Author's response to reviews

Title: Impact On Mortality And Cancer Incidence Rates Of Using Random Invitation From Population Registers For Recruitment To Trials

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Version: 4 Date: 4 February 2011

Author's response to reviews: see over
27th Jan 2011

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Dear Sir/Madam,

As requested, please find attached the manuscript which has been revised in line with your editorial comments.

Reviewer’s report #1
Title: Impact On Mortality And Cancer Incidence Rates Of Using Random Invitation From Population Registers For Recruitment To Trials.
Reviewer: Johannes Blom

Major Compulsory Revisions:
1. Overall, the manuscript is very well written with impressive statistical work. But, is the question posed really answered? The study is more a product of the necessitated revision of the design of the ongoing screening trial (see Conclusions). The ongoing RCT should be highlighted.

The reviewer is not correct in describing the study as a product of the necessitated revision of the design of the ongoing screening trial. Random Invitation from Population Registers was a key design feature in UKCTOCS in comparison to other trials such as PLCO and was undertaken in the anticipation that there would be a diminished HVE. This was detailed in a previous paper - Menon et al. Recruitment To Multi-Centre Trials: Lessons From UKCTOCS – Descriptive Study. BMJ 2008). Throughout the period of recruitment, women were repeatedly turned away if they self referred and all trial publicity included the statement that only those invited could participate.

The ongoing RCT and events that resulted are clearly described in the conclusion.

“In UKCTOCS, the HVE has necessitated revision of the trial design in 2008, with extension of screening in the study arm until 31st Dec 2011 and follow up until 31st Dec 2014.”

2. One of the major determinants of a screening program’s effectiveness (or efficacy within RCT) is the compliance. There will always be a self-selection to screening of more healthy individuals with probably less risk of the disease and early mortality, as compared both to the non-participants and to the general population. This will occur with or without random invitations. This self-selection effect will be less with a high participation rate. The overall compliance in this study is only 16% and this is not discussed at all.

The reviewer has confused ‘compliance’ with ‘acceptance rate’ to participate following invitation, which is usually understood to mean compliance with the study protocol once enrolled. In particular, in a screening trials/programme it means compliance with repeated rounds of screening.

The reviewer raises a valid point that higher participation may have reduced the HVE, and we have included it in the Discussion.

“25% of women invited replied that they would like to participate in the trial but finally only 16% joined the trial [5]. Higher participations rates may have reduced the self-selection effect.”
3. The discussion should be focused on compliance and selection bias. How were the people invited? Usage of reminders? This affects the generalizability of the results to ongoing screening programs. The discussion currently has too many details, e.g. the incidence rates of specific cancers.

There has been a detailed paper on recruitment process – Menon et al BMJ (2008). We have clarified this in Methods “Detailed description of the invitation and recruitment process as well as inclusion/exclusion criteria are detailed elsewhere” ...

...and added to the discussion.

“...self refer or invited through mass mailings using motor-vehicle registrations and health care organization lists which were not generally population based [11]. This introduces additional bias as the type of advertising media (radio station, website, newspaper or magazine) or mailing lists used, limit those who have access to the information.”

We have included details of a variety of cancers so that the information is available to other trialists planning future trials and using similar strategies to recruit patients.

Minor Essential Revisions:
1. How could the younger, as discussed, less morbid people have a higher mortality? This discussion should be extended since it is one of the significant findings.

We agree with the reviewer that this is interesting. We were unable to find in the literature reports where differences in (age-adjusted) SMR were explored by age and this has been added to the discussion (see below).

Currently we have no more data to derive any further insights to explain this finding.

“It is interesting that the younger age groups, specifically 50-54, had higher SMRs. This suggests that women in the younger groups may more closely represent their national counterparts. We were unable to find in the literature reports where differences in (age-adjusted) SMRs were explored by age and if confirmed, one possibility is that there may be less prevalent morbidity that might hinder volunteering at these ages.”

Discretionary Revisions:
1. Is this actually the first report to explore the impact of a "Healthy Volunteer Effect"?

No it is not, but the first to look at the HVE relating to random invitation alone, as mentioned in the first sentence of the discussion. Other reports of HVE in RCTs have been referenced.

2. I suggest that how deprivation is related to mortality and incidence should not be presented. These are secondary findings generating too many details.

The link between mortality and deprivation is of importance as it suggests that we should have, at the end of recruitment, been able to anticipate to some extent a significant HVE. It suggests that such an analysis might serve as a surrogate.

Moreover, the random invited people were more deprived than the national average due to the higher proportion of urban centres.

It is of significance since it shows that personal invitation of more deprived populations still results in volunteers being less deprived than the national average.

