Trial Steering Committee Meeting #7

Wednesday 9th April 2008

[redacted]

Draft Minutes

1. Those present

Independent Members

[redacted]

Non-voting members

[redacted]

Observers

[redacted]

2. Apologies

[redacted]

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: [redacted] should be replaced by [redacted].

4. Matters arising from DMEC meeting of 4th March 2008

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: [redacted] and [redacted] 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 [redacted] 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 their being no lead data manager in post at Barts at present and the fact that the [redacted]. This 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

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

ACTION 7: [redacted] to meet with [redacted] 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: [redacted] to speak with [redacted] 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]

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 [redacted] 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

[redacted] 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 [redacted] s 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 [redacted].

Clinical Rehab was a journal suggested by the TSC for submission.

ACTION 13: All TSC members to give any feedback to [redacted] 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.

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

[redacted] a genetic epidemiologist at [redacted], 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: [redacted] to inform [redacted] to this effect.

f) Other research: MPhil/PhD work

There are associated post doctoral studies taking place. [redacted] is half way through [redacted] PhD on therapist effects and the PACE trial will be included in this.

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

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

ACTION 15: [redacted] to tell [redacted] that there are King's datasets available that [redacted] 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.