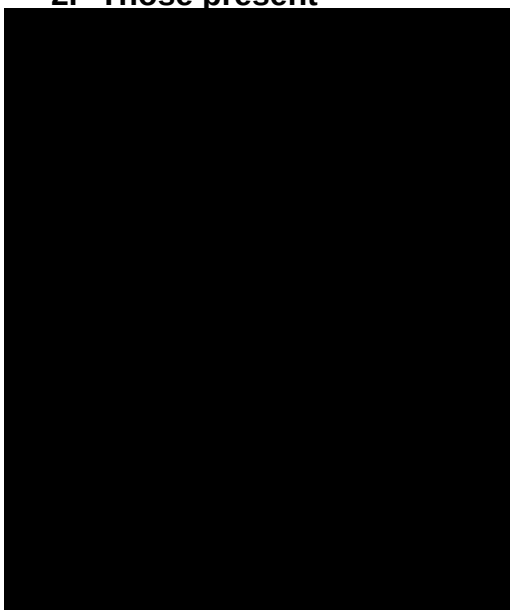
PACE Trial
Trial Management Group Meeting #10

Wednesday 15th September 2004

1. Welcome

Introductions and welcome to new members

2. Those present



3. Apologies

4. Agreement of Agenda
Ref 7c 9b added 8a drop 14 from agenda

5. Previous minutes for TMG #9 (attached)
Previous minutes were accepted, no changes to be made. Discussion of previous minutes followed.

a) [redacted] questioned item 3 – SOP for protocol deviations. Noted that this should be an integral part of the protocol. [redacted] pointed out that this item was likely to be discussed at TSC meeting on 27th September. The SOP would be written in time by [redacted] and [redacted].
b) [redacted] circulate protocol 16/9 at the same time as sending to the TSC.

ACTION 1: [redacted] to contact each centre leader for a copy of the R&D sponsorship and indemnity letter. [redacted] noted that R&D sponsorship could not be confirmed until the protocol had been finalised and sent to each R&D department.

ACTION 2: SOP to be written by [redacted] regarding what is required of an independent expert to (blindly) assure differentiation of the therapies.

ACTION 3: [redacted] to write a SOP on supervision and rating of audio-recordings of therapy sessions.

c) [redacted] suggested that we contact [redacted] of the FINE trial about their initial screening of tapes for help with specifying boundaries.

ACTION 4: [redacted] to contact [redacted] about swapping experts, and also to discuss the use of the Therapy Integrity Scale

d) Videoconferencing – may be able to arrange this through Imperial College, London.

ACTION 5: [redacted] to investigate the use of video teleconferencing for small meetings

e) 4c – it was noted that [redacted] had not yet been contacted for a review of the patient information sheets, but that this would be done after the TSC meeting

f) [redacted] noted inconsistencies in the Patient Clinic leaflet (PCL)

ACTION 6: Any corrections for the PCL to be sent to [redacted]. Any corrections for the Patient Information Sheet (PIS) should be sent to [redacted]

g) It was noted that [redacted] was still without access to email correspondence, and may not have received recent updated items

ACTION 7: [redacted] to send [redacted] the Patient Information Sheet, and copy this to [redacted], [redacted] and [redacted]

h) Discussion: pregnancy is an exclusion from trial at the discretion of the centre leader – agreed that this group should participate as much as possible.

i) [redacted] stated somatisation disorder is not a reason for excluding a patient– the clinic log will detail all refusals and reasons for excluding a patient

6. Piloting of therapies

a) Timing, staging and approvals

Time for complete piloting of the therapy manuals would take 9 months. [redacted] explained that when the protocol is sent to MREC to be approved in October, the Chairman will be contacted, and we will ask if we may send the manuals & PIS again in November. We will explain that only fine-tuning will occur and ask that a rapid sub-committee approval is given to prevent the trial being delayed any further from starting. Piloting should therefore take place in three stages – 13 wks, 24 wks and booster session.

[redacted] – stated that only minor adjustments to manual would be required after piloting, but that it was much easier to consider the manual as a whole rather than splitting it into three sessions, particularly as piloting may involve re-ordering of sessions.

[redacted] stated the importance of very carefully tracking all changes as the MREC will want to see these at a glance. [redacted] also pointed out that anything new to the patient such as a toolbox item or additional information sheet would likely be considered a substantial amendment by the MREC.