Reviewer’s report #2

Title: Impact On Mortality And Cancer Incidence Rates Of Using Random Invitation From Population Registers For Recruitment To Trials

Reviewer: Christine Berg

Reviewer’s report:

REVIEW: Impact on Mortality and Cancer Incidence Rates of Using Random Invitation from Population Registers for recruitment to trials

When designing a clinical trial, whether a screening, prevention or treatment trial it is critically important to be able to project accurately the event rate in the group enrolled in the trial. A lower event rate than anticipated will prolong the study and delay the achievement of the endpoint. This is very important in screening and prevention studies as the event rate is lower and more delayed generally, than for treatment trials. Additionally, if the event rate in the study population is different from what one might expect in the community at large, questions about the ability to extrapolate the trial results do emerge. Therefore, this current manuscript, which assesses the approach of a random invitation to a
population to conduct enrolment in a cancer screening trial, is a valuable contribution to the clinical trials literature. I would recommend acceptance to the journal.

MAJOR COMMENTS:

1. An issue that should be mentioned is that the selection bias that occurs when one recruits into a trial also is a major reason why a randomized clinical trial (RCT) needs to be done in the first place rather than an observational study. This is as vital in screening and prevention trials as in treatment trials and deserves re-emphasis to keep before the minds of trialists. Some investigators are arguing that novel techniques may get us away from the need to do RCTs but this manuscript’s results clearly indicate that particularly for mortality where there are many components to the risk an RCT gives the best available answer.

This is certainly a valid point and we have re-emphasized this as suggested in discussion:

“The data highlights yet again the selection bias that occurs in clinical trials and emphasises the need for randomised controlled trials rather than observational studies to determine efficacy of screening and prevention strategies.”

2. This reviewer does not think that the term “social deprivation” is appropriate for the classification of socio-economic or local community factors. It implies that if the “deprivation” could be remediated the problems could be fixed. Some factors, such as cigarette smoking and obesity (related to some extent to excess caloric consumption) are factors that need to be removed from a group so the group needs to be deprived of them. I am not sure that “The poor will be always with us.” is necessarily accurate but how one chooses to frame a problem and the words one uses can affect the solutions considered. I recognize that the index used by the authors is from a UK specific effort called the “Index of Multiple Deprivation (IMD 2007 (parenthetically when I went to the url for reference 8 the particular page did not have the pdf cited)). This may be the best index available for comparison with the group enrolled in the trial but my recommendation is to at least acknowledge the terminological issue and the reason for the choice of the IMD, particularly indicating if indeed it is the best available for this purpose.

The only way we could estimate socioeconomic class of the 1.2 million women invited and the 202,638 recruited was by using their postcode as a proxy. In the UK, where the term ‘deprivation’ is commonly employed to mean ‘socioeconomic status’, this meant we could use one of three available indices based on census data: IMD, Townsend or Carstairs. The choice of IMD over other measures was based on 1) it being the most up-to-date (the other two are 2001), and 2) more precise in ascribing a score to an individual based on postcode as it is calculated at a much finer spatial scale (Lower Layer Super Output Areas – 32 432 units compared to about 8000 Wards for Townsend). This has now been clarified in methods. (ps. The url still worked when we tried it).

“The PCT provided postcodes and dates of birth for all women invited to the trial. The former was used to estimate socioeconomic class. The Index of Multiple Deprivation 2007 (IMD) [8] provides 32 482 scores at a Super Output Area (SOA) level linked to postcodes for England. It was chosen over the other two census based available indices, (Townsend or Carstairs) as it was the most up-to-date and is more precise in ascribing a score, as it is calculated at a much finer spatial scale.”

Index of Multiple Deprivation has been used as a measure of socioeconomic status and in accordance to reviewer’s comment, we have replaced where appropriate we have replaced the word deprivation with socioeconomic status. This change is tracked in the revised manuscript.

3. The authors have only studied females. The PLCO included males and females and saw the same phenomenon. Would it be useful to comment on potential differences by gender in regard to this issue?

Yes, it would be worthwhile to comment on gender. This has been added to Discussion:

“In the PLCO trial the HVE was less pronounced in men, who had a statistically significantly higher SMR than women for all-cause mortality (46% versus 38%), all cancer mortality, respiratory diseases, diabetes, cardiovascular diseases, and non-Hodgkin’s lymphoma.”

MINOR COMMENTS:

1. Last sentence of abstract: Presumably the authors are proposing that trialists embarking upon new trials utilize the rates presented in this paper. This could be more clearly stated. Also, the available information in the manuscript is for females.

We are of course keen to emphasize this, though perhaps did not want to overplay it. That said, we mention this in the abstract conclusion, and the manuscript itself signs off with this point. We have added ‘women’ to the conclusion of the abstract. In the conclusion in the main article, we had already used the words ‘RCTs of similar design’.

The PCT provided postcodes and dates of birth for all women invited to the trial. The former was used to estimate socioeconomic class. The Index of Multiple Deprivation 2007 (IMD) [8] provides 32 482 scores at a Super Output Area (SOA) level linked to postcodes for England. It was chosen over the other two census based available indices, (Townsend or Carstairs) as it was the most up-to-date and is more precise in ascribing a score, as it is calculated at a much finer spatial scale.”
2. Page 1, Background: The PLCO used mass mailings as well and they were the most effective tool rather than media, but the mass mailings were not generally population based but used motor-vehicle registrations and health care organization lists. The authors may wish to mention this.

We have amended the Discussion to include those
“......self refer or invited through mass mailings using motor-vehicle registrations and health care organization lists which were not generally population based [11]. This introduces additional bias as the type of advertising media (radio station, website, newspaper or magazine) or mailing lists used, limit those who have access to the information.”

3. Incident cancer information is stated on page 3 to take up to three years to reach the trial center. It may be useful to indicate where the delay occurs. Presumably not in sending the information from the tumor registries to the trial center which the sentence implies.

The data is sent to the UKCTOCS trials office on a monthly basis from central NHS Information Centre for England and Wales. The delay quoted of three years is the time quoted by NHS IC for complete registration of all cancers for a given time period. It is mainly related to time delays in the Central office receiving the required information on all cases from the local cancer registries. We have clarified this in methods.

“Information on all incident cancers can take up to 3 years to be recorded with the national registries.”

An earlier comment on the same page mentions that the death certificates were received within three months. This speed is quite impressive and again how is it broken down by time from request to the registry to the trialists versus from the site of completion of the death certificate to the registry?

All women are flagged on the NHS Information Centre for England and Wales and CSA in Northern Ireland. The death certificate data is automatically sent in electronic format monthly to the UKCTOCS coordinating centre. The processes employed to capture this data centrally is different from the cancer registration processes and hence we receive it sooner

4. Increased mortality after bilateral oophorectomy may also be associated with selection bias for referral to the surgery. Reference: Howard BV Circulation 2005;111:1462-1470.

This has already been alluded to in the discussion.

“It is feasible that the other exclusion criteria may also have had health implications. Women who had undergone bilateral oopherectomy were ineligible. Recent reports have shown increased mortality in women in this subgroup who do not use oestrogen replacement until the age of 45 [12-13]”.

5. PLCO had entry criteria that were changed after enrolment to allow women with oophorectomies which are frequently accompanied by hysterectomies into the study. Also, rates of hormone use and type might vary between the populations that could affect endometrial cancer rates

Have inserted this in discussion.

“It needs to be noted that there are subtle difference in the PLCO entry criteria when compared to UKCTOCS such as minimum age (55 versus 50 in UKCTOCS) and inclusion of women who had undergone bilateral oophorectomy.”

6. If primary peritoneal cancer is excluded from UKCTOCS that should be mentioned.

No, primary peritoneal cancers were not excluded from this analysis of mortality or cancer incidence in UKCTOCS.

7. Are melanomas excluded along with the other malignant neoplasm of skin? Presumably the incidence is quite low for melanoma so it may not matter.

No, malignant melanomas (C43) are included in ‘Other cancers’ in the tables, but Other malignant neoplasms of the skin (C44) which were mainly basal cell carcinomas are not included. This is standard in all calculations relating to cancer incidence/mortality on advice from UK Office of National Statistics – “ONS has been advised both by expert epidemiologists and by members of the former Steering Committee on Cancer Registration, that non-melanoma skin cancer (ICD-10 C44) is greatly under-registered. Registration varies widely depending on a registry’s degree of access to out-patient records and general practitioners. This under-registration of non-melanoma skin cancer is not just a problem for the cancer registries in England. Cancer Incidence in Five Continents Volume VI38 reported that cancer registries in the United States, Australia, and parts of Europe, also collected very limited information on these skin cancers. In the commentary that follows, the figures for ‘all malignancies’ (ICD-10 C00–C97) exclude non-melanoma skin cancer (nmsc)” p12 of ONS’s cancer incidence rates [7].
The overall age-standardised rate for females for C43 is about 15 per 100000, which is roughly 1/5 of the rate for the (greatly under-registered) C44: 80 per 100000.

8. Discussion of Clegg paper (reference 18) apparent typo: late-stage rather than late-age. **This has been changed to ‘late-stage’**

We look forward to hearing from you.

Yours sincerely,

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