Trial Management Group Meeting #31
23rd June 2009, [redacted]

Draft Minutes

1. Welcome

Welcome to all present. Congratulations to [redacted]

2. Those present

[redacted]

[redacted]

Observers

[redacted]

3. Apologies

[redacted]

[redacted]

4. Agreement of agenda

The agenda was agreed by all. The only amendment was to discuss centre specific issues under section 12a of the agenda.

5. Previous minutes of TMG #30

All accepted at this meeting with a minor alteration to a sentence under item 11 to read ‘therapeutic integrity’.

6. Ongoing actions from TMG #30

TMG #30 ACTION 22: [redacted] and [redacted] to perform a preliminary look at a few tapes and rate according to the established scale. This will be done in time for review in June.

ACTION 1: [redacted] and [redacted] to meet shortly to do this.

6b. Matters arising from TMG #30.

TMG #29 ACTION 5: CLs should urgently apply to their local R & D departments for trial support costs under the R & D tranche for the year. This has to be started to be spent by April 09.

It was discussed that only Bart's has received money from their local CRN.

ACTION 2: [redacted] recommended that Centres should apply to the director of their local CRN directly for funds as this is a portfolio study.

TMG #30 ACTION 12: [redacted] to clarify exactly what is required with [redacted] before emailing all therapists to request training schedules.

It was agreed that ethical approval should be sought to collect this data from therapists and consent should be obtained from all involved. We have received advice from NRES that approval is not required to present descriptive data as this will be anonymised in the main paper. However an amendment will be submitted to allow this data to be used in a further paper to look at therapist and doctor effects on participant's response to treatment.

ACTION 3: [redacted] and [redacted] to review and [redacted] to submit a substantial amendment requesting to use PACE therapist data in the analysis.

ACTION 4: [redacted] to ask treatment leads to resend therapist data so this can progress.

TMG #30 ACTION 21: [redacted] to arrange for three independent doctors (approved by [redacted] and [redacted]) to look at the NSAE and SAE logs to ensure that these are not SARs.

[redacted] will be discussing this with [redacted] on the 26th June to select the three independent doctors.

7. Update from recent meetings

a) TSC.
There was very positive feedback from the TSC. They agreed that there should be a participant newsletter at the end of the trial to inform them of the results and offer thanks.

[redacted] went through the TSC report and highlighted many positive results including the 107% recruitment rate, low drop outs and extremely good therapy adherence.
The main results are due to be presented to the TSC and DMEC in June/July next year. These should remain confidential within a limited group prior to publication.

b) PACE team day
This was a success, with presentations from [redacted] regarding recent research, [redacted] regarding the FINE trial results, [redacted] on her supervision study and [redacted] on secondary fatigue.
It was expressed at this meeting that those present would like a final PACE meeting to be informed of the results. This was discussed by the TMG with agreement that the results should first be presented to the DMEC and TSC before going to the TMG and finally other staff. This later meeting should only be done when results are stable with a sign-in sheet to guarantee confidentiality, with guidance from the MRC.

ACTION 5: [redacted] to organize dates and venues for these three meetings.

c) Analysis Strategy Group

The ASG had met prior to the TMG and had approved the final Analysis strategy. Discussions focused on multiplicity and analysis of the safety data.

The main analysis will compare combined APT/GET/CBT with SSMC, APT with GET and APT with CBT, without adjustment for multiplicity. Further exploratory analyses will compare each individual therapy versus SSMC and CBT versus GET. These exploratory analyses will be adjusted for multiplicity using Bonferoni's correction. The outcomes of fatigue and disability will be looked at separately and therefore will not require correction. The TMG agreed with this strategy and [redacted] asked that any final comments should be sent to [redacted] as soon as possible so that [redacted] can proceed.

Serious deterioration rates will be compared across treatment arms. Adverse event data will be presented descriptively and events with a twofold increase across treatment arms would be considered of interest.

ACTION 6: [redacted] to send round the final analysis strategy for official sign off by the TMG and TSC.
[redacted] was thanked for all [redacted] hard work on the trial as [redacted] will be leaving shortly.

It is hoped that baseline lock should take place shortly in order for writing groups to be able to commence with the baseline papers. There is however a local centre issue concerning eligibility which needs to be resolved before this lock can

occur and this will be returned to under item 12a. The TMG agreed that the section of the baseline papers which explains the derivation of the sample should be the same for all papers. The group was keen for the baseline data lock to occur only once.

It was noted that there are a small number of outstanding red and black book queries which it is hoped with be rectified shortly.

