings very helpful and thanked members and observers for the advice and support.

Thanks to the PACE team
TSC would like to congratulate the team for achievements to date.

17. DMEC meeting 4th July 2006

18. Date and time of next meeting
Monday 17th July 2006 at 1:45pm (lunch to be provided from 1pm).

ACTION 8: Trial manager to provide additional notes to the Chairman’s agenda for future meetings.

ACTION 9: Trial manager to disseminate the date of next meeting to all people unable to attend this time.
Draft Minutes

1. Present
   Members

   Observers

   Other members

2. Apologies
   Due to the unusually high number of people unable to make this meeting, decisions and recommendations made at this meeting will be sent to absent members for their approval before any actions are implemented.
3. Welcome to new members

The TSC formally welcomed two new members. Unfortunately neither new member was available to attend this meeting:

- [Name] who replaces [Name]

4. Members who have left the committee

[Name] The TSC extends thanks to [Name] to all of [Name’s] contributions to and support of the PACE trial.

5. Previous minutes of TSC #4

These were accepted and signed off.

6. Matters arising from TSC #4 not on the agenda

[Name] will give an update of the progress in the FINE trial at this meeting.

7. Matters arising from DMEC meeting of 4th July 2006 (document from [Name] to [Name])

a) Unblinding of [Name]

The issue of [Name] being unblinded was discussed. This has occurred due to contents of the database (particularly in comments fields) occasionally giving away information as to whether the participant is having a supplementary therapy and occasionally, what that therapy is. It was clarified that the DMEC are not concerned about this as long as [Name] remains blinded to the results of the trial.

The DMEC currently see blinded data.

b) Membership of the DMEC

The DMEC would like to invite another member to join them so that if any member is unavailable to take part in a meeting, there will be enough other available members to make decisions. [Name] has been suggested as someone who might be approached and although [Name] works for [Name] has no formal links with the King’s team so there should not be any conflict of interest. [Name] has identified another potential person that might be approached.

ACTION 1: [Name] will speak to [Name] about people who might be approached as extra members to the DMEC.
Definition of serious deterioration

The DMEC clarified the definition of serious deterioration in an individual participant. The DMEC also discussed deterioration in terms of time to drop out (at least 8 weeks from randomisation). In addition, the DMEC suggested dropping SAEs from the definition, comparing changes in SF-36PF to baseline as opposed to the previous visit, and looking at CGI and SF-36PF both on two consecutive visits as well.

ACTION 2: to:
   i. revise the Definition of Deterioration document
   ii. circulate to DMEC to ensure it matches with their decisions
   iii. include the ‘8 week to drop out’ rule
   iv. circulate the completed approved document to the TSC.

ACTION 3: to circulate the completed Definition of Deterioration document to the TSC with the minutes to this meeting.

All other DMEC issues were deemed satisfactory or are to be raised on the agenda of this TSC meeting.


   a) General TSC report issues

   spoke regarding the TSC report.
   - Recruitment target has been revised due to delays to the second wave centres starting up.
   - The CONSORT diagrams include ‘Health warnings’. These reflect that the complete accuracy of the data is not assured at this time but this is being worked on.
   - An explanation was provided to the TSC for the 119 unknowns listed as ‘awaiting referral decision’ on the CONSORT diagram. A large proportion are believed to be patients who were contacted for the trial by the RN by telephone, but who turn it down or are found to be ineligible before baseline 1.
   - General acceptance rate of the trial is similar to that reported six months ago.
   - In order for the TSC to be able to assess the completeness of the data for future reports, will need information regarding what data has been collected separately from that which has been entered. In practical terms this means having a separate list of completed visits, including dates, per participant per centre. The completeness of data collected at the item level can only be assessed practically once it has
been entered onto the database. The local data managers or research assistants will need to provide this. (It might be helpful if this was built into the monthly updates to the Senior Data Manager for th is individual to check).

- **Non adherence to treatment** – The TSC would like a measure of the level of adherence to treatment to include the number of sessions attended and whether the treatment was adhered to, without including mutually cancelled sessions that would be redundant.

- The trial protocol defines adherence as 10 sessions or more but does not mention these other factors

**ACTION 4:** TMG to further define ‘adherence to treatment’ taking in to account attendance and engagement.

**ACTION 5:** to submit an amendment to protocol as required reflecting the clearer definition of adherence to trial treatment.

b) **Drop outs, withdrawals and losses to follow up by month and as a proportion of those entered**

There have been 3 drop outs from the trial so far. Two have withdrawn from the whole trial, one has withdrawn from treatment only but remains in follow up with the research nurse.

c) **Completeness of database entry**

The majority of the available data has been entered. This is not 100% due to the fact that the database was completed late and centre data managers have had a backlog of data cleaning and entry to clear for this meeting.

d) **Recruitment rate below targets**

The reasons for this were discussed and are summarised as follows:

**01 Barts** – There has been a new service set up in Sussex which has drawn referrals away from Barts’. The trial now has MREC approval to approve from further afield and Sussex patients have started to be referred for the PACE trial at Bart’s.

**02 Edinburgh** – There are plenty of referrals to this centre, but there has been a shortage of available clinic times with the consultants. This has been identified and addressed with the recruitment of a third consultant to the PACE trial and the centre saw a rapid rise in randomisations as a consequence. If one or better two more sessions of clinic time can be freed up, the centre is confident that recruitment will increase by a further 20-30%. This should bring recruitment up to target, and could be met out
of contingent monies within the trial (allocated to back loading the last year).

03 Kings – Have had similar problems with regard to the availability of clinic doctor’s time to assess participants for the trial. Kings has recently been able to allocate more time to the PACE trial, and the centre has increased research staff time by one third in order to increase the rate of referrals to the trial. The centre has noticed some reduction in overall referrals due to NHS funding problems causing PCTs not to refer to a service for which they will be charged.

The TMG also feel that the negative PR surrounding the trial may have adversely affected uptake.

e) Proposed strategic solutions to improve recruitment rate

The TMG discussed the proposals from the TMG to improve the recruitment rate to PACE. In summary, these include:

- Extension of recruitment period by six to eight months,
- Increasing target recruitment in existing centres and
- The addition of two new centres - the costs of this would be start up, salary, staff training, travel and transport. The initial subvention and MRC grant did not take into account staff turnover and maternity leave costs and any future grant would need monies to cover these issues.

It is estimated that an additional two centres plus a six month extension gives an estimated recruitment end point of 597.

A further strategy to improve recruitment would be to loosen the eligibility criteria to allow participants who had suffered a recurrence. TSC rejected this suggestion due to the risks of picking up treatment resistant patients or recruiting patients who are not in equipoise.

Summary of TSC decisions

On consideration of the proposals, the TSC felt it essential to do as much possible as quickly as possible to improve recruitment.

Subvention - TSC agree that it is essential to obtain funding to support NHS staff or the trial may fail to recruit enough patients within budget.

**ACTION 6:** to draft a letter to be sent to DH R&D and to be signed by making a statement of support from the TSC for further NHS funding for PACE.
Budget - Travel and training has cost extra due to staff turnover and cross cover, but in other ways the budget is close to target. The TSC therefore support the use of back loaded funding to get a new centre started up as soon as possible.

Extension to trial - Recommended that an extra six to eight months of recruitment and follow up.

Timelines for implementation

Plan:
1. Recruit one new centre immediately on back loaded funds.
2. Use extra time recovered from delay to starting first six centres to extend the time to recruitment by a few months.
3. Write to the MRC HS Board to requesting an extension to time and funding. The request should be sent by September in time for the November meeting.

ACTION 7: [ ] and [ ] to write a statement for the internal MRC Executive Board regarding non-cost measures to improve trial recruitment.

ACTION 8: [ ] to contact the TSC members not present to ensure that they are happy with the decisions proposed to improve recruitment.

ACTION 9: If further funding is forthcoming, [ ] to contact the MREC to inform them of the extension to trial end and to alter the protocol accordingly.

9. Monitoring of first wave centres (document 3: Summary of outcomes from monitoring visits)

A summary of the findings was presented to the TSC. The only major concern was the report that centres are not using the patient and GP letters as worded in the protocol, and the delay between baseline 2 and randomisation.

ACTION 10: [ ] to send an administrative amendment to MREC regarding the wording of letters to participants showing examples of the centre letters actually being used.

[ ] would like to do a minimum of one monitoring visit per centre per year, more if time and funding allow.
TMG would like to make an amendment to MREC to state that there should be up to one month gap between baseline 1 and randomisations or tests should be repeated. The TSC were happy with this decision.

