Author’s response to reviews

Title: A randomised controlled trial of eicosapentaenoic acid and/or aspirin for colorectal adenoma prevention during colonoscopic surveillance in the NHS Bowel Cancer Screening Programme (The seAFOod Polyp Prevention Trial): study protocol for a randomised controlled trial

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Author’s response to reviews: see over
Response to Referees

Point by point responses to the Referees are listed below. Alterations to the text are highlighted by yellow shading.

Referee 1
The primary end-point is the number of ‘high risk’ participants with one or more adenomas detected at routine one-year BCSP surveillance colonoscopy – do the authors mean new adenoma? Clarify. If so, how do the authors wish to exclude the possibility that the adenoma missed in the first colonoscopy will not be considered as new adenoma on subsequent colonoscopy? Authors did try to defend this by citing literature. But what method will the authors undertake to avoid this?

This Referee is quite right that adenomas detected at the exit colonoscopy will likely be a mix of de novo adenomas and missed lesions from the entry colonoscopy. Please see the justification for this hypothesis on page 6 of the manuscript. There is no way of distinguishing between these two categories. As stated on page 6 of the manuscript, a reduction in adenoma number (as a biomarker of CRC prevention efficacy) in previous similar trials of aspirin and selective COX-2 inhibitors suggests that candidate chemoprevention agents probably induce regression of existing adenomas, as well as prevent development of new lesions, in a similar manner to that seen in short-term RCTs in patients with familial adenomatous polyposis.

There are too many secondary end points
The secondary end-points are listed as in the approved Trial protocol.

“A validated Food Frequency Questionnaire (FFQ) is completed at baseline and at the end of the Trial so that any change in dietary #3 PUFA intake during Trial involvement can be determined” – food frequency questionnaire may have fallacy as it is dependent on recall by the subject. We accept this as a methodological weakness inherent to all retrospective dietary questionnaires. We emphasise that we are using the questionnaire only to determine if there was a change in n-3 PUFA intake as a consequence of participation in the Trial, not to determine absolute intake values. Please note that we will be measuring tissue n-3 PUFA content as a biomarker of n-3 PUFA exposure during the Trial in the ‘no EPA’ arms of the Trial.

How many colonoscopists will perform colonoscopy? How will the method of colonoscopy be standardized to avoid inter-observer variation and inadequate colonoscopic examination?
The Trial is taking place across 60 sites in England and so many Bowel Cancer Screening Programme (BCSP) colonoscopists are contributing to the Trial. Quality assurance (QA) in colonoscopy is excellent in the English BCSP and includes an
accreditation examination for each colonoscopist. QA standards include a caecal intubation rate greater than 90%, withdrawal time of greater than 6 minutes and an adenoma detection rate greater than 35% (see new reference #25), thus minimising operator variability. The text has been amended to emphasise this feature of the BCSP.

Number of words in the abstract is more than 300. Are all these according to the style of the journal? The word count for the Abstract, including Trial registration details, is 345, which is within the word limit.

Writing style needs to be improved. The paper should be shortened and readability needs to be improved. We consider that the manuscript is an acceptable length (less than 5000 words), thereby including sufficient detail of the Trial Protocol to avoid excessive cross-referencing to the publicly available Protocol and details of how the protocol developed (which will be especially relevant to other researchers planning a similar trial).

“No adjustment for multiple significance testing was made in the sample size estimate or will be in the analyses” – why? There is clear designation of primary, secondary and exploratory outcomes in the protocol. P-values will be presented, but conclusions from the trial will focus on the magnitude and clinical importance of between-group estimates and 95% confidence intervals rather than p-values, and we therefore believe that adjustment is not required.

Referee 2
An important issue in the design is that patients at highest risk (of developing adenomas) may get excluded [those having repeat / relook colonoscopy]. There is a theoretical possibility that the overall effect size of the interventions (EPA, aspirin or both) will drop below their theoretical target of 18%. The authors have increased the sample size to account for the changes but have not lowered the effect size. It is clear from the Discussion that the latest version of the Trial protocol does allow randomisation of those individuals who have undergone or who are expected to have a repeat endoscopic procedure. However, a small number of patients who require more than one repeat procedure will continue to be excluded but only because we had no BCSP data to judge what the adenoma detection rate at one-year surveillance colonoscopy would be for an informed sample size calculation. Please also note that 18% is a relative risk reduction, not an absolute difference, and the revised target difference accounting for both treatment effects (44.5% versus 54.5%) retains a relative risk reduction of 18%.

