Author's response to reviews

Title: Study protocol: Evaluating the effectiveness of GP endorsement on increasing participation in the NHS Bowel Cancer Screening Programme: a feasibility trial

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We would like to thank the reviewer for their detailed and helpful comments on the manuscript. Below, we address each of the comments in turn, and show how we have amended the paper in the light of these.

ESSENTIAL REVISIONS

1. **Describe the type of FOBt used: a guiac-based or immunochemical test?**

   The NHS Bowel Cancer Screening Programme uses a guaiac faecal occult blood test. This is now noted in the manuscript (final paragraph, page 4).

2. **Describe how the planned study differs from prior studies showing improved patient compliance to bowel cancer screening with GP involvement.**

   Prior studies have largely been conducted outside of the UK – in Australia, the USA, and elsewhere in Europe. No study has been completed since the introduction of the NHSBCSP in 2006, nor have non-responders to previous invitations to participate in bowel screening been targeted specifically, so the evidence base for the appropriateness of this intervention in England is lacking. Some explanatory text summarising these issues has been added to the background section (top of page 6).

3. **Note that the NHSBCSP sample is already a select group.**

   The NHSBCSP invites all members of the general population who are registered with a general practitioner (GP) to participate in screening after their 60th birthday, repeated every two years until they reach the age of 74. UK government figures from 2010 (“Inclusion health: improving the way we meet the primary health care needs of the socially excluded”) estimate that over 99% of the general population is registered with a GP, thus the NHSBCSP population cannot be considered a select group. We have not modified the manuscript in light of this comment.

4. **Describe the feasibility aspect of this study. Would the definitive study take place in the general population (rather than the NHSBCSP sample)?**

   The feasibility aspect of the study is described in the methods section (page 9), and the outcome measures have been designed to define the parameters which may be important to consider in any definitive trial (design and power, intervention cost-effectiveness, whether or not stratification of the sample would be appropriate). This is also stated in the second paragraph of the discussion section (page 15).

   As noted in our response to point 3 above, patients invited for screening by the NHSBCSP are already as close to the general population as possible, rather than being a select sample, therefore the recruitment process and the patient population included in the research would remain the same in any definitive trial of our intervention.

5. **Add plans to describe non-participating practices, especially in terms of their compliance rates and ideally also including information about how their patient lists differ from participating practices. Specific GP characteristics, if available, would also be beneficial. This would all shed light on potential selection bias and confounders. Such information would assist in execution of a subsequent study.**

   Thank you for raising this important point. The characteristics of the general practices who were invited but who declined to participate (patient list size) have been retained for analysis of responder bias at the practice level after the trial completes. Limited information is also available about GP characteristics in these practices, via the MidReC (Midlands Research Practices Consortium) database, which includes information on whether a practice is single-handed or employs multiple GPs; level of socioeconomic deprivation of the practice catchment area; ethnicity of the surrounding population.

   We have added plans to describe non-participating practices to the Analysis section (page 13).
6. Clarify “completion”, does this mean all three slides are completed? Or at least one?

For the purposes of this feasibility trial, ‘completion’ of a kit means that a kit is returned to the Midlands and North West Bowel Cancer Screening Hub, regardless of the number of slides that are completed. This clarification has been added to page 9 (under the ‘Outcome measures’ heading).

7. Provide a better link between planned decision analyses and the analytic approach used to examine uptake. See suggestion 3 in discretionary revisions. Are subgroup analyses suggested to align with development of decision trees? Could a model based approach also work?

The planned analysis will employ a model-based approach with parallel and complementary decision tree analysis; with decision trees populated using information from the sub-group analyses (as described in pages 12 to 13). The model used will be a non-linear mixed model, which accounts for practices as random effects. Interaction terms between factors will be incorporated (now noted on page 13). The multivariable prognostic model and decision tree analysis will be conducted independently, in order to establish the robustness of the two analytical approaches in identifying factors predictive of delayed participation in the NHSBCSP, and to enable cross-validation between approaches (now clarified on page 13).

8. Describe the average GP list size. Is the assumed list size (2,750) reasonable? Similarly, is there any information about the age distribution to support the assumed 11.8% of patients in the target age range?

The assumed average GP list size used to inform the sample size calculation (page 10) is based on list sizes for general practices in the West Midlands, as derived from the MidReC GP practice database (as mentioned in response to point 5), and therefore represents a reasonable assumption. The assumed age distribution of patients, in which we asserted 11.8% of patients would be in the target age range is based on the most recently published regional census statistics, made available by the Office for National Statistics (ONS) in England.

A reference to the ONS census statistics has been added to the manuscript (final paragraph, page 10), and we now make clear that we have used information from the MidReC database to inform our sample size calculation with regard to average practice list size (final paragraph, page 10).