**ACTION 11:** to send an amendment to MREC to increase the time to randomisation from one day after baseline 2 to within four weeks of baseline 1 to better reflect what is possible in practice.

The greatest concern of the DMEC to the reports was the issue of high turnover of junior doctors giving SSMC at King’s. As described earlier, a consultant who can give more clinic time to the trial has now been identified to take on more of this workload.

10. **Discussion of categorical improvement score on the SF-36**

   The TSC reviewed the categorical threshold for improvement on the SF36 physical function subscale of 70. Although it was noted that this was well within 1 standard deviation of the mean score for the female adult working population (80), the TSC decided that the complementary use of a 50% improvement in SF36 score would compensate for the closeness of these scores.

11. **Start of second wave centres – progress report**

   04 Barts II – this centre has had difficulty in recruiting therapists with some adverts going out several times. All staff are now employed but the GET therapist will not be starting until late July and will require training after that time.

   05 Oxford – There was a delay to starting this centre due to issues with the financial contract. All staff have now been recruited to this centre with the Data manager being the latest appointment. All therapists are fully trained and the site opened to recruitment in April 2006. The centre has recruited to target so far.

   06 Royal Free – This centre has had multiple difficulties; these include agenda for change delaying advertisements of posts, redundancies of almost 500 NHS staff, freeze on recruiting new staff, delay waiting for re-deployment of staff; difficulties in obtaining LREC approval, difficulties in recruiting research staff (first three rounds of interviews did not produce any suitable candidates for the research nurse post). This centre has not yet started recruitment but all therapists are trained.

12. **Relevant published studies since last meeting (to be tabled)**

    Two new papers were tabled at this meeting.
The BioBran trial had no results from placebo and has no bearing on the PACE trial.

The methylphenidate trial did find differences from placebo on both mental and physical fatigue. The effects were only seen whilst the patients were on drug but disappeared when the patients were off drug. This is a common drug for ADHD and may be subject to misuse. This trial is not thought to have any bearing on PACE.

[Insert text]

will be reporting later in the summer so there is no news on the results of RCT yet.

13. PACE trial ancillary studies previously approved
   a) Genomics study
      Genomics was turned down for funding by the MRC.
      The CDC pledged monies and it is hoped that this might be still be used to look at SNPs.
   
   b) Therapeutic process
      This is about to be submitted to ESRC for funding and then MREC approval subsequently.
   
   c) Two year follow-up study
      There have been indications from the DWP that they would consider this carefully regarding supporting this with partial funding.

      The TSC discussed when they thought it would be most sensible to approach the MRC for funding. The advice was that there was a need to be careful not to approach the MRC HSPHRB too late as if the first few patients have passed the two year follow-up time point it may be seen as a perceived weakness by a funding board.

      One suggestion was to seek MREC approval and complete two year follow within the existing budget in the first instance. If this proves possible, the TMG might consider requesting for two year follow up money at the same time as asking for trial extension funding. This latter suggestion was thought to be risky however.

      Originally it was envisaged that follow up would be done as a face to face interview either at clinic or in the patients’ home. Due to the under recruitment situation, it was discussed as to whether the two year follow
up should be done by questionnaire only to reduce the potential burden of extra interviews on the existing research nurses.

A phased plan was suggested for consideration by the TMG:

- Two year follow up, and possibly three year
- Chasing for follow-up information via GPs (some GPs charge circa £50 for any response to research requests however, so this may not be cheap or reliable)
- Costing for this ancillary study needs to include production of new forms, new database, postage and phone call costs and administration time/staff costs.

**ACTION 12:** The TMG should consider the two year follow up study in more depth and prioritise what data from this would be of most use, and use these discussions to further develop this protocol.

d) Supervision process study (document 4)

The supervision study briefly discussed and the TSC were happy to support the proposal.

14. **FINE trial update**

FINE is a RCT of two active treatments versus GP treatment as usual. Patients are recruited from primary care and referred by GPs. The two treatments are supportive listening and active rehabilitation and are delivered by specially trained nurses (each nurse is trained to give both). This is given over 18 weeks with 5 home visits and 5 telephone sessions. Follow up at 20 weeks and 1 year. Patients are assessed in their own homes.

Successes so far: 3 nurse therapists are delivering treatments. Fidelity checks show that treatments are being kept separate, the nurses are happy and there has been no change of staff.

Difficulties: Recruitment is struggling and is currently at 65% but this is improving.

The FINE trial statistician has revised the power calculations and widened confidence intervals to allow for a reduction in target by 80 participants. The original calculations were based upon very conservative assumptions. No decision has yet been made as to whether to follow this revised target. An extension to the study of a two or three
year follow up is being considered as is an extension to the trial recruitment period.

There are various qualitative studies being conducted alongside the main trial. These include interviewing GPs, patients who have accepted and refused the trial, practice nurses etc.,

15. Public relations (documents 5, 6 and 7: Participant Newsletter, Staff newsletter and Website)  
Correspondence to the MRC has slowed down slightly in anticipation of the results of the Gibson enquiry.

There was discussion as to why only King’s participants are being asked for their experience of the trial (qualitative study). This is a local LREC approved study to King’s that sought approval before the PACE trial had begun. The TSC were satisfied with this explanation.

Newsletters & website - The TSC were pleased with the newsletters and website. No feedback has yet been received about the website from the public.

16. Report on PACE National Team Day  
The team reported that they found the day interesting, useful and enjoyable.

17. Date and time of next meeting to be arranged at this meeting
Proposed January dates for next meeting:
Monday 8th January 2007
Monday 22nd January 2007
Monday 29th January 2007

ACTION 13: to circulate these dates to the TSC and inform all when a final date has been selected.

Summary of Action Points

ACTION 1: will speak to about people who might be approached as extra members to the DMEC.
ACTION 2: to:
   i. revise the Definition of Deterioration document
   ii. circulate to DMEC to ensure it matches with their decisions
   iii. include the ‘8 week to drop out’ rule
   iv. circulate the completed approved document to the TMG.

ACTION 6: to draft a letter to be sent to DH R&D and to be signed by making a statement of support from the TSC for further NHS funding for PACE.

ACTION 7: and to write a statement for the internal board regarding non-cost measures to improve trial recruitment.

ACTION 3: to circulate the completed Definition of Deterioration document to the TSC with the minutes to this meeting.

ACTION 5: to submit an amendment to protocol as required reflecting the clearer definition of adherence to trial treatment.

ACTION 8: to contact the TSC members not present to ensure that they are happy with the decisions proposed to improve recruitment.

ACTION 9: If further funding is forthcoming, to contact the MREC to inform them of the extension to trial end and to alter the protocol accordingly.

ACTION 10: to send an administrative amendment to MREC regarding the wording of letters to participants showing examples of the centre letters actually being used.

ACTION 11: to send an amendment to MREC to increase the time to randomisation from one day after baseline 2 to within four weeks of baseline 1 to better reflect what is possible in practice.

ACTION 13: to circulate these dates to the TSC and inform all when a final date has been selected.

TMG
ACTION 4: TMG to further define ‘adherence to treatment’ taking into account attendance and engagement.

ACTION 12: The TMG should consider the two year follow up study in more depth and prioritise what data from this would be of most use, and use these discussions to further develop this protocol.

ACTION 7: [Name of participants] to write a statement for the internal board regarding non-cost measures to improve trial recruitment.
Draft minutes

1. Those present
   Independent Members
   Non-voting members
   Observers

2. Welcome to new members and observers
   was welcomed as the new . was welcomed as an observer.

3. Apologies

4. Previous minutes of TSC # 5
   DMEC membership
   It was agreed that the DMEC does not need a fourth member as long as all three members are available to attend.
ACTION 1: [Redacted] to double check that [Redacted] would not like an extra clinician member of the DMEC. This was completed immediately after the meeting and [Redacted] is happy with the current members as long as they all attend.

Adherence to treatment
The Analysis Strategy Group and Trial Management Group would like to define adequate (or perhaps acceptable or satisfactory) adherence to treatment as the participant receiving ten of the fifteen therapy sessions and at least three sessions of Standardised Specialist Medical Care. This was agreed and it was also agreed that this did not need a REC amendment.

Trial extension
ACTION 2: [Redacted] to submit an amendment to the REC for the extension to the trial recruitment period.

5. Matters arising from DMEC meeting of 29th May 2007
The Trial Steering Committee wished to thank the trial statisticians for the comprehensive report sent to DMEC.

Fractures
Five fractures have been reported in the trial. The TSC and DMEC would like reports on fractures to include the age of the participant, site of fracture, description of event, any evidence of any osteoporotic history or previous fracture history and time from randomisation (as fractures may be a sign of increased activity).