There is no mention about quality assurance for the colonoscopy. It would be advisable to have some quality assurance measures to ensure that the adenoma detection rates are of high quality among the staff doing the colonoscopies. Please see the response to Referee One. The text has been amended.

After the study began the authors have found that the proportion of all subjects
eligible for this trial dropped from their original estimate of 60% to 15-20% due to various reasons. This will be important if this is a positive trial and has to be taken to the community as only a subset of the general population will be eligible. 

*This point will be emphasised in the subsequent trial report. We are collecting data on high risk cases that are screened but found ineligible so we can eventually compare the trial population with the larger group of ‘high risk’ screenees.*

Over all the study is well design to test an important hypothesis. Sufficient details have been provided to replicate the study. The planned statistical analysis is appropriate. However if the highest risk patients are getting excluded the effect size may need to be recalculated.

*Please see the response to the first point made by this Referee.*

Referee 3

The trial has a 2x2 factorial design, so there is an evaluation of aspirin versus no aspirin, yet there is very little mention of this. This should be rectified. 

*The text has been amended to emphasise that the effect of aspirin will be evaluated within the 2x2 factorial design.*

The two primary hypotheses are stated (EPA alone more effective than placebo; EPA and ASP have additive effect) do not fit the standard analyses in a factorial design (i.e. evaluation of EPA; evaluation of ASP). 

*The text has been amended so that the two primary hypotheses are compatible with the 2x2 factorial design of the Trial.*

If 10-15% of patients are expected to drop out, how will missing data be dealt with, especially for the primary endpoint? 

*We will analyse the primary outcome by an ITT analysis without imputation, and in secondary sensitivity analyses impute missing data using extremes and also multiple imputation. This explanation has been added to the text.*

I don’t see why there should be a “potential confounding effect” of missed adenomas; this will simply introduce “noise”, which I don’t think is the same as “confounding”. 

*The text has been amended to remove the word ‘confounding’.*

What is the point of randomly varying block size (this doesn’t make prediction of the next allocation less likely), especially in a placebo-controlled trial where the treatment allocated won’t be known? 

*We agree that the risk of predicting the next IMP allocation is low, but it is theoretically possible that treatments could be identified, so we retained this additional safeguard against prediction.*

The primary endpoint should be adenoma, not the number of participants with adenoma (applies to other endpoints also). 

*The primary end-point is the so-called adenoma detection rate (the number of patients with one or more colorectal adenomas), which has become standard*
practice in polyp prevention trials. Secondary end-points include the number and location of adenomas at surveillance colonoscopy.

I found it confusing that the primary endpoint relates to the “number of ‘high risk’ participants”, suggesting that there are also non-high risk participants; but there aren’t, are there?

This Referee is correct in that all participants in the Trial are ‘high risk’ undergoing annual surveillance colonoscopy. The main text and Abstract have been amended to avoid any confusion.

The sample size is too precise. I do find it quite amusing that people put in various assumptions (that won’t actually be observed exactly in reality – e.g. 10% drop out), along with other factors (such as decision to use continuity correct) that might be varied, but then come up with such a precise sample size as, e.g., 2757 people needing to be screened!

Point taken! We have however retained the same calculation that is stated in the Trial Protocol.

Other changes to the manuscript

In addition, we have altered the title in line with the Editorial request and one of the Authors has been changed to reflect changes in the Trial Statistical support from the Nottingham CTU.

Also, please note that since submission of the first version of the manuscript to BMC Trials, the Trial protocol has been amended to allow recruitment of patients undergoing flexible sigmoidoscopy (FS) screening as per the BCSP protocol. The text has been amended accordingly. Note that the FS screening is offered from age 55 so that age eligibility for the Trial is now 55-73 years.