NHSBSP AGE EXTENSION TRIAL

Minutes of the Data Monitoring and Ethics Committee
28th January 2014
11:00 – 13:00
Room 35, First Floor, Grosvenor Wing,
St George's Hospital, Tooting, London, SW17 0QT

Present
Professor Janet Darbyshire (JD) (chair)
Professor Tom Meade (TM)
Ms Jenny Rusby (JR)

In attendance
Kath Moser (KM)
Professor Sir Richard Peto (RP) (teleconference)
Hayley Abbiss (HA) (notes)

Apologies
Dr Rosalind Given-Wilson (RGW)
Dr Gillian Reeves (GR)

Documents circulated in advance:
- Agenda
- Minutes of DMEC meeting 9 January 2013
- Trial progress as at January 2014 (item 3b)
- Data progress as at January 2014 (item 3b)
- Analyses for DMEC January 2014 (item 4)
- Report on study population data for the first 4 years of the trial (item 4)
- Report on screening data for the first 3 years of the trial (item 4)
- Draft statistical analysis plan (item 4)
- Report of the parliamentary inquiry into older age and breast cancer (background)

1. Welcome and introductions

Professor Janet Darbyshire (JD) welcomed the members of the committee to the meeting. Professor Richard Peto (RP) joined the meeting by teleconference. Apologies were received from Dr Rosalind Given-Wilson (RGW) and Dr Gillian Reeves (GR). Thanks were given to RGW for providing her office to host the meeting.

2. Minutes of the last meeting (9 January 2013) and matters arising

The minutes of the last meeting were accepted as an accurate record of the meeting.

Matters arising:
RP explained inter-cluster correlation and gave reassurance that the trial will have very nearly as much power as an individually-randomised trial would have as the clusters are so small. This aspect will be dealt with in the analysis.

It was agreed that it will be important to look at causes of death other than breast cancer, despite the small numbers for some causes.

Kath Moser (KM) confirmed that nothing further had come of the Freedom of Information request from autumn 2012.

3. Trial update (KM)

a) Progress with ethics, protocol

A substantial amendment (to cover linkage to HES and other NHS datasets; offer screening throughout their 70s to the women who were randomised in aged 71-73 (the women randomised out aged 71-73 are the control group and would not be offered screening through their 70s); revise patient leaflet) was submitted to the Research Ethics Committee (REC) February 2013 but was not approved. Many of the REC's concerns related to the original trial design for which we obtained ethical and S251 approval in 2010. They were not happy that women in the control group did not know they were in a trial and that their records were being used without their consent. However this is all covered by the trial approvals obtained in 2010. They also wanted us to make clear in the trial leaflet that the data in the standard NHSBSP information leaflet applies to women aged 50-70 and therefore does not apply to women entering the trial. This has now been done and data on women aged 47-49 and 71-73 from the pilot study are now included in the trial leaflet.

It had been decided that rather than put in an appeal, it was better to submit a new substantial amendment that only covered linkage to NHS datasets, and a revised patient leaflet. (The proposal to offer screening throughout their 70s to women randomised in aged 71-73 will not be included.)

JP and KM have been redrafting the leaflet, and Public Health England is now assisting in reformatting the leaflet into a suitable style. As soon as the leaflet is finalised we will go back to the REC with a new substantial amendment. References in the protocol to continuing to send invitations to women over 73 will be removed.

There was some discussion around the role of the DMEC in relation to ethical issues. It was clarified that the committee does have ethical oversight.

Action: KM to send revised leaflet and protocol to DMEC before submission to Ethics.

b) Progress with randomisation, numbers, data

KM gave an update on Trial Progress and Data Progress (reports circulated in advance). 60 of the 69 breast screening units (BSUs) due to randomise have now started randomising, and 1.3 million women have now been randomised. 6 of the 9 units who are not yet randomising are expected to do so by the end of March 2014. 3 of the units may never start randomising.

There was discussion as to whether there was a target at the outset of the trial, as in most trials. There was no target but the intention has been to include all BSUs able to participate, and all women of appropriate age within each BSU, and to continue until clear evidence emerges. RP expects results to be seen in the early 2020's for younger women, and late 2020's for older women. Mortality findings will only become meaningful in the later years of the trial.

There has been good progress over the past year with obtaining trial data; the systems are in place and working well and the body of data held in the Cancer Epidemiology Unit (Oxford) is steadily building up.

4. Analyses and reports on data

Four documents were circulated in advance and discussed.

a) Report on study population data.

JR was concerned about why the very small batches are occurring. RP advised smaller batch sizes are better as they give more power than the very large batches. The couple of BSUs that use very large batch sizes are being encouraged by the NHS Breast Screening Programme (NHSBSP) to change their approach.