ACTION 3: [Redacted] will look for data on the incidence of osteoporosis in CFS.

[Redacted] reported a study not yet published showing that incidence of fractures in CFS patients, IBS patients and healthy controls is the same across all groups.

6. TSC Report
Recruitment update (document 3a)
Recruitment is currently at 97% of the revised target.

Drop outs, withdrawals and losses to follow up by month and as a proportion of those entered
Loss to follow up rate is very low. The DMEC monitors this by treatment group and has not expressed concern. Drop out from treatment rate is also very low and the DMEC were very happy with this figure. The TSC
congratulated the trial staff on the excellent completeness of data collection and quality and the low drop out rates.

**PIs report**

Baseline demographics are felt by the PIs to be as expected from clinical experience and previous research.

The majority of participants at 52 weeks have received at least an adequate number of sessions of trial treatment.

The only significant recruitment concerns are related to the uncertainty of the future sources of funding in the NHS for the support costs for research and whether further subvention money may be obtained to cover this. The trial recruitment targets have been revised to end on 30th November 2008 with 11 months funded time and one month unfunded time (funded from the delayed start to the trial of some centres). In future the committee may decide to approach NHS R&D about further funds.

The PACE recruiters are making use of the CFS networks to recruit from wider geographical areas including Sussex, Hertfordshire, Essex and Kent. The NICE guidelines to be published soon reinforce the value of the PACE trial.

The trial protocol has been published in BioMed Central.

The PIs sought TSC advice regarding trial staff retention as the end of the trial approaches. The revised recruitment targets allow a little extra time that might be used at the end to extend some staff contracts. Theoretically some of the research money might be used with MRC permission to extend contracts to ensure adequate centre shut-down and other related research tasks. Therapists are already employed flexibly to cover other staff absences (e.g. [missing text] ) and this could be continued. One potential suggestion for future replacements of NHS staff is to consider secondment of NHS therapists to the research posts part time.

There is some concern that some NHS Trusts may wish to terminate NHS posts according to the original recruitment time, which has now been extended by 12 months. The subvention monies were funded on a per participant randomised basis; the extension to time of the trial does not include an extension to subvention money.

Subvention monies are invoiced quarterly in arrears based upon date of randomisation. Participant treatment lasts for 9 months after randomisation and additional treatment is offered if required after 52 weeks.

The TSC pledged support for seeking extra subvention money if required.
ACTION 4: [Name] to speak with [Name] about accessing further subvention money if needed. ([Name] to do similar in Scotland).

The TSC recommended that a risk assessment is carried out to see what risks there are to the trial of excess treatment costs not meeting therapist’s salaries over projected recruitment time.

CONSORT
The main reason for non-eligibility is not meeting Oxford criteria. This may mean that the participants either do not have CFS/ME or that fatigue is not the primary complaint (e.g. pain or depression may be the main symptom).

The TSC was asked whether it was thought important to review the patients who do not meet Oxford criteria. The TSC suggested that a random sample of notes could be reviewed or that collection of future data could be altered and that the TMG should review whether this could be operationalised. The TSC did not think this would be necessary for the whole trial data.

ACTION 5: The PIs to bring the issue of revising the screening data collection to the TMG.

Completeness of database entry
Data entry is largely up to date. The Royal Free have just been given permission to recruit a data manager which will improve this figure further.

Missing data as reported is as a result of data managers not yet being employed. The Bart’s centre data manager has supplied support to her colleagues at the Free by periodically visiting to complete data cleaning and data entry.

The TSC noted the high level of data queries generated for the King’s centre. It was explained that a portion of this represented incomplete Clinical Global Impression of Change scale data from doctors caused by the high turnover of doctors at this centre which leads to them being unable to make judgements or complete data for participants seen by two or more other doctors over the 52 weeks.

The TSC wanted reassurance that the high level of data queries at King’s can be reduced for the next meeting, although it was reassured that the Clinical Global Impression of Change scale data that is missing is a tertiary outcome measure.
ACTION 6: to discuss the issue of missing and incomplete data for the doctors Clinical Global Impression of Change score with and .

Quality and differentiation of treatments
 is organising an assessment and a blinded assessor is being sought will review recordings for differentiation and identify any therapeutic drift.

A question was raised regarding whether the trial results will be generalisable to severely affected patients. It was hoped that the results of PACE and FINE in combination will give wide ranging information on rehabilitation approaches for CFS/ME patients of differing disability. The FINE trial giving treatment at home found a wide range of disease severity in the participants but did not identify a large number of home/bed bound patients. There is some evidence to suggest that 10-15% of CFS/ME patients are severely affected. PACE is conducted in secondary care clinics but theoretically the trial treatments could be delivered at home.

Pilot studies on home delivered therapy are being conducted at King’s and Bart’s. This is a much more resource intensive treatment approach.

The results of the PACE trial are likely to be available in 2010 but trial results from FINE and a trial by will report within the next 18 months. The TSC noted that the results of these trials may impact on PACE and there will need to be a mechanism in place for disseminating this information to PACE trial participants.

Analysis Strategy (document 4)
The Analysis Strategy Group is meeting regularly and a final draft strategy will be available by September. After this time the TSC and TMG will be given the document for feedback and advice. A design paper is currently being devised that would be published ahead of the main result to tackle issues such as choice of methodological approaches.

7. Monitoring reports (documents 6 & 7: recent monitoring visit reports)
The monitoring reports of the Royal Free Hospital and Oxford (visits conducted since the last TSC) were presented to the TSC. Both centres are running very well with no negative findings to report. The TSC stated that they were very impressed with the quality of monitoring conducted.

8. Start of second and third wave centres – progress report
Bart’s II (now a combined centre with Bart’s I) and Oxford began recruitment in May 2006. The Royal Free start was delayed due to NHS Trust issues and problems with the LREC turnover of paperwork. The Royal Free are recruiting rapidly and catching up to target.
The third wave centre at Bristol began recruitment in April 2007 eight months after first being approached to take part. This centre is recruiting approximately to target.

9. Relevant published studies since last meeting
There have been no studies published in the last 12 months that have any important implication for the need for or the conduct of the PACE trial. A cumulative document of all relevant research was presented to the meeting. All TSC members accepted that this was the case.

10. Authorship of PACE trial papers
A proposal for authorship was presented to the TSC. The authorship would be named papers ‘on behalf of the PACE trial group’. Order of named authors have not been pre-defined but would be determined by the amount of input of each author. If there are any disputes about order of authorship then the TSC will be consulted for advice. This strategy was confirmed to be acceptable by the TSC.

11. PACE trial ancillary studies previously approved
   a) Genomics study
   This study is designed to look at single nucleotide polymorphisms. The CDC have pledged funding but further money is required to conduct this study. The MRC turned down the first application. Centres will assess what local resources are available for collecting and storing bloods.

   b) Therapeutic process
   This is a study to be conducted by researchers out with the PACE trial team reviewing recordings for therapeutic process. At present this remains unfunded. The study was positively reviewed by ESRC but judged as too expensive. Costs have been revised and an application made to the MRC.

   c) Two year follow-up study
   This was regarded as a worthwhile study but there was a concern that this might represent too much extra work for research staff and detract from main trial duties. For this reason, only a minimal data collection would be carried out and the aim would be to collect this by post – Chalder Fatigue Questionnaire, SF-36 physical function scale, Work and Social Adjustment Scale, other treatments received and the Clinical Global Impression of Change scale.

   The TSC recommended that data should be reviewed early (e.g. after the first year’s two year follow up data) to see if most participants went on to additional treatment as this might influence the decision whether to collect follow up on the full 600. There is a precedent in other research (HIV study) that the initial treatment still showed a clear effect after three years.
even though the majority of participants went on to have other treatments after the trial treatment.

d) Therapist supervision study
This is a study of the experience of receiving supervision within a trial. Data are currently being collected from therapists on the trial.

e) Experience of the PACE trial
This is a qualitative study being conducted at King’s looking at participants’ experience of being in the PACE trial.

12. Public relations
ACTION 7: has agreed to review participant newsletters before their distribution.

The MRC provide public relations support for the trial including dealing with Freedom of Information requests.

presented at an Oxford conference to occupational therapists on being involved in a multicentre research trial.

13. Report on PACE National Team Day
The last PACE day took place in June in Oxford. It consisted of half a day of talks and workshops and an afternoon of a guided walk around Oxford colleges.

