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20 March 2015

Dear Professor Bewley and Mr Rose,

I am writing in response to your challenge against the Research Ethics Committee favourable opinion given for the study '*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)* on the following grounds:

1. Abuse of process.
2. The failure to adhere to the standard set by Good Clinical Practice.
3. The characterisation of the research as merely 'epidemiological' rather than a clinical trial.
4. The wrongful claim that the scientific rationale is unchanged since 2010.
5. The failures of logic.
6. The irrelevance of the government's intention.
7. The protocol remains flawed.
8. The design and implied consent.
9. The outcome measures.
10. Misleading information given to the REC.
11. Inadequate reassurance of oversight by the Sponsor.
12. Inadequate oversight by Data Monitoring and Ethics Committee.
13. Lack of concern about consent.
14. The information women receive remains unclear and misleading.
15. The question of the CI being a fit and appropriate person.
16. The CI's refusal to allow publication of the protocol.
17. No timescales.
18. No training plan for NHS BSP staff nor for alerting and informing GPs.
19. No retrospective information to be given to women already enrolled.
20. Specific problems with GCP criteria.

Your challenge was discussed at the National Research Ethics Advisors' Panel (NREAP) meeting on 2nd March 2015 at Skipton House, London. The Panel considered your letter and sought evidence from Dr Jan Downer (Chair, NRES Committee London – Harrow) and Joan Kirkbride (Director of Operations and Approval). The Panel also had access to the full application and supporting documents relating to the study.

Following the meeting on 2nd March, the Panel asked for further assurances from the REC with regard to a number of issues raised by your challenge. A response was received from HRA Operations and the REC Chair and the Panel considered this additional information. Subsequently, Professor Andrew George, Chair of the NREAP spoke further with Joan Kirkbride and Jan Downer in relation to this response.

Following this review, the Panel has provided advice and guidance to the HRA, as the appointing authority, to consider whether the REC is required to review its opinion in light of your concerns or whether the challenge can be closed.

Following this full and comprehensive consideration, the HRA is satisfied that the REC review and opinion was fully compliant with Standard Operating Procedures and all relevant information had been considered. The HRA is satisfied the REC involved in the review of the application is correctly constituted in accordance with policy requirements and included those with appropriate experience and expertise with regard to the nature of the application under consideration. The HRA is satisfied due process has been followed and your challenge has therefore been closed.

Please see appendix 1 for our response to your comments raised, following advice and guidance from the Panel and information provided by the Committee.

Please note, no further challenge relating to the REC opinion will be considered unless this presents further new relevant information.

Yours sincerely,

Stephen Tebbutt
Board Secretary and Chief Executive Business Manager

Appendix 1 – HRA response to points raised in letter dated 29 December 2014

1. Abuse of process

a) The committee do not seem to have addressed, as separate matters, the continuing REC approval of the original study followed by the question of a substantial amendment.

Please see response to 1 c). The Committee has stated that no data (published work, comments by breast cancer specialists) had been provided by you to back up the points made and it was felt that the criticisms of the study had no substance.

The Panel was in agreement with the Committee with regard to this point.

b) They did not admit or hear from scientific and ethical concerns about the study to their deliberations

The original application and approval of this study was by Ealing and West London REC and has additional approval from NIGB under section 251 (NHS Act 2005) in February 2010. The REC was closed in 2011 and work transferred to Harrow. Only one member of that Committee, when the original application was approved, sits on the London - Harrow REC which has reviewed the subsequent Substantial Amendments etc., so the full Committee would have been unaware of the study and its original protocol prior to consideration of the submission at the meeting in October 2014. The revised protocol however was examined by the Committee in light of current science as presented at the meeting, and the Committee did not raise concerns in this regard. Three members of the research team and the sponsor were present at the meeting to provide full responses to the REC questions.

The Panel was unable to find any reference to third party written comments being considered in the REC minutes, however, whilst the final minutes do not explicitly state that the REC considered your representations, the Panel was satisfied that on the basis of communications between the HRA and yourself that the REC did indeed take into account your representations.

c) They did not examine the revised protocol anew as they should have, in view of the change from certainty to equipoise and in the light of changing science. Thus, the REC did not leave themselves open to a proper assessment which would have led to a different decision or outcomes.