ACTION 7: [redacted] to forward these red and black book queries to the CLs so these can be followed up locally.

d) WAPOC

There are currently 12 proposed papers. Any other bids are very welcome and proposals should be sent to [redacted] and [redacted].

8. Bristol CONSORT diagram

94 patients current appear on the Bristol consort diagram and are listed as 'other ineligible reason'. It was confirmed by [redacted] that these patients were never offered the trial as they were regarded as living too far away. It was agreed by all that these patients should be removed from the diagram.

ACTION 8: [redacted] to remove the 94 patients from the CONSORT diagrams.

9. Project milestones and extension of research contracts

[redacted] has made the timelines working back from the current end of staff contracts and it was noted that the time for data cleaning is very tight. It was suggested that staff contracts should be extended to the end of March, with the hope to increase data collection and allow time for cleaning. There are sufficient funds available within the PACE budget to meet the cost of this extension. This was agreed by all.

ACTION 9: CLs to inform staff of this extension and to inform HR so this process can begin.

It was also noted that, in order to try and get the maximum amount of data collected, visits should be scheduled as early as possible within the protocol guidance so that data from the last participants can be collected expeditiously. The group agreed that data could continue to be collected up until the Christmas period. It was confirmed that the protocol allows the 52 week visit to be scheduled up to 1 week early.

ACTION 10: CL to inform RN/As to try and organise patient visits as soon as possible within the patients' visit schedule.

ACTION 11: CLs to inform RN/As to continue to collect follow up data up until Christmas.

10. Publicising results

This was discussed under 7c. Further arrangements for publication have not been arranged yet. It was confirmed that no talks/results should be disclosed outside of the trial before publication of the main paper.

11. Risk assessment

This TSC have requested that the risk assessment should be reviewed as a standing item on the TMG agenda.

Any staff leaving has been handled locally. Swine flu was considered to be a possible risk later in the year, with the possibility of staff and patients being ill for a couple of weeks, this further supports prompt data collection.

12. SAE review

DMEC had requested that SAEs for elective surgery be re-evaluated as it has been suggested that the threshold is too low. Attention was drawn to section 14.1.1.c from the protocol definition of SAEs. Several SAEs involving surgery were discussed. It was agreed that as all SAEs are to be independently reviewed these should be left as SAEs until this point.

ACTION 12: [redacted] to alert independent assessors of this discussion.

It was suggested that the NSAE for PIN 0207[redacted] may need to be looked at again to see if this should be a SAE.

ACTION 13: [redacted] to review the NSAE reported for PIN 0207[redacted].

12.a) Specific Centre issues

Oxford: All fine. The subvention money is to be used to fund the service. [redacted] has left but will complete [redacted] final PACE sessions.

Bristol: [redacted] and [redacted] are due to leave in August and interviews are taking place next week to cover the [redacted] role. [redacted] is due to have a phased return in August. The CBT and GET therapists have reduced their hours but will still have time to cover PACE.

Edinburgh: Two therapists have reduced their hours. [redacted] has finished as DM and a new DM will be joining the team.

ACTION 14: [redacted] to train new Edinburgh DM.

Royal Free: The CBT therapist has reduced [redacted] hours and is [redacted] in September. [redacted] expressed special thanks to [redacted] from all the RF team for [redacted] hard work and support.

Barts: All fine. Both the CBT and APT therapists are being incorporated into the service. The GET therapist has left but will complete treating [redacted] PACE patients.

Kings:
[redacted] monitored before [redacted] left and highlighted several significant issues. [redacted] monitored clinically at the beginning of 2009. Since these reported there have been staff changes with new and existing staff trying very hard to rectify issues. The major issue highlighted was that of eligibility. [redacted] believed 50% of the 20 patients he checked were ineligible. [redacted] checked these patients and the 50 last participants recruited onto the trial.
In summary of the 73 checked: 9 were thought to be ineligible at randomisation.
2 had uncertain eligibility.
21 had minor eligibility issues.
It was agreed that all patients (those that have not been previously checked and the 11 with questionable eligibility) should be reviewed independently. This checking should only use information available at randomisation.
This will delay the locking of baseline data but was seen by all present to be significantly important.

It was agreed that the criteria for ineligibility should be tabulated for clarity (showing which criteria are met and which are not). The TMG agreed that any bias should be towards including participants rather than excluding them. [redacted] kindly volunteered to undertake this checking. [redacted] explained that [redacted] had acted as the medical point of contact for eligibility queries at King's when [redacted] was in post as RN. The email correspondence relating to this can be forwarded if helpful to the review process.

ACTION 15: [redacted] to send [redacted] previous relevant emails, if still available.

ACTION 16: [redacted] to confirm when King's can make the research and medical notes available as a priority and [redacted] to confirm his availability for monitoring.

