



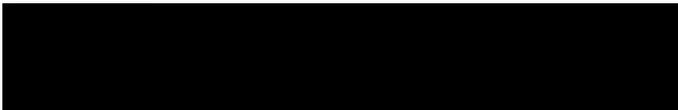
Trial Steering Committee Meeting #5
Monday 17th July 2006



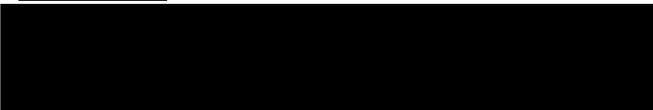
Draft Minutes

1. Present

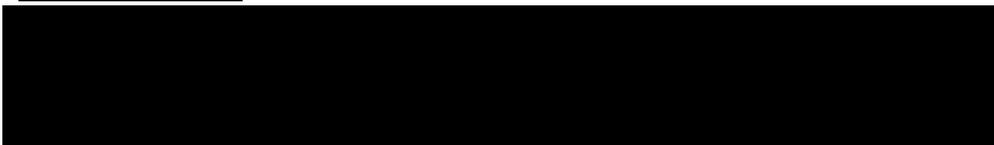
Members



Observers

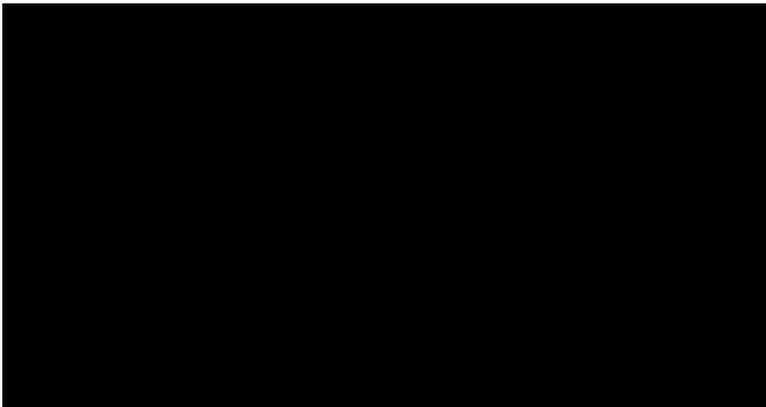


Other members



2. Apologies

Due to the unusually high number of people unable to make this meeting, decisions and recommendations made at this meeting will be sent to absent members for their approval before any actions are implemented.



3. Welcome to new members

The TSC formally welcomed two new members. Unfortunately neither new member was available to attend this meeting:

- [REDACTED] who replaces [REDACTED]
[REDACTED]

4. Members who have left the committee

[REDACTED] The TSC extends thanks to [REDACTED] to all of [REDACTED] contributions to and support of the PACE trial.

5. Previous minutes of TSC # 4

These were accepted and signed off.

6. Matters arising from TSC #4 not on the agenda

[REDACTED] will give an update of the progress in the FINE trial at this meeting.

7. Matters arising from DMEC meeting of 4th July 2006 (document from [REDACTED] to [REDACTED])

a) Unblinding of [REDACTED]

The issue of [REDACTED] being unblinded was discussed. This has occurred due to contents of the database (particularly in comments fields) occasionally giving away information as to whether the participant is having a supplementary therapy and occasionally, what that therapy is. It was clarified that the DMEC are not concerned about this as long as [REDACTED] remains blinded to the results of the trial.

The DMEC currently see blinded data .

b) Membership of the DMEC

The DMEC would like to invite another member to join them so that if any member is unavailable to take part in a meeting, there will be enough other available members to make decisions. [REDACTED] has been suggested as someone who might be approached and although [REDACTED] works for [REDACTED] [REDACTED] has no formal links with the King's team so there should not be any conflict of interest. [REDACTED] has identified another potential person that might be approached.

ACTION 1: [REDACTED] will speak to [REDACTED] about people who might be approached as extra members to the DMEC.

Definition of serious deterioration

The DMEC clarified the definition of serious deterioration in an individual participant. The DMEC also discussed deterioration in terms of time to drop out (at least 8 weeks from randomisation). In addition, the DMEC suggested dropping SAEs from the definition, comparing changes in SF-36PF to baseline as opposed to the previous visit, and looking at CGI and SF-36PF both on two consecutive visits as well.

ACTION 2: [REDACTED] to:

- i. **revise the Definition of Deterioration document**
- ii. **circulate to DMEC to ensure it matches with their decisions**
- iii. **include the '8 week to drop out' rule**
- iv. **circulate the completed approved document to the TSC.**

ACTION 3: [REDACTED] to circulate the completed Definition of Deterioration document to the TSC with the minutes to this meeting.