Schedule of events:

- Manuals to be submitted to the MREC by [redacted] by 15th October after which there will be a 35 day wait for MREC to give approval.
- Approve manuals & PIS in stages, with constant checking with PI's. Therapy leaders piloting to sign off final version and changes by end OCT/ start NOV. Minor changes made will have to be sent to the TSC/DMEC (or Chairs) before sending these to MREC

ACTION 8: [redacted] to talk to MREC about this in advance.

ACTION 9: [redacted] to submit all documentation to MREC on 15th October 2004.

[redacted] noted that rating of competency of therapists, the training of research nurses and the randomisation programme should be completed before the start of randomisation.

b) Audio-recordings

Old tape recorders should be sourced and used to record sessions during the pilot phase of the trial. Digital recording equipment will be purchased for the main trial.

ACTION10: [redacted] to discuss/pilot digital recording with [redacted], and issue of storage of recordings on CD.

c) Feedback so far

The therapy leaders stated that feedback from the therapists had been productive.

7. Update on training of therapists

a) Generic issues

[redacted] raised discussion of how to rate random tapes for competency of therapists. [redacted] suggested using the Therapy Integrity Scales. [redacted] noted that this was an important issue as the quality of therapy given could be criticised when the trial is published. The therapy manuals, if proven, may then go on to be widely used.

ACTION 11: [redacted] to score each scale on the Therapy Integrity Scales for use in grading therapist competency.

ACTION 12: Further to this, [redacted] with all four treatment leaders to discuss the criteria for competence etc., (either by email or in person)

ACTION 13: [redacted] with treatment leaders to review supervision: 1) Generic supervision on site per discipline (e.g. local, OT, PT and psychologist supervision), 2) National supervision by treatment type, and 3) Supervision of SSMC clinicians

b) APT

Pacing participants for piloting - more needed, especially at KCL. [redacted] is completing supervision by telephone.

c) CBT

Training all fine so far, therapists are meeting 1 day per month for supervision.

d) GET

[redacted] reported that training is ongoing and all fine so far. More is planned for next year. [redacted] noted that the therapists had been less experienced than hoped for.

8. Final protocol

a) Timing of research assessments: after randomisation or first treatment session?

The timing of the research nurse assessment visits was discussed in detail. There was particular concern about this issue because there had been a reluctance to lay down treatment windows for therapy sessions as anyone falling outside of this window would be 'deviating from protocol'. However, it was pointed out that research assessments should be carried out at mid-point and end of therapy but patients whose therapy sessions were delayed could have research assessments before therapy had finished.

(This discussion continued by email after the meeting and the final decision taken was that research assessments would be timed from the point of randomisation. First (mid-therapy) follow-up will take place at 12 wks post-randomisation and second (end-therapy) follow-up will take place at 24 weeks. The research nurse should keep in contact with the therapist to ensure that these assessments take place at an appropriate time point.)

In order to ensure that therapy sessions are not allowed to slide, the first therapy session should take place within one week and no more than two weeks after randomisation, and therapy sessions should each take place within five working days of the allocated time point.

[redacted] noted that therapists holiday/absence etc must be allowed for. Timings of assessments should be carefully monitored.

Patients should be able to commit to the appointments required for the trial in order to meet eligibility. A certain amount of flexibility has been built in with the allowance of a restricted number of telephone appointments. Patients who live very far away should be carefully considered for eligibility regarding their likelihood of remaining in the trial, and whether allocated funds will cover their travel expenses.

b) Primary outcome(s)

Discussion took place regarding the primary and secondary outcomes – number of outcomes and efficacy. It was decided that it was acceptable to have several primary outcomes for the trial, and that fatigue and disability could be considered separately and in combination. Cost utility could be considered as a fourth primary outcome. Actigraphy was not considered suitable as a primary outcome, but should remain as a predictor only.

[redacted] noted that the FINE trial assesses disability; null result is possible.

ACTION 14: [redacted] to identify a satisfaction scale and send to [redacted].

c) "Recovery" as a secondary outcome

[redacted] noted that this should be simply defined, and underpinned by a calculation. Possible definitions of recovery (for PACE):

1. Chalder Fatigue 3 or below
2. Physical Subscale score (85 or above) which is the mean for adult working age population
3. CGI score of 1 (very much better)
4. No longer has definition of CFS or ME (not meeting any criteria)

ACTION 15: [redacted] to re-examine Chalder Fatigue Questionnaire

d) Two wave consent for screening then randomisation

A two stage consent process has been introduced to allow the baseline visit to be broken down into two shorter more manageable visits. In the first stage patients will consent to be assessed for eligibility, only once this has been confirmed will the patient consent to the full trial.

e) Adverse events and reactions

The Adverse Events section of the protocol has been revised. For SAEs – events will be separated from the cause and CFS expected events have been defined. Immediate reporting is required to be in line with new regulations. SARs are likely to occur as a reaction to prescribed drug treatments.

f) CSRI revision

The CSRI has undergone further revision and was considered at this meeting. PM noted amendments suggested for this document and agreed to implement them.

