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04 November 2014

Professor Julietta Patnick
Director, NHS Cancer Screening Programmes
NHS Cancer Screening Programmes
Fulwood House
Old Fulwood Rd
Sheffield
S10 3TH

Dear Professor Patnick

Study title:	**EVALUATING THE NET EFFECTS OF EXTENDING THE AGE RANGE FOR BREAST SCREENING IN THE NHS BREAST SCREENING PROGRAMME IN ENGLAND FROM 50-70 YEARS TO 47-73 YEARS**
REC reference:	**10/H0710/9**
EudraCT number:	**N/A**
Amendment number:	**Amendment 3**
Amendment date:	**05 October 2014**
IRAS project ID:	**29856**

The above amendment was reviewed alongside a review of the ongoing ethical approval of the study at the meeting of the Committee held on 14 October 2014. Thank you for attending with Professor Dame Valerie Beral, Professor Sir Richard Peto and Mrs Heather House to discuss the amendment and the study.

Ethical opinion

The Committee requested that changes were made to the wording of the Participant Information Sheet, as specified below. In response to the Committee's request for changes, the Participant Information Sheet was amended as requested, apart from in response to point (h), where different wording was provided by you and your team. The Committee reviewed the amended Participant Information Sheet and subsequent to this agreed the amended wording with you. The Committee confirmed the ethical approval of the amendment on this basis.

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation. In light of the Substantial Amendment and the substantial revisions to the study protocol and participant information, and the addition of the Trial Poster, the Committee confirmed the ongoing ethical approval for the study on the basis of this Substantial Amendment.

The Committee requests that the research summary, at A6-1 of the IRAS form, is revised in light of the protocol amendments, in order that the new research summary can be published on the HRA website.

The Committee reminds you of the necessity of obtaining section 251 support from the Confidentiality Advisory Group to enable access to identifiable patient data without consent and to access HES data.

Changes requested:

The Committee requested the following changes to the Trial Participant Information Sheet:

a. Please amend the document title to read: "Breast screening age extension trial for women who are younger than 50 or older than 70."
b. Please amend the final paragraph on page 1 to read: "If you are younger than 50 or older than 70, we are inviting you for screening as part of this trial. Please read about the trial on the other side of this sheet." Please highlight this paragraph in bold.
c. Please amend the second sentence of the section 'Why do we need a trial?' as follows: "This trial will assess the potential risks of screening (number of women diagnosed and treated for a non-life threatening cancer) and benefits (number of lives saved) for these slightly younger and older women."
d. Please amend the fifth sentence of the same section to read: "It will take until at least the mid-2020s to get reliable information like that for women aged 50-70 years shown in the enclosed brochure 'NHS Breast Screening; Helping you decide'."
e. Please amend the final sentence of the same section to read: "The findings will help the UK government decide whether or not to widen the age range for routine breast screening for all women."
f. Please amend the second sentence of the first paragraph of the section 'What happens if you agree to take part?' to read: "This is done by allocating groups of women (clusters) at random, like tossing a coin, either for the whole group to be invited for screening, or for the whole group not to be invited."
g. Please add the following statement as a final sentence to the first paragraph of the same section: "So for either age range there will be two groups that can be compared over the following years, those women invited for screening and those women not invited for screening."
h. Please add the following statement as the penultimate sentence to the third paragraph of the same section: "It could be that more or less than 4 women need more tests and more or less than a hundred women need to be screened to diagnose 1 woman with cancer. Similarly, on page 11, the information obtained in this study might mean that more or less than 200 women have to be screened to save 1 life from breast cancer."
i. In the section 'What happens if you don't agree to take part?', please amend the second sentence to read: "If you are aged over 70 at the end of this year you will not be invited again for routine screening as that stops at 70, but you can still ask to be screened if you wish."
j. In the same section, please amend the first sentence of the second paragraph to read: "Women aged 47 to 49 who are not invited or initially decline this invitation but then change their mind can still ask to be screened if they live in an area that is participating in the trial."
k. In the same section, please add the following sentence to the end of the second paragraph: "Please ask your GP for details."
l. In the footer of the document, please change 'additional ethical approval' to 'ongoing ethical approval confirmed in 2014'.

Summary of the discussion at the meeting

Social or scientific value; scientific design and conduct of the study

The Committee asked you to justify this study and its social and scientific value.

You stated that the trial is assessing a modern screening programme against modern treatment, and whether there are any benefits or risks of extending the age range of breast screening.

The Committee sought clarification of Public Health England's intentions regarding extending the age range for screening, if it is not being performed as part of this research study.

You stated that you had been unable to get a firm statement on this from PHE recently, as their current strategic priorities are focused on the Ebola outbreak. However, they have stated that they want the study to continue and that they won't roll out the age extension to all eligible women until the results of this study are known.