14. Any other issues
The TSC were very impressed with the high standard of work and the quality of detail of the trial.

A half yearly summary report should be submitted to the TSC in six months time. This should focus upon recruitment and retention and any other problems identified.

Analysis strategy design may be distributed in the form of a draft of a paper on the analysis and trial design rather than distribute the full technical analysis strategy document. This would be in lay language and therefore more easily understood by any non-statisticians.

15. Date and time of next meeting to be arranged at this meeting
Wednesday 9th April 2008 1-5pm
ACTION 8: to circulate the proposed date of next meeting to all TSC members and set a DMEC meeting for a month before.

ACTION 9: to distribute expense claims forms.
1. Those present
   Independent Members

   Non-voting members

   Observers

2. Apologies

3. Previous minutes of TSC # 6
   The fracture report requested last time was the result of an issue raised by DMEC who had inadvertently mis-read the safety report at the 2007 DMEC meeting. Only two fractures have occurred on the trial. There is no evidence from the literature that there is any increased fracture risk for CFS/ME patients or with the GET programme.

   Correction to page 12: should be replaced by .
Trial Steering Committee Meeting #7


DMEC noted that there were no issues raised in the monitoring reports.

DMEC raised a few issues for consideration.

1. Recruitment is going very well and the team is to be congratulated. The team will need to maintain their drive for the last few months in order to achieve the target by year end.

2. Screening data are being monitored and the quality is improved but a large number of queries remain unresolved.

**ACTION 1:** All centre leaders should have this as a standing item on local team meetings.

**ACTION 2:** and to coordinate regular monthly updates for query resolution of the screening data queries.

3. DMEC noted that many patients take a long time to decide whether to join the trial. The DMEC reminded centres that toward the end of the trial, patients need to be made aware that the recruitment period is coming to an end.

**ACTION 3:** All centres to contact those patients who are still not decided to tell them recruitment finishes at the end of November this year.

DMEC recommended that all Serious Adverse Events and Reactions should be reviewed by two blinded (to treatment group) independent assessors at the trial end in order to provide a final opinion on the classification of all SAEs and SARs. The TSC agreed with this decision. More than one assessor should be identified and as some events are psychiatric, at least one assessor should have knowledge of this area. The TSC suggested that a physician and a psychiatrist should be identified to do this.

It was also recommended that the trial team ask what their main safety concerns for PACE treatments are so that particular attention is paid to see if any of these concerns are supported in the trial data.

The issue of whether a review of non-serious adverse events should occur was discussed. A summary of non-serious adverse events could be produced to ensure that none appeared to be mis-classified as non-serious when they were in fact serious, which could be showed to the independent assessors for their views.
**ACTION 4:** The TMG should consider who might be able to review the SAEs and SARs. These persons should not be involved in the PACE trial. Names should be forwarded to [redacted].

**ACTION 5:** [redacted] to be asked by the [redacted] what particular concerns they had about treatment safety and adverse effects.

5. The TSC and DMEC will have a joint meeting at the end of the trial to review the results.

5. **TSC Report**

   [redacted] presented the report to the committee.

**Recruitment**

The trial recruitment rate remains 100% on target.

**Withdrawals**

There has been 1% withdrawal from trial follow-up, which is much lower than the predicted 10%.

There has been 6% withdrawal from treatment including participants randomised to SSMC alone who once in the trial, opt for an active therapy as well. There was a discussion as to whether these participants should be classified as protocol violators or failures of the treatment arm rather than treatment withdrawals. If these participants are classified as drop outs than the treatment withdrawal rate will reduce.

These participants will be analysed under intention to treat, that is they will be analysed as in the treatment arm, as randomised. There will be a note in the analysis that these participants had an additional treatment to the randomised treatment.

**ACTION 6:** [redacted] to remove these cases from the drop out figures, but set up a separate log for participants who have changed treatment [redacted] to bring detailed descriptions of these cases to the next TSC for discussion.

**General organisational issues**

[redacted] discussed general organisational trial issues as reflected in the report.

**Staff retention**

The TMG are concerned that staff will leave before trial end and seek the advice of the TSC for any suggestions to help retain staff.
The PIs have discussed future research project ideas however the fear is that no new project could be started in time. The results of PACE will lead to a number of papers which will keep the core academic team going but research staff and therapists are not likely to have contracts renewed, apart from when a local centre continues to employ them in separate projects or as part of the clinical team. The PIs and local centre leaders will explore opportunities for the staff at a local level.

Publication and release of results
The Trial Steering Committee will nominally exist beyond the trial for any further business such as the review of papers prior to publication. A plan and timetable for release of the preliminary results should be formulated in conjunction with the MRC press office. Things to consider involve confidentiality agreements, release of results at international conferences, discussion with journal editors about timing and method of public release, such as press conference at the Science Media Centre, etc. It was agreed that the main results would be released to the public on the day the paper was published. The TMG will explore how best to inform participants and clinicians.

Data status
Shortfalls in data entry are explained by the fact that the Royal Free Hospital has only just recruited a data manager. Data checking is behind due to there being no lead data manager in post at Barts at present and the fact that the post (at Barts) is to be advertised with the aim of having a replacement in post by summer.

6. Public relations
The Prime Minister’s website endorses the trial in response to a negative petition from members of the public.

The Freedom of Information commissioner upheld the MRC statements regarding the PACE trial in response to a complaint that the PACE team was withholding information about not having a public relations/marketing strategy.

There is a planned campaign to picket the Royal Society of Medicine conference for CFS on the 28th April 2008.

The TSC thanked the MRC for resolving the FoI complaints against the PACE trial.
7. **Analysis Strategy for PACE**

Someone spoke to this document. Someone would like comments and feedback from the TSC and permission to use a complex analysis process on the results.

**ACTION 7:** Someone to meet with Someone to discuss the analysis strategy in detail. This may take the form of a wider meeting with any other interested members on the morning of the next TSC meeting.

Discussions were held as to whether the proposed analysis methods could be applied to pre-existing datasets of other trials to evaluate the accuracy and effectiveness of the methodology.

**ACTION 8:** Someone to speak with Someone for analysis strategies for safety data as this aspect of the strategy plan needs further development.

8. **Proposed recruitment period, extension contracts and ongoing trial finance**

Extension contracts have just been sent out to all centres. Contracts have been adjusted for centres starting late so that all six centres can continue to recruit to the end of the trial if necessary.

The Department of Health have given an increase of 17% to the central subvention for the excess treatment costs of randomised participants from January 2008 and have said that they expect NHS trusts to take up the slack on any further subvention shortfall. This might be achieved by charging the PCTs for any additional post-trial therapy. In Scotland no uplift has been awarded as yet but negotiations are underway. The TSC will be happy to write to the Scottish Chief Scientists Office to support this if necessary.

9. **Clinical research network adoption**

PACE was added to the UKCRN portfolio a year ago. The issue was discussed as to whether PACE should be adopted by the UK and Scottish Mental Health Research Networks (MHRN).

The potential advantage is that UKCRN research support staff could support the trial in the event of staff leaving prematurely. This is more of an issue for centres who are geographically separated from other PACE centres.

Other Network advantages, such as recruitment of new centres, will not benefit PACE as the trial is too far progressed.
The concern of the [REDACTED] and some members of the TMG, is that PACE should not be seen as a mental health trial, especially given the activism against the trial due to the fact that there are psychiatrists and psychologists making up a part of the trial team. [REDACTED] [REDACTED]

As part of the UKCRN, PACE already has the support of the Comprehensive Clinical Research Network (CLRN). Joining a specific network such as the MHRN, would give access to more specific resources such as mental research nurses. The TSC felt that as this would be politically sensitive it should be avoided. [REDACTED]

The TSC agreed that PACE should not be adopted by the MHRN. The TSC will support Edinburgh and King's to ensure that these centres are fully supported to continue in the trial.

**ACTION 9:** [REDACTED] will write to [REDACTED] informing [REDACTED] that the TSC is very eager to ensure that [REDACTED] remains on the PACE TSC and the trial will not join the MHRN.

**ACTION 10:** [REDACTED] to contact [REDACTED] for template risk management plans from MRC CTU.

**ACTION 11:** [REDACTED] to write a letter for [REDACTED] to support PACE not being registered with the MHRN at the IoP.

**10. Relevant published studies since last meeting**

[REDACTED] spoke to relevant research in the last 12 months. No recently published study is likely to impact on the continuation of the PACE trial. The research team declined to allow us access to the raw data of the Chicago RCT of non-pharmacological treatments, which has been difficult to interpret as presented in the main paper.