All other DMEC issues were deemed satisfactory or are to be raised on the agenda of this TSC meeting.

8. TSC Report (document 2: TSC Report)

a) General TSC report issues

[REDACTED] spoke regarding the TSC report.

- *Recruitment target* has been revised due to delays to the second wave centres starting up.
- *The CONSORT diagrams* include 'Health warnings'. These reflect that the complete accuracy of the data is not assured at this time but this is being worked on.
- An explanation was provided to the TSC for the 119 unknowns listed as 'awaiting referral decision' on the CONSORT diagram. A large proportion are believed to be patients who were contacted for the trial by the RN by telephone, but who turn it down or are found to be ineligible before baseline 1.
- *General acceptance rate of the trial* is similar to that reported six months ago.
- In order for the TSC to be able to assess the completeness of the data for future reports, [REDACTED] will need information regarding what data has been collected separately from that which has been entered. In practical terms this means having a separate list of completed visits, including dates, per participant per centre. The completeness of data collected at the item level can only be assessed practically once it has

been entered onto the database. The local data managers or research assistants will need to provide this. (It might be helpful if this was built into the monthly updates to the Senior Data Manager for this individual to check).

- *Non adherence to treatment* – The TSC would like a measure of the level of adherence to treatment to include the number of sessions attended and whether the treatment was adhered to, without including mutually cancelled sessions that would be redundant.
- The trial protocol defines adherence as 10 sessions or more but does not mention these other factors

ACTION 4: TMG to further define ‘adherence to treatment’ taking in to account attendance and engagement.

ACTION 5: [REDACTED] to submit an amendment to protocol as required reflecting the clearer definition of adherence to trial treatment.

b) Drop outs, withdrawals and losses to follow up by month and as a proportion of those entered

There have been 3 drop outs from the trial so far. Two have withdrawn from the whole trial, one has withdrawn from treatment only but remains in follow up with the research nurse.

c) Completeness of database entry

The majority of the available data has been entered. This is not 100% due to the fact that the database was completed late and centre data managers have had a backlog of data cleaning and entry to clear for this meeting.

d) Recruitment rate below targets

The reasons for this were discussed and are summarised as follows:

01 Barts – There has been a new service set up in Sussex which has drawn referrals away from Barts’. The trial now has MREC approval to approve from further afield and Sussex patients have started to be referred for the PACE trial at Bart’s.

02 Edinburgh – There are plenty of referrals to this centre, but there has been a shortage of available clinic times with the consultants. This has been identified and addressed with the recruitment of a third consultant to the PACE trial and the centre saw a rapid rise in randomisations as a consequence. If one or better two more sessions of clinic time can be freed up, the centre is confident that recruitment will increase by a further 20-30%. This should bring recruitment up to target, and could be met out

of contingent monies within the trial (allocated to back loading the last year).

03 Kings – Have had similar problems with regard to the availability of clinic doctor's time to assess participants for the trial. [REDACTED] has recently been able to allocate more time to the PACE trial, and the centre has increased research staff time by one third in order to increase the rate of referrals to the trial. The centre has noticed some reduction in overall referrals due to NHS funding problems causing PCTs not to refer to a service for which they will be charged.

The TMG also feel that the negative PR surrounding the trial may have adversely affected uptake.

e) Proposed strategic solutions to improve recruitment rate

[REDACTED] discussed the proposals from the TMG to improve the recruitment rate to PACE. In summary, these include:

- Extension of recruitment period by six to eight months,
- Increasing target recruitment in existing centres and
- The addition of two new centres - the costs of this would be start up, salary, staff training, travel and transport. The initial subvention and MRC grant did not take into account staff turnover and maternity leave costs and any future grant would need monies to cover these issues.

It is estimated that an additional two centres plus a six month extension gives an estimated recruitment end point of 597.

A further strategy to improve recruitment would be to loosen the eligibility criteria to allow participants who had suffered a recurrence. TSC rejected this suggestion due to the risks of picking up treatment resistant patients or recruiting patients who are not in equipoise.

Summary of TSC decisions

On consideration of the proposals, the TSC felt it essential to do as much possible as quickly as possible to improve recruitment.

Subvention - TSC agree that it is essential to obtain funding to support NHS staff or the trial may fail to recruit enough patients within budget.

ACTION 6: [REDACTED] to draft a letter to be sent to DH R&D and to be signed by [REDACTED] making a statement of support from the TSC for further NHS funding for PACE.

