

Women's Health Academic Centre

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29 December 2014

Dear Stephen Tebutt

Re: Appeal against REC Favourable Opinion and continuing approval for the age extension trial

We refer to all previous correspondence. This appeal letter replaces that of 8 December 2014.

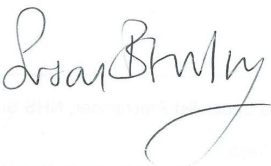
We thank Joan Kirkbride for her prompt and thorough assistance. We commend the REC for agreeing with many of our concerns and dealing with some of the trial's problems such that the researchers have at last made substantial changes to the Patient Information Sheet (PIS).

However, we wish to appeal the 14/01/14 Favourable Opinion decision on the following grounds (outlined in more detail in the Table attached):

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.

We find the REC process inadequately informed. The decision is unjustified and perverse.

With many thanks in advance for taking this seriously.



Susan Bewley MD FRCOG
Professor of complex obstetrics



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No	Complaint	Comment
1	<p><u>Abuse of process.</u></p> <p>a) The committee do not seem to have addressed, <i>as separate matters</i>, the continuing REC approval of the original study <i>followed by</i> the question of a substantial amendment.</p> <p>b) They did not admit or hear from objectors who have scientific and ethical concerns about the study to their deliberations. Thus, they did not fully take on board the critique.</p> <p>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.</p> <p>d) The redaction of REC committee member names is not justifiable.</p> <p>e) Please also refer to a recent publication inviting more legal scrutiny about the trial governance¹.</p>	<p>All these matters are against natural justice.</p> <p>There was no possibility of revoking the initial decision of another committee that may have made a mistake.</p> <p>The committee was addressed by, and did not take account of, the conflicted Chief Investigator and her scientific credibility.</p> <p>The REC de facto approved the v1 2009 protocol at the same time as finding it needed to be substantially improved.</p> <p>The REC members cannot be held to account.</p>
2	<p><u>The failure to adhere to the standard set by Good Clinical Practice.</u></p> <p>Whilst the present trial does not involve an investigational medical product, and is thus not subject to clinical trials legislation, it is described as the largest ever randomised clinical trial and the protocol states that harms as well as benefits will be assessed. We would therefore ask how anything less than best practice, i.e. ICH Good Clinical Practice (GCP) standards², would apply, especially as it is publicly funded.</p>	<p>The EU has adopted ICH GCP and member states have in turn transposed EU law into national law. All reputable UK medical researchers, whether in universities or the pharmaceutical industry, work to GCP standards. We expect no less of this trial and believe others would expect the same. Without GCP, it is only the research ethics committee (REC) process that protects members of the general public who are invited to participate in research that may harm them.</p>

¹ Bewley S. Legal scrutiny of the age extension breast screening trial is required. *Medico-Legal Journal*. 2014;82(4):167-8

3	<p><u>The characterisation of the research.</u> The minutes refer to an “<i>epidemiological</i>” study. It is not. It is a <i>clinical trial</i>.</p>	<p>The researchers have used misleading information to recruit participants, inviting healthy citizens for a screening mammogram, now known (since the Marmot review³) to be of uncertain benefit at these ages, but definitely risking anxiety and mutilating surgery. Even if it were an epidemiological trial assessing or monitoring a government policy before in an ‘opportunistic way’, then it cannot be the same now with ‘equipoise’.</p>
4	<p><u>The claim wrongful claim that the scientific rationale is unchanged</u> since 2010. The researchers previously thought screening to be a benefit (see the original 2009 protocol, still in operation) and that overdiagnosis was only a “<i>so-called</i>” phenomenon. The Marmot review only endorsed a trial in principle, not this trial in particular. The Marmot team had not seen the protocol. What the CI told the REC is different from the trial website⁴, which still says today: “<i>The age extension will proceed regardless of whether this study goes ahead or not, and therefore regardless of whether the phasing-in is randomised or not.</i>” She now says that roll-out will depend on trial results. So something dramatic has changed; we believe the previous certainties around the evidence changed into uncertainties and thus the rationale changed.</p>	<p>It is recorded in the DMEC minutes from Jan 2014 that the roll-out will not proceed until trial results are available. The research team has known for about a year that this is a trial that is ‘in equipoise’ (and should have realised from much earlier). Once the researchers had agreed about the equipoise, the DMEC should have been alerted and immediately insisted on amending the procedures to reflect that (or halting the trial until the procedures were amended). The trial webpage needs to be updated.</p>
5	<p><u>There are failures of logic.</u></p>	<p>If nothing changed in the scientific rationale, then why was a substantial amendment and new protocol required? If the researchers recognised that a higher standard of information was required, how was it acceptable for them to continue with a lower standard of information for so long, and how does it remain acceptable so many weeks after the REC meeting?</p>

² International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

<http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/good-clinical-practice.html> Good Clinical Practice (GCP) is an international quality standard that is provided by ICH, an international body that defines standards, which governments can transpose into regulations for clinical trials involving human subjects.

