

NHSBSP AGE EXTENSION TRIAL

Minutes of the Data Monitoring and Ethics Committee

8th November 2011

14:00 – 15:30

**** Phone conference ****

Present

Professor Janet Darbyshire (JD) (chair)

Dr Rosalind Given-Wilson (RGW)

Professor Tom Meade FRS (TM)

Dr Gillian Reeves (GR)

Ms Jenny Rusby (JR)

In attendance

Professor Dame Valerie Beral (VB)

Kath Moser (KM)

Professor Sir Richard Peto (RP)

Documents circulated in advance:

- agenda
 - draft revised protocol
 - trial progress to end Oct 2011
- Plus for background information:
- original application for ethical approval
 - patient information leaflet
 - J Medical Screening paper on the pilot study

1. Welcome and introductions

Professor Janet Darbyshire (chair) and Kath Moser (trial co-ordinator) welcomed the members of the committee to the first meeting of the Data Monitoring and Ethics Committee for the NHSBSP age extension trial. It was agreed that this meeting would be an open session.

2. Trial update (KM)

Kath Moser summarized the **background** to the NHSBSP age extension trial. A pilot study was undertaken before deciding to proceed with the main trial to assess the feasibility and acceptability of randomization (see Moser K, Sellars S, Wheaton M, et al. Extending the age range for breast screening in England: pilot study to assess the feasibility and acceptability of randomization. *J Med Screen.* 2011; 18(2):96-102.)

The **aim** of the main trial is to evaluate the effects of offering one additional screening invitation at age 47-49 years and, separately, to evaluate the effects of adding one additional screening invitation at age 71-73 years. The main outcome is breast cancer mortality up to age 60 for women offered an extra screen at age 47-49 years and up to age 80 for women offered an extra screen at age 71-73 years.

Originally **randomization** was planned to continue over 3 years i.e. over one screening round. Now, following the Department of Health's 'Improving Outcomes' publication in Jan 2011, phasing-in will continue until at least 2016 i.e. over 2 screening rounds.

Ethical approval was originally obtained for randomizing over one screening round, for follow-up for deaths and cancer registrations, and for clinical screening outcomes in women randomized in. More recently additional ethical approval had been received to cover randomization over two screening rounds and including data from the pilot study in the main trial.

Since the original **protocol** was agreed and given ethical approval it has become apparent that a more refined approach is required – hence the circulated draft revised protocol. The revisions include:

1. Linkage with historical screening records (in order to look at screening compliance which would increase the statistical power of the trial).
2. Linkage with HES data (in order to look at investigations and procedures).
3. Linkage with, as yet, unspecified NHS data.

Ethical approval will need to be sought for the above changes to the protocol.

Trial progress to date

KM provided an update on the progress of the trial as of the end of October 2011. 40 breast screening units (BSUs) have started randomizing (out of 73 due to randomise). These 40 units include 5 pilot sites (started June 2009), 8 units starting in 2010 and 27 units starting in 2011. An additional 7 units will not be randomising (6 use non-standard method of creating screening batches; one private sector unit). There is not yet any trial data on the exact number of women in the trial, but it is estimated 330,000 women have been randomized to date. It is estimated that by the end of 2011 380,000 women will have been randomized. It is expected that 9 more BSUs will start randomising before the end of 2011, with 6 more expected to start early in 2012.

It was questioned whether there was any concern that many BSUs had not yet started randomisation. It was explained that this delay was inevitable because, before randomisation could start, units needed to be in possession of a digital machine, be meeting NHS breast screening targets, and have obtained R&D approval; there were also resource issues. RP stated that the delays had been minimal considering that most randomisation was only due to start this year.

It was questioned when it could be expected that all 73 sites would have started randomising. It was stated that the majority of sites should have started in the next six

months, and most by the end of 2012, except for those with problems. It was asked whether further dropouts of units could be expected.

Action. KM to find out situation from the NHS breast screening programme.

Trial data

Study population data: This comes from National Breast Screening System (NBSS) local databases. The data will be downloaded annually at each BSU and sent to their regional QA Reference Centre (QARC) who will collect together the downloads for their region and send on to the Cancer Epidemiology Unit (CEU), University of Oxford. CEU has been getting permissions and procedures in place for the transfer of patient identifiable data from BSUs to QARCs to CEU where the trial data will be held. CEU has recently received first test extracts of these data and will shortly be ready to proceed with downloading study population data for all trial participants in batches randomized in periods 1 April 2009 - 31 March 2010 and 1 April 2010 - 31 March 2011.

Screening data for women randomized in: Data come from NBSS with similar process to above. Annual downloads of women offered a first appointment during 12 months 1st April - 31st March. These data are routinely finalized and cleaned on NBSS in October so our screening downloads will be taken each autumn to fit with this cleaning cycle.

CEU will issue instructions to BSUs on how to run extracts and transfer the data to their QARC. QARCs need up to date software for zipping the data before they can be uploaded to the CEU secure system.

Flagging for cancers and deaths at NHSCR: The permissions are all in place for this and once CEU have started accruing study population data batches will be sent for flagging at NHSCR.