**11. Monitoring reports**

[REDACTED] has completed four monitoring visits since the last TSC meeting in June 2007. The Bristol Centre will be monitored in late April and the Royal Free visit is scheduled for June.

Additionally, centre leaders also complete monitoring visits of other centres to ensure that all are in agreement about interpretation of trial eligibility. They do this by reviewing the research and medical notes of randomly chosen participants, in order to ensure that participants are eligible.
12. **Authorship of main PACE trial paper**

Spoke to further consideration by the TMG to name authors on publications rather than only publish as the PACE trial team. First authors would be those who had written the paper but authors have not yet been selected. Authorship will vary by paper.

Oversight of papers may be conducted by subcommittees or representatives of the TMG and TSC for some/several years.

At the end of the trial the dataset may need to be freely available in accordance with MRC guidelines. This might be with the caveat that this will only occur when all analyses are complete and that data are only released to other research groups for the purpose of re-analysis or further analysis, and only where it is clear what would be done with the data.

**ACTION 12:** The PIs to clarify with the MRC at what point data have to be made publically available.

13. **PACE trial ancillary studies previously approved**

a) **Follow-up study**

This study has ethics approval. The case report forms are in preparation. These will be distributed to centres and the extra workload on research staff monitored. If this proves too much extra work, a single person will be employed to run the entire sub-study.

b) **Therapist supervision study – presentation of paper**

This paper reflects upon supervision experiences of PACE trial therapists and therefore comments upon, and describes aspects of the conduct of the trial. The TMG would like the TSC to review and approve this paper for submission by Clinical Rehab was a journal suggested by the TSC for submission.

**ACTION 13:** All TSC members to give any feedback to by Monday 14th April 2008.

c) **Genetics study**

The CDC pledged £400,000 toward this study to look at single nucleotide polymorphisms. This is not enough money to run the entire study. The MRC turned down the request for additional funding.
Since this decision was taken, there have been further developments that increase the viability of conducting this research.

Since the original idea, buccal smear methodology has improved making this now a cheaper and easier study to facilitate.

[This will be meeting with X] to see if the FINE trial participants may also be approached to increase the population studied. A case control study is now also proposed.

[This a genetic epidemiologist at Y] has expressed interest in being involved in this study.

Further funding will be sought.

d) Therapeutic process
This study was turned down for funding as it was considered too expensive. However, the recordings are kept as part of normal trial procedure and all participants consent to analysis of this data so this study may be revisited in the future.

e) A qualitative study of the experience of the PACE trial
This study has been completed but the TSC recommended that publication will be delayed until after the main trial paper has been published.

**ACTION 14:** [X] to inform [Y] to this effect.

f) Other research: MPhil/PhD work
There are associated post doctoral studies taking place. [This is half way through] PhD on therapist effects and the PACE trial will be included in this.

[X] is looking at Occupational Therapy measures in CFS/ME and would like access to PACE baseline data.

[X] will be using PACE trial data to look at predictors of response to specific trial treatments.

**ACTION 15:** [X] to tell [Y] that there are King’s datasets available that may access on the Chalder Fatigue Scale and the Work & Social Adjustment Scale.
14. **GET patient self help guide**

This was presented to the TSC for their information. This was written for reasons of equipoise as there are already publications available for CBT and Pacing.

The TSC supported the majority of the guide content and lay language but expressed concern about Appendix 1:
- the statement that stretches should be done after warm up contradicted other content in the guide; and
- the stretches might cause harm in an unsupervised individual.

There is no evidence that stretching enhances performance but can cause micro tears and muscle shortening. Gentle walking is more advisable. Some of the stretches in the guide are considered superfluous or possibly damaging if carried out incorrectly.

**ACTION 16:** [Redacted] to feedback concerns about the guide to [Redacted] to pass on to the GET team. [Redacted] to send an electronic version to [Redacted].

**ACTION 17:** The GET team should consider publishing the guide so that it may be made available for other CFS centres outside of PACE.

There was concern about differing ease of participant access to self help information. CBT advice is available on the King’s website, the Pacing guide is available on the [Redacted] website and so the GET guide should also be put on a website. The provision of all three website addresses would provide better equipoise.

**ACTION 18:** The TMG should consider the issue of adding the GET guide to a website.

**ACTION 19:** [Redacted] to add the [Redacted] Pace guide link to the King’s website.

15. **Any other issues**

The next PACE trial team day will take place in June.

The TSC praised the entire PACE team for their hard and high quality work.
16. **Date and time of next meeting**

Wednesday 29th April 2009, 11am analysis strategy meeting, 1pm lunch, 1.30pm TSC.
1. Those present:

Non-voting members
[Names]

Observers
[Names]

Changes to TSC members since the last meeting:
[Name] has retired and [Name] will take place. [Name] replaces [Name] and [Name] will take on the role of Secretary in place of [Name]. All new members were welcomed to the TSC.

2. Apologies
Trial Steering Committee Meeting #8

3. Agreement of agenda
   It was decided to move item number 8: Feedback from morning presentation of Analysis Strategy to the end of the meeting to allow discussions to continue from the morning meeting.

4. Previous minutes of TSC # 7
   All agreed the minutes were an accurate reflection of the previous meeting

5. Matters arising from TSC # 7 not on the agenda
   TSC#7 ACTION 4: The TMG should consider who might be able to review the SAEs and SARs. These persons should not be involved in the PACE trial. Names should be forwarded to
   
   [redacted] explained that the purpose of this review was to check the accuracy of SAE reporting. A group of independent assessors would review the SAEs blindly in the first instance and then re-check them after the treatment group has been revealed. A summary of all non-serious adverse events would also be reviewed.

   It was decided that [redacted] should approve this list of assessors jointly with [redacted] as Chair of the TSC. It was felt that the group should include both a physician and a psychiatrist. [redacted] suggested we could consider having clinicians who are familiar with the pharmacovigilance requirements for clinical trials but who may be independent of CFS. [redacted] said we need to be sensitive to possible accusation of bias and should therefore do whatever [redacted] thinks is the most stringent measure to ensure we are not underreporting events. [redacted] agreed [redacted] input was important and added that we should include assessors who know about CFS as they would be viewed as sympathetic. The jobs titles of the those put forward include:
   - i.neuropsychiatrist
   - ii. physician rheumatologist,
   - iii. physician immunologist,
   - iv. ID physician,
   - v. liaison psychiatrist,

   [redacted] added that [redacted] has collaborated with [redacted] (ii) and [redacted]'s name should therefore be removed from the list as [redacted] could not be considered as independent. [redacted] also suggested [redacted] at Bart's should be considered.

   It was agreed that this list was not contentious and that all assessors should work for the NHS, so there cannot appear to be a financial bias for people with personal investment in a particular treatment.
ACTION 1:  to agree final group of assessors with  and

TSC#7 ACTION 6:  to remove these cases from the drop out figures, but set up a separate log for participants who have changed treatment.  to bring detailed descriptions of these cases to the next TSC for discussion.

confirmed that these cases had been removed from the dropout log. As there were only two cases it was not felt necessary to review these in detail.

TSC#7 ACTION 10:  to contact for template risk management plans from MRC CTU.

The risk assessment was reviewed. commented that the cross cover of therapists has worked very well especially in London. added that some moderate risks may become high risk as we move towards the end of the trial, for example research staff leaving their contracts. agreed that if centres cannot extend contracts locally that research staff will start looking for another post 2 months or so before their PACE contract ends. Losing staff at this late stage would hinder final data cleaning.

The use of research staff across centres was discussed and it was noted that this would be more of a problem for Edinburgh. It is hoped that centres will be able to find local solutions to allow staff to continue employment post PACE. The issue of staffing was returned to under item 7 of the agenda.

highlighted that there is a possibility that one of the Centre Leaders may leave the trial but at the moment this is unresolved.

suggested the TMG should review the risk assessment as the TSC do not meet as frequently

ACTION 2:  TMG to consider risk assessment on an ongoing basis

TSC#7 ACTION 12:  The PIs to clarify with the MRC at what point data have to be made publically available.

This had not been resolved and was discussed explained that the MRC promotes data sharing in a timely fashion but that there is no set timeframe for this. It is important however that the trial team have a strategy for how data would be made available, taking into account archiving arrangements at each local centre.
The public should have access to the main outcomes of the trial within 6 months of publication e.g. via Pub Med. The results should be accessible and therefore not published in a closed journal. confirmed the Lancet should be acceptable as has had many trials published there. The trial should be published where it will make the maximum impact internationally.

suggested to have a look at the MRC population health sciences research network (PHSRN) website.

stated that no requests had been made for PACE data and the PIs would be notified of any requests. added that the MRC does not have ownership of the data and it is not theirs to give away. Any requests of this nature would be dealt with by explaining trial data will be publicised through publication in an academic journal.