³ Marmot MG, Altman D, Cameron D, Dewar J, Thompson S, Wilcox M. The Benefits and Harms of Breast Cancer Screening: An Independent Review. Cancer Research UK and the Department of Health (England) 2012

⁴ ISRCTN website <http://www.isrctn.com/ISRCTN33292440>

6	<p><u>The irrelevance of the government’s intention.</u></p> <p>It is puzzling why the government’s intention would be relevant to the REC’s determination about science and ethics. The government’s intention should have been clarified before the REC meeting, rather than being allowed to be formulated after (and dependent upon) the REC determination.</p>	<p>Were the REC making their determination dependant on this intention, or trying to second-guess it?</p> <p>You may be aware that the House of Commons Science and Technology Committee have asked Public Health England (PHE) for the evidential basis of the age extension.</p> <p>These considerations could look as though the REC was ‘bullied’ into approving the trial in the first place, and is now again deferring to the government’s will.</p> <p>If the government wishes to defend a changed position from the previous policy of extension (when there was no evidence), it is likely to now use this HRA REC ‘approval’ as a <i>retrospective justification</i> to hide behind.</p> <p>Thus, there is a danger that the independence of the REC process itself will be brought into disrepute, both nationally and internationally.</p> <p>No trial should be ‘too big to fail’ if it has not been asking a proper and answerable scientific question in an ethical fashion for many years.</p>
7	<p><u>The protocol remains flawed.</u></p> <p>The new protocol is now 11 pages long with 11 references (virtually entirely self-citation). It still does not appear to have sought or received the benefit of peer review. The background is descriptive, rather than making the case for a trial and contains an odd ‘opportunistic’ justification. There is no research question, just an assertion under ‘Aim’ that <i>“The cluster-randomised Age Extension Trial will assess reliably the risks and benefits of offering an extra screening invitation”</i>.</p>	<p>Attached at the end of this table (at 20) are a number of further observations about how the protocol fails GCP standards.</p>

8	<p>The design and implied consent. We do not accept that the case for continuing with implied consent was made well enough (indeed it was not made at all in the ‘new, improved’ 2014 protocol).</p> <p>Additionally, the comparison made with screening services is irrelevant; <i>“The researchers stated that this [procedure for implied consent] is the same for all the national cancer screening programmes, and this study is not being conducted any differently”</i>.</p>	<p>The REC should have held this team who are playing ‘catch-up’ on good research practice to a high threshold. We disagree that it is not feasible to gain individual consent – indeed it is vital. It is a poor and weak argument that the cluster design has to remain simply because that’s how it started. The new PIS goes some way to redressing the problem but not far enough.</p> <p>The researchers seem to wilfully elide the distinction between service and research. It is irrelevant that there is implied consent for other screening programmes. This isn’t a normal screening programme. It is an RCT, i.e. a human experiment, and the REC should have recognised the difference.</p>
9	<p>The outcome measures.</p> <p>There is no proper primary outcome measure. It is extraordinary, given the planned size, that the researchers have not chosen all-cause death as an endpoint, nor any other measures of harm. If matters are uncertain, surely the chance of causing more harm than good would be missed by such a biased approach? All-cause death is not mentioned in the Data Collection section although it is in the summary. The last paragraph on page 5 (primary analyses) is very woolly indeed.</p>	<p>We would have anticipated a properly referenced discussion - with data - on arguments for and against all-cause mortality as an endpoint, especially given this issue being raised by Marmot 2012, rather than an admission that it hasn’t even been formally addressed; it’s just ‘expected’ not to work rather than calculated (<i>“there is expected to be insufficient power for crude analyses of all-cause mortality to assess reliably the effect of additional breast screening on all-cause mortality”</i>) and another composite outcome <i>“may well come from combining”</i> measured effects with reported effects <i>“assuming no other effects on mortality”</i>. Quite! This assumption cannot be made, and this study (the only one large enough to confirm or refute the assumption) resolutely won’t look! Surely this is critically important, or the whole trial is a waste of time and money?</p>
10	<p>Misleading information given to the REC</p> <p>If the CI stated verbally to the REC (as per minutes) that <i>“1 life is saved for every 200 women screened”</i>, then the committee was misled.</p>	<p>There has been no evidence of an impact on all-cause mortality, only a reduction in deaths from breast cancer (again confirmed by Marmot and Cochrane⁵ reviews). The eliding of deaths from one cause with ‘saving a life’ is simplistic, and might be used in the public domain, but is inappropriate in a serious research context. There are also unreferenced assertions and assumptions made regarding the trial. For example, no source is cited in the last paragraph of page 6 for the <i>“about 1500”</i> women who would be estimated to die between 48 and 60 of breast cancer.</p>