Data management system at CEU: On arrival at CEU, encrypted files will be transferred to a restricted area on the CEU network to which only one or two named users will have access. Files that are received will be noted on the system on arrival and then processed to generate ID numbers and new data files. Personal details will be stored in a separate database but can be linked through ID numbers. All data is routinely backed up.

Other discussion points

Uptake of screening

The very low uptake of breast screening in London Kings in the pilot study was noted - it brought down the overall uptake rate in the pilot study. RP raised the issue of the statistical power of the trial, and the need to try and predict who, if invited, would come for screening. The possibility was discussed of obtaining data on previous uptake of cervical screening in the case of women aged 47-49, and previous uptake of breast screening in women aged 71-73, in order to predict the likelihood of attending breast

screening when invited. It was commented that it may not be feasible to link cervical screening records to breast screening records, and anyway previous uptake of cervical screening may not be predictive of uptake of breast screening. For women in the 71-73 age group, however, it should be possible to obtain information on the uptake of previous breast cancer screening invitations. It was concluded that there is a need to establish what factors are predictive of likelihood of attending screening.

Consent

With respect to consent, the standard procedures of the NHSBSP apply, whereby attending screening is taken as implied consent. Women aged 47-49 who are randomised out can request screening, if they wish. Women aged 71-73 can already request screening, as part of standard NHSBSP policy. It was questioned whether there had been many objections to this. It was clarified that there had not been objections in the pilot study. KM had regular meetings with the pilot sites during the study. Forms were completed by staff at the units to monitor the nature of the phone calls that were received from women who participated in the pilot study. Most calls concerned changing appointment times, although some from women in the lower age group were concerned as to the suitability of screening for women with breast implants or breast feeding. It was questioned whether women randomized out were informed that the trial was happening in their area. It was clarified that only the GPs are told. This approach has been approved by the ethics committee.

Action: The trial patient information sheet needs to be updated in light of the fact that there will now be two rounds of randomization.

3. Discussion and adoption of terms of reference

The DMEC discussed the following terms of reference as listed in the draft revised protocol:

- *To advise the Trial Management Group on any ethical issues that arise*
It was agreed by all members of the committee that the DMEC should take on an advisory role in both data and ethical issues.

- *To respond to any ethical concerns that are raised about the trial. (Such concerns should at first be communicated to the trial coordinator)*
It was agreed that the trial coordinator (KM) would bring any ethical concerns to the attention of the DMEC and that direct approaches could also be made to the DMEC, in both cases to JD as the Chair. As there is no formal independent trial steering group, it was agreed that the role of the DMEC should be to function independently of the trial team, and provide support and advice to the trial team.

- *To advise the Trial Management Group if, in the opinion of the DMEC, there is at any stage proof beyond any reasonable doubt that an additional screening invitation at ages 47-49 years (or at ages 71-73 years) is not appropriate for some or all women*

- *To advise the Trial Management Group if, in the opinion of the DMEC, there is at any stage proof beyond any reasonable doubt that an additional screening invitation at ages 47-49 years (or at ages 71-73 years) will definitely reduce breast cancer mortality by age 60 (or by age 80) without any material adverse effect on other mortality*

Action: It was agreed that the brackets around the reference to (or at ages 71-73 years) and (or by age 80) should be removed as they make older women look less important.

TM noted that the DMEC Terms of Reference will need to develop over time as issues arise.

RP noted that there would be no answers regarding the effect of screening on mortality until the late 2020s. Data on procedures etc should be available earlier.

JD summarized that the role of the DMEC will be as an advisory role to the Trial Management Group, and would make recommendations but not act as a decision making body. The DMEC members were happy with the terms of reference.

Action. TM asked that on the protocol his details were amended, deleting 'ethicist' and amending LSHTM ethics committee dates to '2001-08'. JD asked that 'information specialist' was deleted from her details.

4. Any other business

4.1. Ethical approval

It was questioned whether ethical approval had been received for two rounds of randomization. Kath Moser clarified that it had been and that she would circulate the letter granting permission for two rounds of randomization. Due to the amendments to the draft protocol, the ethics application will need to be resubmitted to include details of linkage with HES and cancer registry data.

Action: Kath Moser to circulate the letter granting permission for two rounds of randomization.

4.2. Recent press coverage/criticism of breast cancer screening

JD asked whether the recent press coverage and announcement of a review of breast cancer screening might have an impact on the trial. VB stated that this should not affect the trial, and will strengthen the reasons for doing the trial. Most of the criticism says that screening does more harm than good, and the linkage with HES data proposed as part of the trial will help inform this.

4.3. The structure of future DMEC meetings

The structure of future DMEC meetings was discussed. It was suggested that the meetings should be structured into three parts. The first part being an open session with the investigators, the second session a closed session with only the DMEC members and the trial statisticians present (Richard Peto and Gillian Reeves) to

discuss any issues regarding unblinded data, and a third part, a closed session, with members of the DMEC only.

5. Date of next meeting

It was agreed that the DMEC should meet annually (preferably in person rather than by teleconference), usually in October/ November to fit in with the schedule for the annual cycle for receiving screening data. It was suggested that the next meeting of the DMEC should take place as an in person meeting on the same day as the NHSBSP age extension trial management group meeting.