This is the first time such a challenge has been received and there will obviously be some lessons to be learned from the process. The Committee noted you, and others, were in regular correspondence with the HRA about this study raising various concerns which were responded to in a timely manner. It was agreed that under SOPs (10.107), the REC would review outstanding concerns and review the ethical opinion for the study. There was no formal request for a single letter from you to fully detail your concerns and in future this should be requested. The content of the email attached was drawn to the attention of the REC (not the email itself) and this is what was considered at the meeting in addition to reviewing the substantial amendment ((SA) no 3) provided in response to previous unfavourable substantial amendment letters (no 1 and 2).

Additionally, the REC did review the 3rd version of the trial protocol as requested when considering whether the study should be allowed to continue. The Committee has advised it believed that the minutes of the meeting provide the evidence to support this review in that a number of issues outside those of the SA 3 were discussed and minuted. For example, consideration about the science and the need for the study was addressed (p3), further details re numbers etc. (p4), suitability of Prof Patnick was addressed (p5). Consideration was made at a full REC meeting with four members of the research team in attendance. The REC was reassured that the risks of mastectomy were being addressed because treatment data and outcome would be obtained for the women in the cluster trial.

d) The redaction of REC committee member names is not justifiable.

Committee members are not personally held to account as the decision made by any Committee is a joint agreed decision and the HRA provides indemnity to RECs under the Governance Arrangements for Research Ethics Committees (GAfREC – Annex D: Functions of Appointing Authorities). Members are able to dissent a decision if they do not agree with the decision made by the Committee, but this was not the case in this circumstance. There was some concern that individual members may be targeted by those with issues regarding the study in the light of the continued correspondence referenced above.

e) Please also refer to a recent publication inviting more legal scrutiny about the trial governance.

The Panel noted that neither the HRA nor the Harrow REC is obliged to take note of this publication as part of their response to this challenge. The HRA accepts this recommendation.

2. The failure to adhere to the standard set by Good Clinical Practice.

The running of the study in accordance with the principles of ICH GCP is primarily the responsibility of the Sponsor but adherence to these principles is inherent in the considerations that had to be satisfied before giving REC approval. However, it has not been clearly explained or substantiated what are the supposed failures to adhere to ICH GCP.

The Panel agreed that the challenge letter does not clearly explain or substantiate the supposed failures to adhere to ICH GCP.

3. The characterisation of the research.

The Panel agreed that the labelling of the study is a matter of semantics that does not impact upon the appropriateness of the ethical review of study. The HRA accepts this advice.

4. Wrongful claim that the scientific rationale is unchanged since 2010.

The conclusions of the Marmot Report endorse a study. It does not specifically state this particular study, but the Terms of Reference for the Marmot review would not have been to review any particular study. With regards to cost effectiveness, this is one of the outcome measures for the study.

The Committee was aware that the rollout of the age extension trial is occurring in some areas of the country irrespective of whether the study is going ahead. Where this is happening, those attending for breast screening receive the standard national screening leaflet and not the additional trial information.

What is stated on the trial website and by the Data Monitoring and Ethics Committee (DMEC) etc. is not the responsibility of the REC, but of the Sponsor. The Committee acknowledge that the website could be updated though, as the figures provided are from 2012.

The Panel was in agreement with the Committee with regard to this point.

5. There are failures of logic.

The HRA notes Committees have to largely trust researchers to submit amendments. The HRA has already acknowledged that the time lag between the submission of the original amendment and the submission of the final approved amendment was too lengthy. The HRA has now flagged this on its HRA Assessment and Review Portal (HARP) database to ensure that where amendments are required to be resubmitted, that an alert to chase is in place. The Committee has advised the amendments made to the study make it more robust. The Substantial Amendments that were not approved did include some other

changes that were not subsequently adopted in the revised protocol, such as the additional scans post 73 years.

6. The irrelevance of the government's intention.

RECs are independent and impartial. The Committee considered the Substantial Amendment and ongoing ethical approval in isolation to any interventions from any party. The Committee was interested to know the Department of Health's intentions, but it would not have influenced the Committee's decision.