It was suggested later in the meeting that a good way to publicize results would be through a patient newsletter and this would be a good opportunity to thank participants for their involvement.

TSC#7 ACTION 19: to add the Pace guide link to the King’s website.

confirmed that this link was present on the Bart’s website.

6. Matters arising from DMEC meeting of 10th March 2009

has stood down as Chair for the DMEC, and will continue and it was not felt a third member was required to replace at this stage. The DMEC congratulated the trial team on the low number of withdrawals, increase in data entry and improvement in the amount of missing data. The SAEs were reviewed and it was decided another face to face committee meeting was not required unless there was a significant increase in the number of SAEs. The committee have asked to receive a brief report including data on withdrawals, rates of serious deterioration and SAEs by mid September. The importance of the DMEC continuing to exist in a virtual setting was agreed and it was confirmed that is the medically qualified member.

added that the DMEC will be attending the final results meeting which will be held jointly with the TSC and DMEC.

congratulated the team on the positive feedback from the DMEC and suggested could write to the DMEC to thank them for their contribution.
ACTION 3: [REDACTED] to write to the DMEC to thank them for serving the trial so well

7. TSC Report

[REDACTED] presented the report to the committee.

Recruitment

[REDACTED] congratulated the team on excelling their recruitment targets. [REDACTED] commented that it was a very unique to have a trial where each centre has contributed so well to recruitment. The Royal Free were especially commended on their accrual figures.

Withdrawals

There has been a 3% withdrawal from trial follow-up and a 6% withdrawal from treatment only. [REDACTED] commented that this is better than we had hoped for.

Session attendance

It was noted that compliance with trial treatment is very good, with a slight increase in the departure from treatment in the SSMC treatment group. It was noted that some participants had receive 18 visits. [REDACTED] clarified that there is no upper limit on the number of visits and explained this would usually occur where the participant has a comorbid condition or was experiencing suicidal thoughts.

General organisational Issues

[REDACTED] discussed general organisational trial issues as reflected in the report.

Staff retention

The possibility of extending research staff contracts to the end of February was discussed. This would allow more data to be collected during December if the last few participants 52 week visit falls late.

[REDACTED] queried if UKCRN staff may be able to cover any gaps at PACE centres if staff were to leave prematurely. [REDACTED] suggested [REDACTED] should contact [REDACTED] sooner rather than later to explore this possibility. [REDACTED] explained that the Clinical Research Networks employ research support staff not research staff, although it was acknowledged that the distinction between the two is a grey area. It would be worth asking [REDACTED] if there are any opportunities in the local networks to provide permanent employment post PACE for some of the research staff. The networks may also be able to
provide staff if PACE staff leave prematurely. The email to [redacted] should state the location of the PACE centres, timescales and the tasks to be completed.

[redacted] thanked all Centre Leaders for their hard work which has contributed to the success of the PACE trial. [redacted] suggested that the TSC could write to the Centre Leaders to thank them for their contribution and this should be considered for all PACE staff.

**ACTION 4:** [redacted] to ascertain when research staff contracts end and discuss at the next TMG

**ACTION 5:** [redacted] to provide [redacted] with contact details for [redacted]

**ACTION 6:** [redacted] to write to [redacted]

**ACTION 7:** [redacted] to write to all Centre Leaders on behalf of the TSC offering thanks.

Archiving
All agreed that data should be kept for 20 years to comply with current regulations. [redacted] quoted a case where MRC data was accessed from years ago to resolve a query raised. The need for clarity on what needs to be kept and where, to avoid duplication was discussed. It was hoped that the MRC may be able to provide more specific guidance on this. [redacted] suggested that this would vary depending on the nature of the data but suggested that [redacted] should liaise with the MRC regarding archiving arrangements. It was felt that the TSC should review the archiving plan.

**ACTION 8:** [redacted] to liaise with the MRC in order to complete archiving plan and SOP

**ACTION 9:** TSC to review archiving arrangements once plans have been finalised

Data status
It was noted that [redacted] has been working extremely hard to clean the baseline data ahead of data lock which is scheduled for the end of May. Most data queries have now been resolved and the hard work at each local centre to achieve this was also acknowledged.

It was noted that the Royal Free are still slightly behind on data entry but overall the level of data entry was very good. [redacted] commented that the low numbers of missing data and serious data queries were encouraging. It was
also noted that more queries had been raised at the baseline 2 visit compared with baseline 1. Explained this is because there are more forms at baseline 2 and the forms themselves are more problematic, for example the economic data.

Quality report

Explained that there have been a few issues identified at the King’s site requiring attention, including a number of ineligible participants and missing adverse event data. The King’s team were praised for their hard work in addressing the problems highlighted. Confirmed that any participants deemed as ineligible would be excluded from the per protocol analysis. Explained that it would be possible to review all medical and research notes to log adverse events not reported previously and it would be documented where data has been recorded retrospectively. It would be possible to compare the data collected at King’s with other centres to check for consistency.

Consort Diagram

Explained that the consort figures are not quite final as the priority at the local centres has been data cleaning.

Clarified that in Figure 20.1 1004 participants were ineligible as they did not meet the Oxford diagnosis of CFS/ME. This number includes those without CFS/ME at all, but for the purposes of consort these figures have been combined.

Also highlighted that 94 participants at Bristol were listed as unable to comply with the protocol. This number appears high as when Bristol initially started recruiting, they were hoping to include patients seen by GPs in Cheltenham and Gloucester as well as Bristol. These form the bulk of the participants unable to comply with the protocol as they would have further to travel. Felt that as these patients were not actually screened they could be removed from the consort diagram. This should be discussed further at the TMG in June.

ACTION 10: TMG to consider consort data for Bristol

Feedback from morning presentation of Analysis Strategy

Thanked and for an informative presentation which lead to a good discussion.

Health Economic Analyses

Commented on the high quality of the health economics aspect of PACE, which includes both cost effectiveness and societal costs. There may
be issued of multiplicity to return to, but there were no issues that required the TSC’s input.

The importance of the 2.5 year follow up study for looking at economic differences including patient’s return to walk was discussed. Agreed that this data would be important but explained that it is unlikely the DWP would be able to offer any financial contribution to this as the DWP generally fund research where return to work is the final outcome. Although this is relevant to PACE, the main outcome is clinical.

Main Analysis

**ACTION 11:** Actions for the statisticians regarding the dummy data presented are summarised below

A footer stating that tables and figures are composed from dummy data should be listed on each page of the “Presentation of the PACE analysis strategy” and future versions of mock presentations in addition to stating the data is not the actual PACE data on the first page.

Table 1: Responders of Disability (SF36-PF) and Fatigue (CFQ) by treatment group and time, was considered too “busy”. To improve the table only percentages will be shown rather then displaying the patient count and percentage in each cell. The total number of participants at each treatment group and time point will be displayed so that the reader can calculate the data we no longer will include in the table.

Figures 1 to 4 and 6 will not be included in the primary paper. Figure 5: Percentage of responders to Fatigue and Disability by treatment and time was deemed to be the best way to display the outcome for the primary paper. The final figure will also include confidence intervals.

Figure 7: Comparing response to Fatigue and Disability in the treatments CBT and GET, displayed a scenario where the TSC considered whether they should combine CBT or GET. It was noted that the profiles did not match that of figure 5. It was decided that in order to combine CBT and GET the difference between the response in CBT and GET must be no greater than 10% at each time point (12, 24 and 52 weeks). When analysing the real data a line plot of the proportion of difference in response between CBT and GET will be displayed with 95% confidence intervals.

Figure 8 and table 2 will be included in the study report only.

The TSC was happy with the way the analysis was displayed in table 3, 4, 5 and 6.

Figures of odds ratios and 95% Confidence intervals: It would be preferred if unadjusted differences and 95% confidence intervals were displayed rather
than odds ratios to ease interpretation for the reader. It was planned for the primary paper that 2 figures would be displayed side by side. The first figure would display results of Fatigue and the second displaying Disability. It was also planned that the sensitivity analyses could be displayed within each figure although this idea might be dropped if the figures look overcrowded.

The TSC approves the PACE analysis strategy principles but will give extra time to TSC members to approve the PACE analysis strategy text.

Action: to circulate an email to TSC members asking for comments by June. If no comments are received by that date it will be assumed that the relevant TSC member agrees with the analysis strategy.