Recruitment arrangements and access to health information, and fair participant selection

The Committee sought confirmation that not all areas of the country are participating in the age extension.

You stated that there are 81 breast screening units nationally. In 10 areas, some screening units have implemented the age extension for all women aged 47 to 70 or 50 to 73, others only invite women aged 50 to 70 as the clinic standard care, and all these women will only receive the standard screening leaflet, with no additional information. The women in these areas are not randomised when they are invited for screening, and they are not included in the study. In these areas, the decision to include or not include all women in the age extension was made locally, based on local politics and the method that they use to invite women for screening. You do not have access to the data from these women. Some of the data is publicly available as the screening data is reported, but it is not included in the study.

The Committee sought clarification that women in the age extension groups, who are not randomised to an invitation to screening, but who self-refer, will be screened.

You confirmed that women in the age extensions who do not get invited for screening due to randomisation can request to be screened, and this will be available to them. You will include this data in the study as intention-to-treat. You stated that there is technically no upper age limit to national screening; any woman over 70 can request to be screened. However, if a 90 year old woman requested screening, this data would not be included in the study.

The Committee queried whether they anticipated that large numbers of non-invited women would self-refer for screening.

You stated that this was unlikely, and you did not see this effect in the pilot phase of the study.

Favourable risk benefit ratio; anticipated benefit/risks for research participants (present and future)

The Committee sought clarification of the numbers of women to be involved in the study before you have an answer regarding the risks or benefits of extending the age range. The Committee noted that you will now also access Hospital Episode Statistics to assess any harms of the age extension, such as over-diagnosis and over-treatment, as well as mortality data.

You stated that you were always looking at data on over-diagnosis and over-treatment, but the amended protocol will now allow you to access and link with more detailed data. You stated that the effects of the extended age range will be seen more over the long term than in the next few years. The true results of the study will become apparent in approximately the next 15 years. Due to current treatments, that are now more conservative, particularly

when it is an early diagnosis, you are unlikely to see significant effects on mortality in the next 5 years as deaths from breast cancer are due to the cancer having spread. Screening programmes aim to diagnose cancer early to enable earlier, more conservative treatments.

You stated that, for the benefits and risks of the age extension to be known, you need to conduct the study with large numbers of participants and conduct long term follow-up. Therefore the true results will not be known until the 2020s it is possible that some results will be seen from 2015. Currently, approximately 500,000 women are enrolled into the study, roughly one third of whom are aged 70 – 73, and two thirds of whom are 47 – 50. You stated that study power calculations have been performed, and more reliable data will emerge with larger numbers, but you will still need a long-term follow-up period. Whilst uncertainty remains as to any benefits and harms of the age extension, it might be that the randomisation of women to screening continues in the extended age ranges, until clear evidence emerges as to whether it is beneficial or harmful. You confirmed that you need to see the natural history of breast cancers and the effects of time, to see whether the age extension has any effects on the incidence of breast cancer, the mortality data and treatments for breast cancer. You confirmed that the effects of more screening would normally be that more cancers will be detected, but at earlier stages and thus subsequent morbidity effects will also be seen earlier.

You stated that one of the reasons it was so important to conduct this study here in the UK is the wealth of NHS data that is available. The ability to link results with hospital data is essential as it enables you to look at treatment data, as well as other morbidities.

You stated that there are strong opinions on screening from various parties, but clear evidence is needed on the benefits and harms. You stated that you do not have strong feelings for or against screening; their primary aim is to obtain clear evidence on benefits and harms.

Care and protection of research participants; respect for potential and enrolled participants' welfare and dignity

The Committee noted that the women that are randomised to not be invited to screening as part of the age extension trial, do not receive any breast screening information at all. Women aged 70 - 73 will be aware from the standard screening leaflet, that they received with their previous screening invitations, that they can ask to be screened every 3 years after the age of 70, but women aged 47 – 49 will not be aware that they can ask to be screened from the age of 47.

You stated that this is why you have now produced a study poster. The screening units have a defined roster for carrying out screening, and invitations are sent out to women according to this roster. It is based on geographical area, not birthdates as in some other screening programmes (such as cervical screening), so women are not invited immediately they turn 50. You stated that, because of the way the screening programme is run in standard care, it means women are aged between 49 – 52 when they are invited for their first screening visit. Currently, GP practices in the area to be screened will be sent a letter informing them that women in that area are being invited to attend screening. You now intend to send the poster with this letter to the relevant GPs, and will ask the GPs to display the poster in their surgery in order to make women aware of the research, so that if they are randomised to not being invited for screening they can, if they wish, request screening from the age of 47. You confirmed that the current standard screening leaflet was revised in light of the Marmot review to reflect the increased risk of treatment for a non life threatening cancer and to clarify that 1 life is saved for every 200 women screened

The Committee requested that the Trial Poster is displayed in the mobile and static breast screening units, as well as in GPs surgeries. The Committee stated that it needs to be displayed as widely as possible to reach as many women as possible.