7. The protocol remains flawed.

Under GAfREC, appropriate peer review is the responsibility of the Sponsor and which should provide assurance to a REC. RECs are not required to request additional peer review where peer review will have been undertaken by funding bodies. The protocol co-authors are leaders in their field; the study is funded by the Department of Health via Public Health England, Cancer Research UK and the Medical Research Council and was discussed at a multidisciplinary group including patient representation before obtaining the initial ethical approval. The data monitoring and ethics committee contains a wide range of appropriate expertise which can be viewed as providing ongoing peer review. So the Committee do not see that additional peer review is required, or which additional individuals would be required to review the study. The Committee has advised it did not need to see additional peer review to reassure it on the scientific justification or design of the study.

The Committee has advised it was aware of a recent Dutch study, '*Effect of implementation of the mass breast cancer screening programme in older women in the Netherlands: population based study*' (ref 1) which stated the following:

> "*Interestingly, Cancer Research UK is currently undertaking a large randomised controlled trial (clinical trials register NCT01081288) within the UK National Health Service breast cancer screening programme in women aged 71-73 years in which an age extension from 70 to 73 years is randomly phased in, allowing the investigators to evaluate the effects of screening on breast cancer incidence and mortality. Until the results of this trial become available, we propose that routine breast cancer screening in women aged more than 70 years should not be performed on a large scale."*
> *Ref 1} BMJ 2014; 349 doi: http://dx.doi.org/10.1136/bmj.g5410 (Published 14 September 2014) Cite this as: BMJ 2014;349:g5410*

Following the review by the Panel, it did not consider that you had demonstrated that the protocol is 'flawed'. The panel further noted that the length of a protocol is not related to its quality.

8. The design and implied consent.

The Committee has advised that the consent issue was considered thoroughly. The Committee agreed that if a participant is presented with information and they attend their appointment, the Committee was satisfied that consent was implied as the trial represents the conditions that are in place for the routine NHS breast screening programme in which the age extension is being assessed. Those attending in the trial also receive the national breast screening information leaflet in addition to trial specific information. With regards to women who are randomised not to be invited to the study, the Committee requested and agreed that new measures should be put in place, such as the poster for GP surgeries, to improve the robustness in trying to inform all women, including the controls, and if women request screening who are not invited in the 47-50 or over 70 groups, it will not be denied to them. After the researchers left the Chair recalls asking the Committee if it was satisfied with the response about using implied consent, as used in the national screening programme and the comment was made that it should replicate the current screening process. It was also felt that the improvements made to the trial

participant information sheet also made it more clear that the age extension was part of a clinical trial and that there was uncertainty about the risks or benefits of an additional screening visit.

Following discussion between Andrew George and Jan Downer, in which it was indicated that this was a critical area of consideration both in the rejection of the earlier amendments and for the third amendment, the Panel accepted that, on the balance of probability, this issue was adequately discussed by the REC. The REC will be asked to revisit this point at their next meeting to ensure that there is an audit trail of the discussions.

9. The outcome measures

'All-cause mortality' is not a suitable outcome measure as the trial is not powered for this outcome.

The Committee has advised it sees this as a difference of opinion to your own. The researchers have stated in the Protocol that they will look at and report on all-cause mortality, but they do not know until they get to the end of the study whether any differences seen will be significant or not. The Committee was satisfied with the equipoise demonstrated by the researchers and this is why it is an epidemiological study, as the researchers are looking at this data over a long period of time. The researchers cannot have a fixed endpoint over this period of time as there are too many variables over the next 15 – 20 years, which is the duration of the study.

The Panel was in agreement with the Committee with regard to this point.

10. Misleading information given to the REC

The Committee has advised the reference *"1 life is saved for every 200 women screened"* which you are referring to was in the standard breast screening leaflet, *'NHS Breast Screening, helping you decide'* which is outside the remit of the review by the REC. The Committee has advised with regards to there being no references on page 6 of the Protocol that this is because the researchers are referring to their own data that they have obtained.

The Committee has advised this study is assessing the effects of age extension extra scans, not the totality of breast screening. The researchers considered that there would be insufficient power to assess reliably the effect of additional breast screening on all-cause mortality. The researchers' opinion was supported too by Prof Jane Wardle 'Academy of Medical Sciences' in her evidence to the Science and Technology Committee published in October 2014.

The Panel was in agreement with the Committee with regard to this point.

11. Inadequate reassurance of oversight by the Sponsor.

The Committee and Panel agreed it is not the REC's responsibility to monitor the conduct of the trial; that lies with the Sponsor.

