



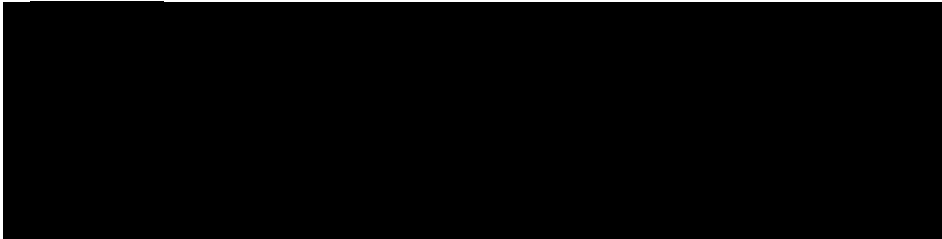
Trial Steering Committee Meeting #4
1.45 pm – 5 pm, Monday 23rd January 2006



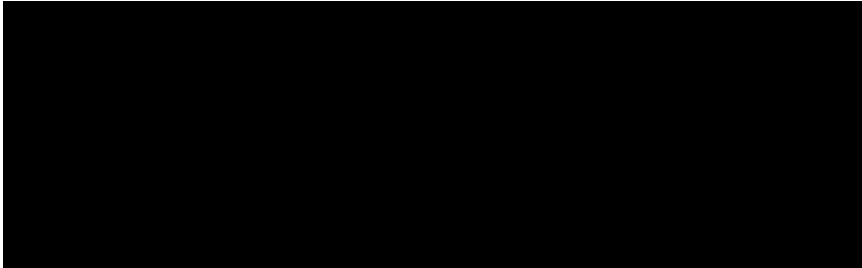
Draft Minutes

1. Those present

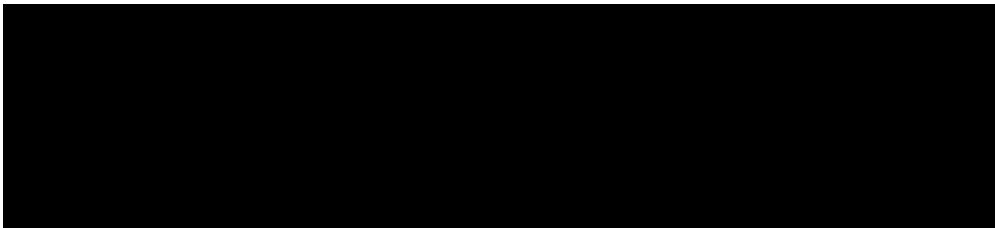
Members



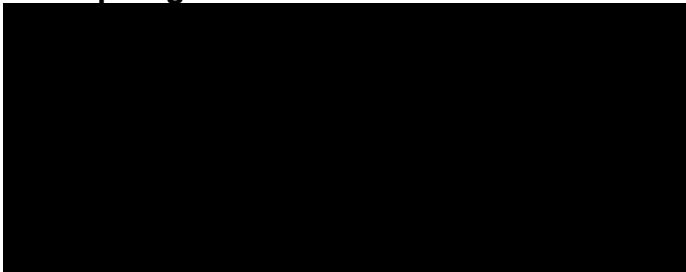
Observers



Other members



2. Apologies



3. Welcome of new members

The PACE TSC would like to send their thanks to [redacted]
[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 allowed 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: ■■■/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: [REDACTED] to write a letter to [REDACTED] 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 or 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.
- [REDACTED] 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: Pls 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 [REDACTED]

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.

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

Conflict of interest

It was noted that [REDACTED] 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 [REDACTED] 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.