⁵ Gøtzsche PC, Nielsen M (2011). Cochrane database of systematic reviews (1):CD001877

11	<p><u>Inadequate reassurance of oversight by the Sponsor.</u> We are worried that the REC did not explore the role of the sponsor who is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol and applicable external requirements</p>	<p>For example, we found the enrolment figures confusing. DMEC minutes in 2014 estimated that 0.8m women are already enrolled, the REC minutes state 0.5m, and yet the PIS says 1.5m. This looks sloppy and does not reassure that the researchers have a handle on recruitment, or that the trial master file is maintained or site monitoring happening.</p>
12	<p><u>Inadequate oversight by Data Monitoring and Ethics Committee.</u> There is no description of this in the protocol, and see comment above in (3) about a lack of ethical oversight with the change in rationale. What are the monitoring systems for looking for adverse events?</p>	<p>For example, how would the triallists recognise an unintended consequence (say a rise in suicide or heart disease), or a dramatic rise in bilateral mastectomy? What would lead to stopping the trial for futility or for harm before 2026 (the end date on the website, though no date given in the protocol)?</p>
13	<p><u>Lack of concern about consent.</u> We note the comment (top of p7 in protocol) that <i>“Improved compliance would increase statistical power”</i>. This has replaced a previous claim that <i>“it is essential to get 100% coverage”</i> as if this mattered more than the science or ethics.</p>	<p>We are concerned that the previous lack of information to participants was deliberate, in order to enhance compliance. We are surprised that there is no detailed discussion about the new rationale for changing to a more explicit approach (albeit with no formal record of understanding and consent) or the impact this might have on uptake rates, and thus the viability of the trial.</p>

14	<p><u>The information women receive remains unclear and misleading.</u></p> <p>The proposed PIS is somewhat more honest and informative than before. It should be a ‘tailored’ invitation leaflet for the trial. It is wrong to post it out along with the accompanying NHS leaflet⁶ - the latter designed to encourage 50-70 year olds to attend -as the information regarding a <i>service</i> simply does not apply to them in a <i>research</i> trial.</p>	<p>The trial continues to be entangled and entwined within the NHS BSP. Although the NHS information has changed during the period of the study, it does still not spell out the risk of ‘overdiagnosis’ in terms of specifying this means anxiety, surgery, chemo and radiotherapy. But that is a different objection to be addressed elsewhere.</p> <p>The smooth presentation of the pink booklet contradicts the necessity for trial participants to understand the uncertainties, and thus will only confuse. What is the point of having one leaflet saying ‘the numbers in the other leaflet don’t apply’?</p> <p>In addition, the REC has given no instruction regarding the covering invitation letter which often says “<i>remember, screening can save your life</i>” in very large font (maybe driven by attendance targets) which contradicts the caution in the PIS. Women will continue to believe that they are simply being invited for regular screening.</p> <p>The PIS wrongly states that it is not known whether more or less women will need more tests; the researchers themselves have published a doubling of recalls in 47-50 year olds⁷, and much higher overdiagnosis rates have been reported in women over 70.</p>
15	<p><u>The question of the CI being a fit and appropriate person</u> was inadequately addressed.</p>	<p>Noting Professor Patnick’s day job role and qualifications in the minutes was not an appropriate way to assess her suitability for the <i>research role</i>, which demands scientific credibility and integrity.</p> <p>Our concerns and objections remain unanswered.</p>

⁶ Gigerenzer G. The Art of Risk Communication. Breast cancer screening pamphlets mislead women BMJ 2014;348:g2636

⁷ Moser K, Sellars S, Wheaton M, Cooke J, Duncan A, Maxwell A, Michell M, Wilson M, Beral V, Peto R, Richards M, Patnick J. 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. doi: 10.1258/jms.2011.011065.