ACTION 16: [redacted] to revise the ethnicity questions so that 'Other Black' is switched.

ACTION 17: [redacted] to amend 6 months to 24 weeks

g) ME criteria: London or Canadian

This was to be left for now as it would be discussed on the 27th by the TSC.

h) Therapy measures (alliance, expectations, integrity, feedback on therapy approach) ([redacted])

These measures are in review.

ACTION 18: [redacted] to supply scales to [redacted] for inclusion in the CRF when fully decided upon.

i) Ethical approvals

[redacted] explained the new requirement for site specific approvals and asked everyone to ensure that if their patients are to be recruited from more than one trust SSAs (Site Specific Approvals) would be required. This will be pertinent to Bart's second centre. [redacted] asked that KCL check they only need approval from one trust and that the SL&M approval is sufficient (and a second Kings approval is not needed). [redacted] tated that joint approval is given at Kings.

[redacted] noted that approval had been delayed for the Royal Free, [redacted] suggested that new centres wait until final MREC approval is given as R&D and LREC approvals can only be given once a final protocol is received, and the PACE protocol is yet to be finalised.

9. Standardised Specialist Medical Care (SSMC)

a) Timing of first session with SSMC doctor

It has been decided that to ensure that participants in the SSMC arm properly engage in the trial and do not feel that they have been told to 'go away', that the SSMC sessions should be coordinated (minimum of 2 or 3 sessions in 12 months).

It was agreed that all participants being seen by their SSMC doctor within one month of randomisation.

ACTION 19: [redacted] will design SOP for these.

Training programme

ACTION 20: [redacted] to write the training programme for the SSMC doctors.

b) Letter to patient prior to first appointment [redacted])

ACTION 21: [redacted] to write the patient appointment letter.

10. Training programme of research nurses/associates

a) Generic issues
b) Screening of potential participants
c) Recruitment of participants

ACTION 22: [redacted] with [redacted] to design the training programme for the research nurses which will cover screening, recruitment and retention issues as well as specific tests and trials methodology training.

d) CIDI

ACTION 23: [redacted] to identify what parts of the CIDI should be used.

e) CSRI

ACTION 24 [redacted] to lead on training for this

f) Actigraphy

ACTION 25: [redacted] to work on training for this.

g) Step test and walking test

Step tests – training has been organised in principle by [redacted], and [redacted] has agreed to run this.

11. Training programme of database managers/secretaries ([redacted]

[redacted] noted that part of the data manager training could involve helping pilot the database; training would also need to be carried out once the database is finalised. The database cannot be completed until the CRFs are done, which in turn are dependent on agreement of the protocol

ACTION 26– [redacted] to liaise with Data Managers in January for training.

Due to time constraints, the following items were not discussed at this meeting but will be discussed next time.

Contract for centre leaders

Trial stationery, questionnaires and manuals

Schedule of tasks before first participant recruitment

Ancillary studies

Second wave Centres

a) Agree target dates of employment (therapists 01.04.05; research staff 01.07.05) and first randomization (15.09.05)
b) Recruitment of therapists

[redacted] pointed out that [redacted] will be away on 15/9/05, and asks if we should consider starting [redacted] centre 2 weeks earlier?

[redacted] advised that the second wave of centres recruit soon for January employment start.

c) Recruitment of research staff

ACTION 26: [redacted] to send job descriptions & personnel specifications for all therapists and research staff. Therapy Leaders to help new centres in recruiting research staff.

12. Other Centre reports

No problems were reported.

13. For information only: Joint meeting of the TSC and DMEC; 2-5pm Monday 27th September

14. ME Association

MEA have agreed to publish the response to their article campaigning to stop PACE and FINE. It was noted that there had been resignations of trustees due to divisions in the MEA about PACE and FINE.

15. Dates/times for TMG in 2004

See below

16. Do we need a short meeting in early October for some TMG members?

ACTION 27: [redacted] to meet in early October

17. Date of next TMG #11 meeting

1pm to 5pm, Thursday, 4th November 2004 in [redacted]

18. Date of TMG #12

1pm to 5pm, Friday, 10th December 2004 in [redacted]

[redacted]