12. Inadequate oversight by Data Monitoring and Ethics Committee.

The REC was satisfied that a DMEC is in place with appropriate expertise and confers no less than once a year. The REC has no responsibility for the DMEC; they just need to be satisfied that there is one.

The Panel was in agreement with the Committee with regard to this point.

13. Lack of concern about consent

The Committee and Panel agreed this is opinion only and therefore we are unable to comment further.

14. The information women receive remains unclear and misleading

The Committee advised it would be ideal if women aged 47-49 and 70-73 had separate Patient Information Sheets, but the REC understood that studies need to be designed with practicality in mind, so took a pragmatic approach and accepted the researchers' argument. Most of the women will not be new to screening anyway, only the 47-49 year olds. The Committee acknowledged that it is known that a first call for screening is always more likely to mean a recall, irrespective of the woman's age, as there is a lack of prior data for comparison, and women also have denser breast tissue at a younger age so screening is more difficult.

With regards to the Invitation Letter, the Chair acknowledges that the Committee should have seen this alongside all the other information. However, it is a standard letter that is sent to all women regardless of the study, and is outside of the REC remit to review.

The Committee noted with interest that the standard clinical information leaflets were produced in collaboration with King's Health Partners.

15. The question of the Chief Investigator being a fit and appropriate person

The Committee advised it approved the whole research team and noted the eminence of the collaborators in their respective fields. Someone always needs to sign the IRAS form as Chief Investigator, but is not approved in isolation. Professor Patnick is best placed to organise the research in the cancer screening units while the data analysis is undertaken by very experienced researchers.

The Panel was satisfied by the Committees response to this point.

16. The CI's refusal to allow publication of the protocol

The Committee was unable to comment, but the HRA supports publication of protocols as part of its transparency agenda. Under the HRA's Freedom of Information Guidance, however it is recognised that *Section 41 – Information provided in confidence*, could be considered in certain cases as the protocol could reasonably have been submitted with the view that it is information provided in confidence.

17. No timescales.

It is the responsibility of the Sponsor to ensure compliance and there is an expectation that researchers will do this.

18. The researchers have described no training plan for NHS BSP staff nor for alerting and informing GPs about the dramatic change in the quality and quantity of information women will get.

The Committee has advised that posters will be displayed in GP practices. The Committee noted it is the job of screening staff to conduct screening therefore the committee was satisfied staff would be suitably qualified as this was their day job. The screening programme will have protocols in place for managing distress etc. as part of routine care, not research. Again, it was felt this is expressing a personal opinion. The women in this trial will have or have had breast screening as part of the NHS routine screening programme thus DCIS would be picked up in subsequent routine scans for the age 47 cohort.

19. There is no retrospective information to be given to women already enrolled in the light of these changes

The Committee advised it accepted the original PIS needed improvement however agreed the original was also sufficient for its purpose at the time. The Committee noted women recruited in the past would have been treated in the same way as the ongoing trial - albeit with better information but this applies

to all women in the screening programme as the standard leaflet has been improved over time and in light of the Marmot report thus there would not be a need for retrospective consent.

The Panel accepted this response.

20. Specific problems with GCP criteria

The Committee advised the DMEC and Trial Steering Committee (TSC) will be monitoring the study, and the REC approves the whole team, not the CI in isolation. In terms of organising and running the study, the Committee advised Professor Patnick is the most appropriate person as she is the best placed person to understand how to approach the study population and design the study with regards to the standard screening programme.

The Committee has advised Prof Patnick has co-authored many scientific papers, is a visiting professor cancer screening in Oxford and a fellow of the faculty of Public Health.

4.8.3. The Committee has advised the new standard leaflet and the trial leaflet are clear that although lives are saved from breast cancer, some women will be diagnosed and have treatment for breast cancer that would not have become life-threatening; the 'risk' of breast screening.

4.8.8. The Committee has advised that written informed consent is the gold standard, but many studies do not have this as they also have to be pragmatic. There has not been a change in the 'consent' position. The researchers have always been in a position of equipoise – hence the reason for the trial.

4.8.10. The Committee was satisfied with the information provided. The study is concerned with the age extension of the existing NHS breast screening programme.

5.1.1 & 5.1.3. The Committee has advised these points are the responsibility of the Sponsor and not the REC.

The Panel accepted this response.