16	<p><u>The CIs refusal to allow publication of the protocol.</u></p> <p>We obtained the original protocol only after several FOI requests and put this into the public domain.</p> <p>We have been refused permission to do this again, ostensibly as it may impact on the ability to publish in peer review journals.</p>	<p>It would appear that the researchers have not heard of the current standards of transparency and are unaware that it is considered better scientific practice to publish your protocol in advance, so as to be held account to it. Commercially sponsored protocols are commonly published in full, not just as a very brief summary as for this trial's original protocol. Publishing the protocol would not impact on the ability to publish, unless there was unjustifiable deviation (which would be poor practice).</p> <p>The CIs refusal to give permission to publish the new protocol will only add further suspicion that the safety processes and 'many eyes' of science are not working; those of competency, humility and transparency amongst others.</p> <p>Additionally, it is not for the CI to decide, as it is the sponsor who owns it, not the CI.</p> <p>This is very worrying as it adds to concerns that the sponsor is not able to exert oversight. The researchers may be eminent, but they should not command undue respect.</p>
17	<p><u>No timescales.</u></p> <p>The REC has found that the present protocol and procedures must be substantially improved, and yet it has allowed the (presumably substantially poorer) study to continue in the meantime.</p>	<p>All these improvements were required from the outset and certainly should have been initiated by a competent research team over two years ago. The REC has given a green light and 'open-ended' Favourable Opinion, with no deadlines by which to receive materials nor even to have seen whether they are improved.</p> <p>Today, nothing has changed. The same letters, leaflets and misleading information are still being sent out. Indeed, I have just received the very same information myself. The REC is toothless and women are not being protected.</p>
18	<p>The researchers have described <u>no training plan for NHS BSP staff nor for alerting and informing GPs</u> about the dramatic change in the quality and quantity of information women will get.</p>	<p>How will staff all over the UK who've been implementing the almost hidden age extension trial be able to handle questions from women that may arise now it's more explicit? Particularly, how will they answer questions from women who went through the trial over the past four years, or women who are only found to have very distressing abnormalities such as DCIS because they are in a research trial? We note that GCP requires all trial personnel to be properly trained, and for this to be documented.</p>

19	There is <u>no retrospective information to be given to women already enrolled</u> in the light of these changes	The number is thought to be somewhere between 0.5-1.5 million women. Will they be sent an explanation, or receive a copy of the new PIS with an apology for having previously been misled and ill-informed about taking part in the RCT? If not, why not? Having determined that the information should be improved, this backlog is still within the responsibility of the HRA REC.
20	<u>Specific problems with GCP criteria</u> outlined below	
	<p>4. Investigator</p> <p>4.1 Investigator's Qualifications and Experience.</p> <p>4.1.1 The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or the regulatory authority(ies).</p>	Although the ICH doesn't say anything directly about conflicts of interest, we believe that is a given, considering scientists have to be alert to the problem of bias. The CI is highly-conflicted; by history, funding, employment and 'marking her own homework'. All trial personnel must be qualified by education, training, and experience. Professor Patnick has no science qualification, has not shared her training record, and does not even attend or send apologies to the study's Data Monitoring and Ethics Committee.
	<p>4.8 Informed Consent of Trial Subjects</p> <p>4.8.2 The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent (our bold). Any revised written informed consent form, and written information should receive the IRB/IEC's approval/favourable opinion in advance of use. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.</p>	The written information was inadequate from the outset. The information sheet was not amended in a timely manner. Informed written consent is not taken. There is no documentation of the communication.
4.8.3 Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.	The covering letters (containing large font injunctions such as "Remember, screening could save your life") and the 16 page pink leaflet, along with the misleading trial information act to unduly influence participation in the trial.	

	4.8.8 Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.	The consent situation changed; (a) because of Marmot 2012 and (b) because the researchers are now saying that the full roll-out will await trial results. So this is now an investigational trial where the sponsors are (apparently) in equipoise.
	4.8.10 Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:	The guidance provides a long list of items to be included. It might not be appropriate to insist on all these, but a lot of key ones have been missed, even in the new leaflet.
	5. Sponsor	
	5.1 Quality Assurance and Quality Control	
	5.1.1 The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).	There is no reference to this in the protocol or DMEC minutes.
	5.1.3 Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.	There is no reference to this in the protocol or DMEC minutes.

<p>6. CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT(S)</p> <p>6.1 General Information</p> <p>6.2 Background Information</p> <p>6.3 Trial Objectives and Purpose</p> <p>6.4 Trial Design</p> <p>6.5 Selection and Withdrawal of Subjects</p> <p>6.6 Treatment of Subjects</p> <p>6.7 Assessment of Efficacy (ie beneficial outcomes)</p> <p>6.8 Assessment of Safety (ie adverse outcomes)</p> <p>6.9 Statistics</p> <p>6.10 Direct Access to Source Data/Documents</p> <p>6.11 Quality Control and Quality Assurance</p> <p>6.12 Ethics</p> <p>6.13 Data Handling and Record Keeping</p> <p>6.14 Financing and Insurance</p> <p>6.15 Publication Policy</p> <p>6.16 Supplements</p>	<p>The protocol remains inadequate. It has expanded somewhat from 8 to 11 pages, and from 2 to 11 references (largely self-cited).</p> <p>GCP guidance lists the main sections of a protocol (see left). It does not have to be slavishly followed, and headings can be modified. However, the emboldened ones are essential for this trial.</p> <p>The EU Directives require a full set of protocol appendices; team CVs, data capture tool, statistical methods, Quality Control of analytical equipment, standards for reading mammograms and much more.</p>
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