The analysis strategy will be presented to the Mental Health Research Network (MHRN) Methodology group on the 7th July.

After taking the MHRN’s comments on board a TSC teleconference will be held to finalise the analysis strategy. During the teleconference it will be decided who will be responsible for signing of the analysis strategy. The data of the TSC teleconference will be decided by email.

9. Relevant published studies since last meeting

spoke to relevant research in the last 12 months. summarised that there had been little relevant research over the past year and there are no implications for PACE based on the studies published.

added that the FINE trial TSC was on the 13th May and would be presenting the results. will also be presenting the results at the PACE team day in June. The FINE trial has had a 16% dropout rate which the team are pleased with. It was not felt that the results of the FINE trial would have any implications for PACE as the study is looking at a different population in a different setting.

suggested updating the participants and doctors involved in PACE with the results of the FINE trial and explaining any implications for them. This could be achieved via a newsletter.

ACTION 12: and to review implications of FINE trial and consider feedback to PACE participants and doctors

10. Monitoring reports

explained that had monitored all sites except Oxford in the year since the last TSC. monitored Oxford at the end of April and was very impressed with the record keeping and high degree of organisation. is due to follow up on issued identified in the King’s monitoring report at a visit scheduled for the end of May and will visit all sites
one last time to follow up any findings from previous reports and discuss local archiving arrangements.

11. **PACE Trial Writing and Publication Oversight Committee (WAPOC)**

explained that the Analysis Strategy Group has been superseded by the Writing and Publications Oversight Committee (WAPOC). The purpose of the group was to facilitate and monitor the trial publications. The group reviewed the Excel spreadsheet maintained by which acts as a summary of WAPOC activity. commented that it was an excellent idea to review timelines using the spreadsheet and to meet regularly to maintain oversight. added a request that the MRC are notified in advance of publications so that the press office can be prepared in case they receive queries relating to any papers. It was agreed that WAPOC would notify the MRC when papers have been accepted.

added that the MRC press office would work together with Bart’s and the Lancet to commonly agree the PR exercise. confirmed that the Lancet has asked us to use their fast track process (usually 4 weeks). also suggested we should work with the Science Media Centre who can help to assimilate a press briefing. It is possible to gather together the key scientific journalists to deliver a presentation. may be able to offer advice regarding this and it was suggested as knows that may be the best person to get in touch. also suggested the Eurekalert website, as another method of targeting serious scientific journalists. The site displays cropped press releases.

The need to carefully select the person who writes the editorial on the main paper was also discussed.

**ACTION 13:** to speak to regarding the Science Media Centre

12. **Timing of project milestones**
The group reviewed the tabled document. asked what would happen if staff were to go on annual leave as the timelines for research staff are very tight. explained that the timelines would be reviewed at the peer day so that people know in advance where they stand. also added that if we were to extend the research staff contracts until February 2010, these timelines could be adjusted.

The aim is to share the main analysis results with the TSC in June 2010. clarified that the analysis report would be available at that time and not the main paper. added that as discussed with the statisticians if the data cleaning was extended by a month that it may be possible to carry out the main analysis in 3 months rather than 4 as set out in
the milestones document. added the caveat that this would depend on how full time the new Statistician will be and how big the therapist variation issue is and therefore how much input needs to have ( ).

suggested that the TSC have 2 dates in their diary to review the main analysis in case more time is required. It was suggested that these dates should be set in June and July 2010 and the meeting should include the TSC DMEC and TMG. recommended that if the data is to be presented to the team before it is published that confidentiality agreements should be signed. Any documents should be numbered and collected in following the meeting. It is not advisable to have members on conference calls as you cannot be sure who else may be listening. suggested could discuss with the best methods for maintaining confidentiality. The greater the time between the results being made available and publication the more opportunity there would be for leaks. There are special pressures associated with this trial and the TMG should think carefully about who should be informed of the results prior to publication and when. It is also important to be clear about the interpretation of the results before these are shared. suggested only the TSC and DMEC should review the results initially as they may have comments to take on board. agreed the TMG could be involved before the publication stage when the paper is being tracked.

recommended that the team are generous with time as we would not want to rush things at this stage.

**ACTION 14: TMG to decide schedule for notifying the various PACE committees/team members of the results**

**13. PACE trial ancillary studies previously approved**

a) Therapist supervision study – presentation of ’s paper
This paper is now in press

b) Follow-up study
There are 2 issues associated with the 2.5 year follow up study. Firstly rates of data return have been slow and approximately 50% of data has been returned to date. Secondly the ethics committee have stated that we may only send one follow up reminder letter after sending the booklet and can make no telephone calls. explained that the committee felt that phoning participants could be viewed as coercion. is in the process of appealing this decision with MREC via NRES. added comments on behalf of who is the least convinced of the PIs that this study is worth continuing with as the return rate is so low. The TMG are due to review the progress of this study in June and if there is no improvement may
decided to discontinue with this data collection, which would be a shame. [Redacted] suggested the sample who have returned the booklets should be reviewed as it may be that we have received a biased sample e.g. those who have improved most. [Redacted] commented that we don’t even know if the participants have received the booklets and a phonecall was therefore necessary. He also added that it would be possible to obtain a minimal amount of data from the GPs in terms of the number of visits made by the participants if the data collection were to be abandoned. [Redacted] commented that as a patient representative he felt that follow up phone calls show the researcher cares. [Redacted] suggested the MREC’s response could be a reflection of new legislation about who can contact patients. The TSC strongly supported the decision to follow up participants by phone and this could be used to support the appeal to MREC.

[Redacted] clarified that the MRC would be happy for PACE funds to extend the research staff contracts and efforts to support the main trial results should be prioritised over gathering extra follow up information which if only at a 50% return rate would not give a robust answer to the questions raised. It is therefore a case of weighing up the cost versus the benefit which [Redacted] felt was [Redacted]’s standpoint. [Redacted] emphasised the importance of the data but felt that satisfactory rates of return would not be achieved with just one reminder letter.

ACTION 15: [Redacted] to evaluate whether the sample returning the booklets is biased in terms of outcome at 52 weeks and treatment group

ACTION 16: [Redacted] to emphasise the TSC’s standpoint on telephoning participants to assist with the NRES appeal

c) Genetics study [Redacted]

[Redacted] explained that the aim is to link single nucleotide polymorphisms with sub phenotypes of CFS/ME. Saliva samples from 3,000 volunteers from the CFS clinicians network would be collected, including 900 patients from the PACE and FINE trial as we already have well defined phenotypes for these people.

d) Psychiatric diagnosis study [Redacted]

This paper aims to review the rate of misdiagnosis by psychiatrists compared to physicians.

[Redacted] mentioned a methodological paper that uses PACE as an example. [Redacted] said that the MRC would like to receive all papers relevant to PACE.

ACTION 17: [Redacted] to provide a copy of the paper to [Redacted]
14. **Trial finances and under spend**

confirmed it was possible to use any underspend until 13 September 2010 when the award ends. Any use of funds after that time would require another application. The MRC would not release the final quarter of the budget to Bart’s until the final financial report has been received by the MRC according to their normal procedure.

suggested that if the return rates of booklets for the 2.5 year follow up study reached 70% an application could be made post September 2010 to gain extra funding to support this. The health economic issues discussed previously would be a key justification for this extension. This new application would need to be made relatively soon, but suggested this could not be done until the return rates had improved or it would be rejected.

asked if the MRC still do time only extensions. confirmed they do however you would need to make a full case for extension and this trial has already had an extension and supplement. Due to the additional end point this would require a new application.

15. **Clinical research network funding**

Discussed under item #7

16. **Public relations**

explained that the NICE guidelines judicial review was won by NICE.

added that was running a 2 day workshop at the MRC in October/November. was the last FOI request dealt with by the MRC.

explained that the referees report from the original grant (and the CI’s response to these) was requested under FOI for PACE and FINE. The FINE trial team have agreed to this but PACE have argued that referee reports should not be released as this sets a precedent. The MRC backed this decision.

17. **Graded Exercise Therapy (GET) patient self help guide**

After review by the TSC at the last meeting, the guide has been taken to medical illustration at Bart’s. The Rahere association (a charity looking after Bart’s patients) has funded 3000 copies of the guide. comments have been incorporated and the wording has been made more accessible to the lay public. Appendix 1 has been left in as the team felt it wouldn’t be a guide without demonstrating the stretches. The front cover and acknowledgements should be completed by the end of May ready for printing.
All trusts will have a web link to the document and patients will be able to print their own copy from the web. The TSC congratulated the GET team on the completion of the self help guide.