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Budget - Travel and training has cost extra due to staff turnover and cross cover, but in other ways the budget is close to target. The TSC therefore support the use of back loaded funding to get a new centre started up as soon as possible.

Extension to trial - Recommended that an extra six to eight months of recruitment and follow up.

Timelines for implementation

Plan:

1. Recruit one new centre immediately on back loaded funds.
2. Use extra time recovered from delay to starting first six centres to extend the time to recruitment by a few months.
3. Write to the MRC HS Board to requesting an extension to time and funding. The request should be sent by September in time for the November meeting.

ACTION 7: ■ and ■ to write a statement for the internal MRC Executive Board regarding non-cost measures to improve trial recruitment.

ACTION 8: ■ to contact the TSC members not present to ensure that they are happy with the decisions proposed to improve recruitment.

ACTION 9: If further funding is forthcoming, ■ to contact the MREC to inform them of the extension to trial end and to alter the protocol accordingly.

9. Monitoring of first wave centres (document 3: Summary of outcomes from monitoring visits)

A summary of the findings was presented to the TSC. The only major concern was the report that centres are not using the patient and GP letters as worded in the protocol, and the delay between baseline 2 and randomisation.

ACTION 10: ■ to send an administrative amendment to MREC regarding the wording of letters to participants showing examples of the centre letters actually being used.

■ would like to do a minimum of one monitoring visit per centre per year, more if time and funding allow.

TMG would like to make an amendment to MREC to state that there should be up to one month gap between baseline 1 and randomisations or tests should be repeated. The TSC were happy with this decision.

ACTION 11: ■■■ to send an amendment to MREC to increase the time to randomisation from one day after baseline 2 to within four weeks of baseline 1 to better reflect what is possible in practice.

The greatest concern of the DMEC to the reports was the issue of high turnover of junior doctors giving SSMC at King's. As described earlier, a consultant who can give more clinic time to the trial has now been identified to take on more of this workload.

10. Discussion of categorical improvement score on the SF-36

The TSC reviewed the categorical threshold for improvement on the SF36 physical function subscale of 70. Although it was noted that this was well within 1 standard deviation of the mean score for the female adult working population (80), the TSC decided that the complementary use of a 50% improvement in SF36 score would compensate for the closeness of these scores.

11. Start of second wave centres – progress report

04 Barts II – this centre has had difficulty in recruiting therapists with some adverts going out several times. All staff are now employed but the GET therapist will not be starting until late July and will require training after that time.

05 Oxford – There was a delay to starting this centre due to issues with the financial contract. All staff have now been recruited to this centre with the Data manager being the latest appointment. All therapists are fully trained and the site opened to recruitment in April 2006. The centre has recruited to target so far.

06 Royal Free – This centre has had multiple difficulties; these include agenda for change delaying advertisements of posts, redundancies of almost 500 NHS staff, freeze on recruiting new staff, delay waiting for re-deployment of staff; difficulties in obtaining LREC approval, difficulties in recruiting research staff (first three rounds of interviews did not produce any suitable candidates for the research nurse post). This centre has not yet started recruitment but all therapists are trained.

12. Relevant published studies since last meeting (to be tabled)

Two new papers were tabled at this meeting.

The BioBran trial had no results from placebo and has no bearing on the PACE trial.

The methylphenidate trial did find differences from placebo on both mental and physical fatigue. The effects were only seen whilst the patients were on drug but disappeared when the patients were off drug. This is a common drug for ADHD and may be subject to misuse. This trial is not thought to have any bearing on PACE.

██████████ will be reporting later in the summer so there is no news on the results of █████ RCT yet.

13. PACE trial ancillary studies previously approved

a) Genomics study

Genomics was turned down for funding by the MRC.

The CDC pledged monies and it is hoped that this might be still be used to look at SNPs.

b) Therapeutic process

This is about to be submitted to ESRC for funding and then MREC approval subsequently.

c) Two year follow-up study

There have been indications from the DWP that they would consider this carefully regarding supporting this with partial funding.

The TSC discussed when they thought it would be most sensible to approach the MRC for funding. The advice was that there was a need to be careful not to approach the MRC HSPHRB too late as if the first few patients have passed the two year follow-up time point it may be seen as a perceived weakness by a funding board.

One suggestion was to seek MREC approval and complete two year follow within the existing budget in the first instance. If this proves possible, the TMG might consider requesting for two year follow up money at the same time as asking for trial extension funding. This latter suggestion was thought to be risky however.