You agreed to this point and said it could also be displayed in hospital outpatient and breast surgery units.

Informed consent process and the adequacy and completeness of participant information

The Committee noted that there is no formal consent for screening or for the study.

You stated that screening, and subsequently the study, is run on the basis of implied consent. Women are invited for screening and are sent an information leaflet explaining potential benefits and harms, so if they attend for screening, it is implied that they have made an informed decision based on the information supplied to them. You stated that this is the same for all the national cancer screening programmes, and this study is not being conducted any differently. You stated that some women do withdraw from screening, either before or during the procedure. All staff are trained to be sensitive to this, and women are not pressured to continue with the screening.

The Committee noted that the new Age Extension Information Sheet has been significantly revised, but needs to state clearly that it is currently not known whether more or less harm is caused by the additional screening. The Committee stated that they will provide you with the wording that they require.

You agreed to this point.

Suitability of the applicant and supporting staff

The Committee requested that the Chief Investigator explain her professional background.

You stated that you are the Director of NHS Cancer Screening Programmes at Public Health England. You stated that this is for all Cancer Screening Programmes, not just breast cancer screening.

Independent review

The Committee sought clarification of how often the study data will be analysed.

You stated that the Independent Data Monitoring Committee will review the data at least annually, and they can request additional meetings and information or data as they see necessary. You stated that the terms of reference for the IDMC state that they can influence the Trial Steering Committee, for example, if evidence shows that one type of patient needs screening more than others, or one extended age range needs screening more than the other. You confirmed that trials such as these will influence national and global screening protocols for decades to come. Screening protocols are often based on pragmatic decisions, as well as the evidence that is currently available.

Other ethical issues were raised and resolved in preliminary discussion before your attendance at the meeting.

Approved documents

The documents reviewed and approved are:

Document	*Version*	*Date*
Copies of advertisement materials for research participants [Age Extension Trial Poster]	1	14 October 2014
Covering letter on headed paper [Response to REC concerns re amendment 1 and 2]		05 October 2014
Notice of Substantial Amendment (non-CTIMP)	Amendment 3	05 October 2014
Other [Response to Committee's comments on amendment]		28 October 2014
Other [Report of the Independent UK Panel on Breast Cancer Screening]		30 October 2012
Other [NHS Breast screening programme patient brochure]		01 January 2013
Participant information sheet (PIS) [Age Extension PIS]	3.3	31 October 2014
Research protocol or project proposal	3	05 October 2014

Additional documents reviewed as supporting documents, but not approved, were:

Document	*Version*	*Date*
Other [Protocol V2-3 TRACKED]		05 October 2014
Other [Protocol Amendment 2]	2	02 May 2014
Other [Protocol Approved 2010]	1	26 November 2009
Other [Protocol V1.2-3 TRACKED]		05 October 2014
Participant information sheet (PIS) [Trial PIS Approved 2010]	1.2	01 May 2014
Participant information sheet (PIS) [Trial PIS Amendment 2]	2	02 May 2014
Participant information sheet (PIS) [Trial PIS V2-3 TRACKED]		05 October 2014
Participant information sheet (PIS) [Trial PIS V1.2-3 TRACKED]		05 October 2014
Participant information sheet (PIS) [Trial PIS Amendment 3]	3	05 October 2014
Participant information sheet (PIS) [Trial PIS Amendment 2]	3.1	28 October 2014
Participant information sheet (PIS) [Trial PIS Amendment 3]	3.2	31 October 2014

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

10/H0710/9: Please quote this number on all correspondence

Yours sincerely

pp.

Dr Jan Downer
Chair
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Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Ms Heather House, Clinical Trials & Research Governance*
Ms Kath Moser

NRES Committee London - Harrow

Attendance at Committee meeting on 14 October 2014

Committee Members:

Name	*Profession*	*Present*
Mr David Anderson-Ford	Director of Research Ethics and Governance	Yes
Mrs Veronika Bernstein	Translator	Yes
Mr Andrew Caunce	Chief Pharmacist	Yes
Mr Kevin Coughlan	Retired	No
Dr Jan Downer	Consultant Anaesthetist (Chair)	Yes
Dr Annette Gilmore	Research Nurse	No
Miss Shelly Glaister-Young	Barrister (Alternate Vice-Chair)	No
Dr Mary Leung	Clinical Psychologist	Yes
Ms Ann Malkin	Consultant Psychologist	Yes
Reverend Catherine McBride	Vicar	Yes
Professor Liz Meerabeau	University Professor (Vice-Chair)	Yes
Mr Jim Wood	Retired IT Consultant	Yes

Also in attendance:

Name	*Position (or reason for attending)*
Miss Libby Watson	REC Manager