9. Provide a more complete description of power calculations. What statistical analysis are these based on (e.g. two-sample t-test? Logistic regression?) and does the assumed approach take into account nesting of patients within GPs? Power calculations should account for this nesting and should also state the assumed within-provider correlation.

The sample size calculation was derived using a comparison of proportions test (now clarified on page 11). The assumed approach cannot take into account nesting of patients within general practices at this stage, as the data on which such calculations, including those relating to within-provider correlation, would be based is as yet unknown. However, should interim analyses demonstrate that significant nesting within practices is occurring, the sample size will be adjusted accordingly to ensure adequate power is maintained (added to first paragraph, page 11).

10. Clarify the sentence “the proposed sample size will be sufficient to estimate the uptake of screening with a precision of at least 3.25% in each group”. Do you mean that for any degree of uptake, the resulting precision of estimated uptake in both the control and intervention groups would be plus or minus 0.0325? Is this based on a normal approximation to the binomial assuming the worst case (50% uptake)? Because point estimation is not the focus of the proposed study, it may be best to focus on the power for detecting differences between groups.

We agree that this causes some confusion. We have clarified the wording used in the sample size calculation, to make clear that this is a power-based rather than a precision-based sample size calculation. We have therefore removed the reference to the precision of the estimate, to focus solely on the power for detecting differences between the intervention and control groups (first paragraph, page 11).
11. Please be more specific about the analyses that will be used. The manuscript states that a non-linear mixed effects model will be used. Do investigators plan to use a model for dichotomous outcomes? If either a logit or probit model are planned, then say so and use this assumption in power calculations.

The planned model will be based on dichotomous outcomes (screening uptake vs. no screening uptake), and will be a logit model. This assumption has already been used to inform the power calculation. We have added some explanatory text to the analysis section (page 13).

DISCRETIONARY REVISIONS

1. It might be useful to examine whether prior contact with the GP has any impact on the effectiveness of the reminder. The idea is that contact with the GP is an imperfect proxy of the degree of connectedness between GP and patient.

We agree that some analysis of prior contact with the GP would be useful, and we intend to explore this in the qualitative element of the study as part of the interview topic guide. However, investigating the degree of prior contact with the GP for each patient in the intervention and control arms of the study is beyond the scope of the feasibility work, as we are only able to collect prospectively (anonymised) data on GP consultations that occur during the trial period. Contact with the GP is nevertheless something that we will incorporate into any future definitive trial if the feasibility work shows that the intervention appears to be effective in increasing screening uptake amongst previous non-responders.

2. Why are patients excluded only if they’ve had colonoscopy in the last 2 years? After colonoscopy, patients are not eligible for re-screening for another 10 years (if results are negative). In the US, if colonoscopy results are positive, patients are recommended for re-examination with colonoscopy in the next 1 to 5 years. In light of this, it seems patients with colonoscopy in the last 10 years should be excluded.

The exclusion criteria for the feasibility trial are based on NHSBCSP standard practice for excluding patients from being invited to participate in screening. In the NHSBCSP, a previous colonoscopy is not an outright exclusion factor for participation; if invited patients have had a colonoscopy within the previous two years, they are encouraged to contact the screening Hub when they receive their FOBt kit so that a check can be made as to whether the individual is on a surveillance programme. As the feasibility trial was designed to deviate as little as possible from standard national screening practice in England, we decided to employ the same inclusion/exclusion criteria for the trial as are used routinely by the screening Hub.

3. The planned analysis focuses on subgroup analyses. I suggest using a model-based approach that would allow direct comparison of uptake across groups of interest. For example, by including a gender effect and appropriate interaction terms, investigators could test for differences in uptake and differential effects of intervention for men and women.

Thank you for this suggestion. The analysis for the feasibility trial already plans to use a model-based approach that will allow direct comparison of uptake across groups of interest, and the study has been powered to allow such comparisons to be calculated. Interaction terms and gender effects etc. will be incorporated into our analysis as part of the prognostic model we describe (and reference to this is now made on page 13).

OTHER CHANGES

We have added the details for Professor Richard Hobbs to the author list. The omission of Prof Hobbs from the first version of the manuscript was an oversight, which we have taken this opportunity to rectify.

We have changed the title of the paper to make clear that this feasibility trial relates to the operation of the NHS Bowel Cancer Screening Programme in England specifically. The title now reads "Study protocol: evaluating the effectiveness of GP endorsement on increasing participation in the NHS Bowel Cancer Screening Programme in England: a feasibility trial".

As requested, we have added a sentence explaining trial status at the time of manuscript submission.