Reviewer's report

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

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Reviewer: Christine Berg

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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 enrollment 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.

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.

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?

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.

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.

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. 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?

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.

5. PLCO had entry criteria that were changed after enrollment 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

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

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.


**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests.