



Trial Steering Committee Meeting #8
Wednesday 29th April 2009

[REDACTED]

Draft Minutes

1. Those present:

[REDACTED]

Non-voting members

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

Observers

[REDACTED]
[REDACTED]

Changes to TSC members since the last meeting:

[REDACTED] has retired and [REDACTED] will take [REDACTED] place. [REDACTED] replaces [REDACTED] and [REDACTED] will take on the role of Secretary in place of [REDACTED]. All new members were welcomed to the TSC.

2. Apologies

[REDACTED]



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].

[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, [REDACTED]
- iii. physician immunologist, [REDACTED]
- iv. ID physician, [REDACTED]
- v. liaison psychiatrist, [REDACTED]

[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: [REDACTED] to agree final group of assessors with [REDACTED] and [REDACTED]

TSC#7 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.

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

The risk assessment was reviewed. [REDACTED] commented that the cross cover of therapists has worked very well especially in London. [REDACTED] 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. [REDACTED] 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.

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

[REDACTED] 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. [REDACTED] 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. [REDACTED] confirmed the Lancet should be acceptable as [REDACTED] has had many trials published there. The trial should be published where it will make the maximum impact internationally.

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

[REDACTED] stated that no requests had been made for PACE data and the PIs would be notified of any requests. [REDACTED] 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: [REDACTED] to add the [REDACTED] Pace guide link to the King's website.

[REDACTED] confirmed that this link was present on the Bart's website.

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

[REDACTED] has stood down as Chair for the DMEC. [REDACTED] and [REDACTED] will continue and it was not felt a third member was required to replace [REDACTED] 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 [REDACTED] is the medically qualified member.

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

[REDACTED] congratulated the team on the positive feedback from the DMEC and suggested [REDACTED] could write to the DMEC to thank them for their contribution.

ACTION 3: ██████████ to write to the DMEC to thank them for serving the trial so well

7. TSC Report

██████████ presented the report to the committee.

Recruitment

██████████ congratulated the team on excelling their recruitment targets. ██████████ 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. ██████████ 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. ██████████ 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

██████████ 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.

██████████ queried if UKCRN staff may be able to cover any gaps at PACE centres if staff were to leave prematurely. ██████████ suggested ██████████ should contact ██████████ sooner rather than later to explore this possibility. ██████████ 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 ██████████ 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. [REDACTED] 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

[REDACTED] 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. [REDACTED] confirmed that any participants deemed as ineligible would be excluded from the per protocol analysis. [REDACTED] 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

[REDACTED] explained that the consort figures are not quite final as the priority at the local centres has been data cleaning.

[REDACTED] 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

[REDACTED] 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. [REDACTED] 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

8. Feedback from morning presentation of Analysis Strategy

[REDACTED] thanked [REDACTED] and [REDACTED] for an informative presentation which lead to a good discussion.

Health Economic Analyses

[REDACTED] 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 work was discussed. [REDACTED] 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 than 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: [REDACTED] 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

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

[REDACTED] added that the FINE trial TSC was on the 13th May and [REDACTED] would be presenting the results. [REDACTED] 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.

[REDACTED] 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: [REDACTED] and [REDACTED] to review implications of FINE trial and consider feedback to PACE participants and doctors

10. Monitoring reports

[REDACTED] explained that [REDACTED] had monitored all sites except Oxford in the year since the last TSC. [REDACTED] monitored Oxford at the end of April and was very impressed with the record keeping and high degree of organisation. [REDACTED] is due to follow up on issues 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. [REDACTED] 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 [REDACTED] needs to have ([REDACTED]).

[REDACTED] 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. [REDACTED] 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 collecting in following the meeting. It is not advisable to have members on conference calls as you cannot be sure who else may be listening. [REDACTED] suggested [REDACTED] could discuss with [REDACTED] team 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. [REDACTED] suggested only the TSC and DMEC should review the results initially as they may have comments to take on board. [REDACTED] agreed the TMG could be involved before the publication stage when the paper is being tracked.

[REDACTED] 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 [REDACTED]'s paper

This paper is now in press

b) Follow-up study [REDACTED]

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. [REDACTED] explained that the committee felt that phoning participants could be viewed as coercion. [REDACTED] is in the process of appealing this decision with MREC via NRES. [REDACTED] added comments on behalf of [REDACTED] 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 [REDACTED] 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 [REDACTED]

[REDACTED] 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.

[REDACTED] 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 [REDACTED] suggested this could not be done until the return rates had improved or it would be rejected. [REDACTED]

[REDACTED] asked if the MRC still do time only extensions. [REDACTED] 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 [REDACTED]

[REDACTED] explained that the NICE guidelines judicial review was won by NICE.

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

[REDACTED] 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. [REDACTED] 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: [REDACTED] to arrange date and venue for next meeting