JR asked that where possible batch data are provided for women aged 47-49+71-73 (i.e. women in the trial only), instead of the whole 47-73 age range.

There have been some du/triplicate records where women were randomised more than once, as explained in the report. RP confirmed that where a woman is randomised more than once her first randomisation status will be used in the analysis, with subsequent randomisations ignored; he reassured that this will not damage the trial.

Action: KM to investigate why the very small batches are occurring.

Action: KM to provide batch data for women aged 47-49+71-73 only.

b) Report on screening data.

JD requested data on 'screening uptake, and reasons for not attending' and 'screening outcomes of women screened' for women aged 50-70 to see how the figures compare with the trial age groups.
The expectation is that all units will be using digital machines by April 2015, as the old analogue machines are being phased out.

Action: KM to try and obtain screening data for the 50-70 age group.

c) Draft statistical analysis plan.

KM confirmed this was drafted in Autumn 2013 and that it is a rolling document.

d) Analyses for DMEC.

KM confirmed that the data presented on breast cancer incidence by age group and randomisation status were unblinded. There was lengthy discussion over whether the TMG should have access to these data. RP argued that they were process indicators and therefore should be available to the TMG. TM and JR had concerns that the more people who saw the data the more possibility there was of leakage and speculation.

The DMEC accepted RP's comments on the importance of looking at the process of the trial. RP accepted the DMEC's concerns about data being leaked out from the TMG, particularly as this could prove damaging to the Trial. It was agreed that the TMG should not see unblinded breast cancer incidence data.

There was further discussion as to whether co-investigators Valerie Beral (VB) and Julietta Patnick (JP) could see unblinded breast cancer incidence data. It was agreed that for the time being these data should not be shared with VB and JP. JD suggested the DMEC have an open session with VB and JP at their next meeting to discuss the issue.

It was agreed that everyone, other than the DMEC, RP and KM, should be blinded to mortality data. In other words neither the TMG nor the co-investigators (with the exception of RP and KM) can see unblinded mortality data.

RP and KM will feedback these recommendations to VB and JP at a trial team meeting.

Action: RP and KM to feedback to VB and JP the DMEC concerns about sharing of unblinded data.

5. Future plans

Continued screening invitations of women aged 74+ (of women randomised in aged 71-73):
It was noted that the Report of the parliamentary inquiry into older age and breast cancer was very interesting and recommends continued screening invitations after age 73 of women in the trial. PHE has endorsed the continued screening of women through their 70s. RP stressed the importance of offering screening to women throughout their 70s in order to make the trial a study of worldwide importance. He estimated continued screening invitations to the age of 79 of women randomised in aged 71-73 would create an additional cost of £9 million per annum. Members of the trial team plan to meet with Prof Dame Sally Davies, Chief Medical Officer, who it is hoped will be supportive.

Main immediate priorities are:-

To submit a new substantial amendment to the REC as soon as possible.

To find a way of extending the trial at older ages by continuing to invite women for screening throughout their 70s.

6. Any other business

JD requested that future reports circulated for meetings are numbered clearly to correspond with numbered agenda items.

KM said that JP reported that PHE are very supportive of the trial; they want results before extending routine screening to women under age 50 and over age 70 and so have indicated that randomisation will continue until evidence is obtained.

7. Date and plans for next meeting

The Trial Management Group (TMG) has suggested a longer meeting next year. It is proposed to start with some presentations including one from RP on the importance for trial evidence of continuing to invite women for screening throughout their 70s. Both the DMEC and TMG members would be invited to attend these. The DMEC would then be invited (as usual) to observe the TMG meeting, and the DMEC meeting would follow on after the TMG meeting. It was agreed this was a good proposal. The meeting would be held in Oxford early in 2015. Date TBC.

At the end of the above meeting DMEC members wrote the following statements.

Report from the DMEC to the TMG following meeting of 28 January 2014

The DMEC congratulates the Trial Team and Breast Screening Units on the progress of the trial to date and was pleased to see some early data.

The DMEC was concerned to hear that the Trial Team are experiencing some difficulties in securing REC approval of the substantial amendment to the protocol. The delay in updating the trial documents is of immediate concern but the delay in beginning to plan for the linkage to other NHS records will be increasingly important as the trial progresses.

Confidential note from the DMEC to the Trial Investigators following meeting of 28 January 2014

The DMEC discussed access to data on cancer mortality and incidence by randomisation group and agreed that:-

1. Mortality data by randomisation group should only be available to the DMEC
2. Further consideration should be given as to whether incidence data by randomisation group should also only be available to the DMEC

Action: KM to circulate the above 'DMEC report to the TMG' to the TMG.

Action: RP and KM to convey the above 'DMEC confidential note to Trial Investigators' to JP and VB.