18. Any other issues

19. Planned DMEC/TSC/TMG meeting to discuss main results

ACTION 18: to arrange date and venue for next meeting
Draft Minutes

1. Those present:
   DMEC:

   TSC Independent Members

   TSC Non-voting members

   TMG Observers
Changes to TSC members since the last meeting:

[Redacted name] has replaced [Redacted name] at the [Redacted position] and was welcomed to the TSC.

2. Apologies

DMEC

[Redacted name]

TSC

TMG

3. Previous minutes of TSC # 8 (document #1)

All agreed the minutes were an accurate reflection of the previous meeting with a minor correction to [Redacted name] title.

4. Ongoing actions from TSC #8

TSC #8 ACTION 16: [Redacted name] to speak to [Redacted name] regarding the Science Media Centre.

5. Matters arising not on the agenda

A complaint has been received by the MRC regarding the PACE trial. The Corporate Advisory Group is reviewing the dossier submitted to determine the nature of the complaint, and continues to do so.

6. No cost extension

An extension has been awarded to use the remaining trial underspend on achieving the PACE objectives until 13th May 2011. [Redacted name] was thanked for [Redacted support] with this application to the MRC.
7. The background to the PACE trial and context of its results

The aim of the afternoon’s meeting to present the preliminary results to the TSC, DMEC and TMG and receive feedback. All committee members were thanked for their involvement in PACE and in particular the trial funders:
- Medical Research Council (MRC)
- Chief Scientist’s Office (CSO) - Scotland
- Department of Health (DH)
- Department of Work and Pensions (DWP)

In addition all local centre staff were praised for their hard work which has resulted in high quality data and well delivered treatments.

The context of the original PACE trial application was revisited. Back in 2002, both cognitive behavioural therapy (CBT) and graded Exercise Therapy (GET) had been shown to be effective in a series of small trials and reviews were cautiously supportive of the treatments. The scientific evidence appeared to be contrary to the views of the charities set up to support patients whose general enthusiasm for APT was not based on such evidence. Concern had also been raised by the charities about the potential harm of GET. This lack of consensus set the scene for the development of the PACE trial.

8. Presentation of statistical analysis for main paper

Presented an overview of the statistical analysis strategy for the trial. The changes made to the analysis since the original protocol was drafted were highlighted and it was noted that the analysis plan was agreed by the TSC and signed off before analysis commenced.

ACTION 1:

To ensure that the review and sign off of the analysis strategy by the TSC is well documented

9. Presentation of preliminary main results

All were reminded that information presented at the meeting remains confidential until the main paper is published. will notify all committee members when publication occurs and thanked all those that contributed to the analysis he presented.

10. Therapy differentiation and integrity

summarised the review conducted using the audio recordings of therapy sessions to assess the treatment integrity. A random sample of recordings (two per therapist) were reviewed by two raters (blind
to treatment) to establish whether treatment was delivered as per protocol. Session 10 was chosen as differences between therapies were considered more likely. Two items per therapy were used to assess the extent to which aspects of therapy had occurred and each item was rated on a 7 point Likert scale. Overall therapeutic alliance was assessed by 1 item using a 7 point scale.

The outcome of the review was presented and the Treatment Leaders were praised for their excellent job in keeping the treatments on track. This process was aided by the very detailed treatment manuals and a dedicated team of therapists who were also thanked for their contribution.

11. Interpretation of preliminary main results

summarised the main trial findings and asked the TSC to consider:

a) What they considered to be the most interesting findings
b) What were the limitations of the research
c) What the thrust of the main paper should be

12. Discussion of preliminary main results by TSC and DMEC

The TSC and DMEC praised the trial team for the low dropout and high follow up rates which are indicative of a very well conducted trial. The rigour with which the trial has been conducted gives confidence in the results on behalf of the MRC commented on the excellent oversight of the trial by the TSC and DMEC and was very pleased to see a robust outcome.

All those in a care providing role were asked to consider how the PACE trial results would affect how they treat patients. This is a potential way for results to leak if colleagues/participants become aware of a change in their clinical practice.

**ACTION 2:** All to bear in mind the implication of learning the outcome of the PACE trial and to discuss any concerns with the PIs.
NB: A detailed record of the points discussed was made, but will not be circulated for reasons of confidentiality.

13. **Presentation of preliminary health economic results**

presented the objectives and preliminary outcomes of the health economic analysis.

14. **Discussion of preliminary Health Economic results by TSC and DMEC**

was thanked for hard work on the complex health economics analysis. The TSC felt that there was more work to do and specific actions will be recorded separately.

It was suggested that a comparison with the FINE trial would be very interesting although this data has not yet been analysed.

**ACTION 3:** was asked to liaise with colleagues to complete health economics analysis for the FINE trial as soon as possible and contact to assist with a comparative analysis

15. **Authors and acknowledgements for main paper**

A list of the planned authors and acknowledgements for the main paper was circulated. The TSC, DMEC and TMG were asked if they were happy to be acknowledged by name in the main paper.

**ACTION 4:** Any committee member wishing to opt out of acknowledgement in the main paper to please contact to circulate this message to all not present)

16. **Publication strategy:**

a. **Preliminary plans for public dissemination of main results**

The intended publication strategy was discussed. The Lancet is the first choice for publishing the paper and they have already agreed to fast track the submission. The aim is to submit by the end of October. All the relevant press offices (sponsor, funders, and MRC) should be notified at the point of submission (or when the likely submission date is known). It will be important to work with the press offices so that an explanatory press statement is ready ahead of time. The sponsor’s press office should take the lead in drafting the press release and accompanying frequently asked questions. The MRC’s press office, The Lancet (if accepted) and will work closely with the team at Queen Mary
University of London and it will be important for all press offices to present the same message, working from a single set of FAQs.

[Name] will need to brief his colleagues at [Name] regarding the results and will require permission from [Name] as [Name] to do so.

A participant newsletter should be drafted ready to distribute at the time of publication.

**ACTION 5:** Writing and publication oversight committee (WAPOC) to plan a timetable of when the results will be disclosed and to whom (with confidentiality agreements in place)

**ACTION 6:** [Name] to complete draft of main paper ready for submission by end of October

**ACTION 7:** [Name] to clarify with MREC whether ethical approval is required for a participant newsletter after trial end and to take a lead in producing this.

It was agreed that this would be the last formal meeting of the TSC but that the committee would have a useful role in reviewing the final report before publication and commenting on issues around access to data.

The MRC would like to see a copy of the manuscript when submitted along with the accompanying FAQs. All communication including results should be password protected with a caveat that this is not to be passed on.

**ACTION 8:** [Name] to contact all press offices to identify any precedence for handling a press statement (e.g. Department of Health may require 30 days notice) and to liaise appropriately with all communication teams at the time of submission

**b. Release of manuals on PACE website**

A further request has been made for access to the trial treatment manuals and in the spirit of scientific openness the PIs felt the manuals should be made available on the PACE trial website with a statement regarding their use in place. The TSC were happy with the draft statement circulated but did not support release at this time, and favoured release at the time of
publication of the main paper. It was suggested the PIs may wish to rethink their decision.

**ACTION 9:** PIs to revisit decision to publish manuals in light of TSC’s comments

c. **Policy for third party access to data**
The intention to publically release PACE data to legitimate researchers in line with the MRC policy on data sharing was discussed. It was agreed the first priority is to release the results of the trial into the public domain. The trial team could then consider releasing part or all of the dataset to external third parties however it was noted that coming to a dataset cold with no access to the trial team for clarifications would be difficult. There could be more potential for harm than good if the data was analysed incorrectly or misinterpreted. There would also be a cost associated with data extraction and manipulation to create a format suitable for distribution.

**emphasised the aim of the MRC to maximise the use of public money whilst maintaining high quality outputs. It was suggested that in response to enquiries about data sharing, the team should emphasise that the trial has been registered with ISRCTN, the protocol has been published, the treatment manuals will be publically available on the trial website and the results are due to be published in a peer reviewed journal. Access to raw data can be available by request to the PIs but only after receipt of a robust, fully funded and ethically approved proposal written by bona fide scientists. The TSC were happy with the draft statement circulated.**

17. **Update for information only**
An update on publications and presentations from the trial was circulated prior to the meeting and the TSC were pleased to see more papers are in the planning and publication stage.

The long-term follow-up study also appeared to be proceeding well with current return rates of 75%. The importance of this data for the health economic outcomes was noted.

18. **Any other business**
The procedure for obtaining feedback from the TSC and DMEC was discussed. Documents should be circulated with a deadline to respond and no response by that time will be taken as approval.