ACTION 17: [redacted], [redacted] and a King's SSMC doctor should meet for a debriefing, at the end of [redacted]'s visit, to discuss the participant's highlighted as ineligible for final agreement and sign off either consensually or by majority view.

The team discussed whether participants without a diagnosis of CFS should be excluded from the intention to treat analysis. However it was agreed by all that to ensure the results can be generalized the participants deemed eligible at randomization but ineligible at review or monitoring should be included in the ITT analysis but excluded from the per protocol analysis. The statisticians confirmed this is standard practice in clinical trials. It was confirmed that this issue had been discussed previously and agreed with regards to a specific case of ?lupus.

The TMG felt it would be appropriate to review whether there are eligibility issues at other centres and this could be achieved by reviewing the clinician's monitoring reports. All centre leaders confirmed that they had undergone monitoring in the past and would be willing to undergo further monitoring if required.

ACTION 18: [redacted] to forward the previous email correspondence regarding the intention to treat analysis to [redacted].

ACTION 19: [redacted] to review all clinician's monitoring reports and arrange for further monitoring visits at sites as required.

13. Measure of therapeutic differentiation

WAPOC agreed that the independent review of session recordings to look at therapy differentiation should begin sooner rather than later. The group will be drafting a protocol for how to differentiate therapies which will include:

1. Which treatment is it?
2. Is this an adequate implementation of the relevant manual? Yes/No

It was suggested that this could be supplemented with notes on why the rater had reached this decision.

Actions carried over from WAPOC:

ACTION 20: WAPOC team to develop a protocol for therapy differentiation

ACTION 21: [redacted] to collect together the CDs for review

There is a second issue of therapeutic alliance as a potential mediator and [redacted] will be considering how to evaluate this as part of [redacted] paper.

14. Homework compliance

The purpose of this data was to give a broader description of adherence to treatment and this has been included in the analysis strategy. [redacted] reported that this is supposed to be recorded electronically and the deadline for this is September. The data for this should have been recorded on paper.

ACTION 22: Bristol and Bart's are slightly behind with this and this should be monitored locally by CLs.

15. Ancillary studies

a) 2.5 year follow-up study:
This will now be reviewed in November as it was thought that there has not been enough time since MREC approval of follow up letters and phone calls to make an impact on response rates. [redacted] reported that there has been a 57% response rate. The TSC believed this to be an important study and is worth pursuing if a better response rate is achieved.

ACTION 23: RN/As to continue to make a push on collecting this data and CLs to review this locally on a regular basis.

b) Genetics study:
[redacted] has completed [redacted] part of the proposal for this and this is awaiting input from the geneticists in Bristol before proceeding to costing and ethics.

c) Proposal for case control study of actigraphy:
[redacted] suggested that healthy controls could be recruited if ethical permission was granted so that this could be compared with the actigraphy data from PACE participants, and asked for the groups' opinion of whether this data would be valuable. It was discussed that recruiting healthy controls would be difficult; with [redacted] highlighting that group matching would be too heterogeneous for valuable analysis. The TMG had mixed views but it was decided that it was best to maximize what we could do with the information already available.

d) Review of content of therapy sessions:
[redacted] explained that [redacted] had tried unsuccessfully to get funding to conduct this. However the data remained important and [redacted] would try again to enable us to make use of the recordings.

16. Archiving arrangements

[redacted] is currently looking for guidance on this on a local and central level in order to produce an SOP. [redacted] fed back that in [redacted] experience it is much easier to separate out patient identifiable data from the main CRFs to prevent needing to blind the data at a later stage if a non-trial team member has permission to access the records. This would help to facilitate any secondary analysis of the data.

ACTION 24: [redacted] to write a SOP to detail archiving arrangements.

ACTION 25: Centres should look into archiving locally with the issues being: Location, cost, duration, accessibility and local R&D SOPs. [redacted] to email this list to all RNs/Centre leaders.

17. Centre specific issues
Addressed under 12a

18. Therapy/treatment specific issues

No treatment leaders were present to report on this, but no issues had been reported.

19. Any other business

None was discussed.

20. Proposed dates and venues for next TMG meetings:

Wednesday 4th November, 1pm lunch, 1.30 - 4.30pm: TMG [redacted] observers welcome)
Thursday 11th February, 1pm lunch, 1.30 - 4.30pm: TMG (location TBA).

ACTION POINT SUMMARY LIST

WAPOC

ACTION 20: WAPOC team to develop a protocol for therapy differentiation

PIs/CLs

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<u>Research Nurses/Assistants</u>

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[redacted]

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