Originally it was envisaged that follow up would be done as a face to face interview either at clinic or in the patients' home Due to the under recruitment situation, it was discussed as to whether the two year follow

up should be done by questionnaire only to reduce the potential burden of extra interviews on the existing research nurses.

A phased plan was suggested for consideration by the TMG:

- Two year follow up, and possibly three year
- Chasing for follow-up information via GPs (some GPs charge circa £50 for any response to research requests however, so this may not be cheap or reliable)
- Costing for this ancillary study needs to include production of new forms, new database, postage and phone call costs and administration time/staff costs.

ACTION 12: The TMG should consider the two year follow up study in more depth and prioritise what data from this would be of most use, and use these discussions to further develop this protocol.

d) Supervision process study (document 4)

The supervision study briefly discussed and the TSC were happy to support the proposal.

14. FINE trial update

FINE is a RCT of two active treatments versus GP treatment as usual. Patients are recruited from primary care and referred by GPs. The two treatments are supportive listening and active rehabilitation and are delivered by specially trained nurses (each nurse is trained to give both). This is given over 18 weeks with 5 home visits and 5 telephone sessions. Follow up at 20 weeks and 1 year. Patients are assessed in their own homes.

Successes so far: 3 nurse therapists are delivering treatments. Fidelity checks show that treatments are being kept separate, the nurses are happy and there has been no change of staff.

Difficulties: Recruitment is struggling and is currently at 65% but this is improving.

The FINE trial statistician has revised the power calculations and widened confidence intervals to allow for a reduction in target by 80 participants. The original calculations were based upon very conservative assumptions. No decision has yet been made as to whether to follow this revised target. An extension to the study of a two or three

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year follow up is being considered as is an extension to the trial recruitment period.

There are various qualitative studies being conducted alongside the main trial. These include interviewing GPs, patients who have accepted and refused the trial, practice nurses etc.,

15. Public relations (documents 5, 6 and 7: Participant Newsletter, Staff newsletter and Website)

Correspondence to the MRC has slowed down slightly in anticipation of the results of the Gibson enquiry.

There was discussion as to why only King's participants are being asked for their experience of the trial (██████████ qualitative study). This is a local LREC approved study to King's that sought approval before the PACE trial had begun. The TSC were satisfied with this explanation.

Newsletters & website - The TSC were pleased with the newsletters and website. No feedback has yet been received about the website from the public.

16. Report on PACE National Team Day

The team reported that they found the day interesting, useful and enjoyable.

17. Date and time of next meeting to be arranged at this meeting

Proposed January dates for next meeting:
Monday 8th January 2007
Monday 22nd January 2007
Monday 29th January 2007

ACTION 13: █████ to circulate these dates to the TSC and inform all when a final date has been selected.

Summary of Action Points

██████████
ACTION 1: █████ will speak to ██████████ about people who might be approached as extra members to the DMEC.

██████████
ACTION 2: ██████ to:

- i. revise the Definition of Deterioration document
- ii. circulate to DMEC to ensure it matches with their decisions
- iii. include the '8 week to drop out' rule
- iv. circulate the completed approved document to the TMG.

ACTION 6: ██████ to draft a letter to be sent to DH R&D and to be signed by ██████ making a statement of support from the TSC for further NHS funding for PACE.

ACTION 7: ██████ and ██████ to write a statement for the internal board regarding non-cost measures to improve trial recruitment.

██████████
ACTION 3: ██████ to circulate the completed Definition of Deterioration document to the TSC with the minutes to this meeting.

ACTION 5: ██████ to submit an amendment to protocol as required reflecting the clearer definition of adherence to trial treatment.

ACTION 8: ██████ to contact the TSC members not present to ensure that they are happy with the decisions proposed to improve recruitment.

ACTION 9: If further funding is forthcoming, ██████ to contact the MREC to inform them of the extension to trial end and to alter the protocol accordingly.

ACTION 10: ██████ to send an administrative amendment to MREC regarding the wording of letters to participants showing examples of the centre letters actually being used.

ACTION 11: ██████ to send an amendment to MREC to increase the time to randomisation from one day after baseline 2 to within four weeks of baseline 1 to better reflect what is possible in practice.

ACTION 13: ██████ to circulate these dates to the TSC and inform all when a final date has been selected.

TMG

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ACTION 4: TMG to further define 'adherence to treatment' taking in to account attendance and engagement.

ACTION 12: The TMG should consider the two year follow up study in more depth and prioritise what data from this would be of most use, and use these discussions to further develop this protocol.

██████████

ACTION 7: █████ and █████ to write a statement for the internal board regarding non-cost measures to improve trial recruitment.