Trial Steering Committee Meeting #6

Wednesday 27th June 2007, [redacted]

Draft minutes

1. Those present

Independent Members

[redacted]

Non-voting members

[redacted]

Observers

[redacted]

2. Welcome to new members and observers

[redacted] was welcomed as the new [redacted] [redacted] was welcomed as a [redacted]. [redacted] was welcomed as an observer.

3. Apologies

[redacted]

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. [redacted]) 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: [redacted] to speak with [redacted] about accessing further subvention money if needed. ([redacted] 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: [redacted] to discuss the issue of missing and incomplete data for the doctors Clinical Global Impression of Change score with [redacted] and [redacted].

Quality and differentiation of treatments

[redacted] 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 [redacted] 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: [redacted] has agreed to review participant newsletters before their distribution.

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

[redacted] 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: [redacted] to circulate the proposed date of next meeting to all TSC members and set a DMEC meeting for a month before.

ACTION 9: [redacted] to distribute expense claims forms.