PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A feasibility study to assess the impact of a lifestyle intervention ('LivingWELL') in people having an assessment of their family history of colorectal or breast cancer
AUTHORS	Anderson, Annie; Dunlop, Jacqueline; Gallant, Stephanie; Miedzybrodzka, Zosia; Mutrie, Nanette; O'carroll, Ronan; Stead, Martine; Steele, Robert; Taylor, Rod; Vinnicombe, Sarah; Berg, Jonathan

VERSION 1 – REVIEW

REVIEWER	Kevin Monahan Consultant Gastroenterologist Family History of Bowel Cancer Clinic West Middlesex University Hospital Chelsea and Westminster Hospitals NHS Trust Twickenham Road Isleworth, Middlesex TW7 6AF, UK
REVIEW RETURNED	26-Sep-2017

GENERAL COMMENTS	This is an important document which paves the way for further research in to this field, and will potentially impact favourably in patient care. I have a few comments/suggestion for amendments 1. Abstract: 78 (40%) were randomised - perhaps it would be better to state the % of the total 480 patient approached rather than those who expressed interest as this reflects the feasibility of population intervention more accurately Introduction paragraph 3: Although 45% of CRC risk may be attributable to these factors, the impact of intervention (i.e. healthy lifestyle) is not clear and may not be equivalent. Page 5: This sentence doesn't make sense, the phrase ' by increasing beliefs' is stated twice.... is this a typo? Methods: Page 6 Intervention section paragraph 2: Whjys is the term 'LivingWELL' used? What does this mean? Also in this paragraph the use of the term 'lifestyle coaches' is not clear to me, as such clinicians are not standard in England, and refer sometimes to unqualified independent practitioners. It may be worth clarifying this term.

	Intervention outcome measurements - general comments: Is the ultimate outcome measure and clinic goal reduction in risk of colorectal cancer? I know this study doesn't ask this question but perhaps a longitudinal study would, perhaps with assessment of adenomas number/size/progression would be useful. It may be worth discussing in the conclusions. The main drawback of this study is low uptake amongst the potential patient population, especially amongst those of lower social classes. It would be good to know how this could be enhanced. Was this related to the intensity required on the intervention (which meant that the LCs deviated from protocol due to time constraints)? Is greater justification required before developing a RCT? Overall it is also important to understand why clinician uptake, for example amongst genetic counsellors, is not higher - is this related to training or other issues?

REVIEWER	Dr Nerys M Astbury Department of Primary Care Health Sciences University of Oxford Radcliffe Primary Care Health Sciences Radcliffe Observatory Quarter Woodstock Road Oxford OX2 6GG
REVIEW RETURNED	12-Oct-2017

GENERAL COMMENTS	This paper reports a pilot and feasibility study comparing a lifestyle intervention with usual care for patients referred to NHS genetics as they had been identified at higher risk of breast and colorectal cancer. Given that risk of developing these cancers is associated with increased body weight and poor lifestyle, there is a need for this kind of intervention. I have a few minor comments which should be addressed by the authors before I would recommend this manuscript be suitable for publication in BMJOpen. It would be nice to know the number of patients referred to these genetic counsellors (per clinic), so that the reader can judge whether these clinics are best placed to identify this patient population– and whether there are sufficient number of patients referred to these clinics to conduct a full RCT. Generally recruitment was lower than expected. I am surprised that no new patients contacted by letter did not go on to be randomised, thus the face-to face contact was preferred method of identification. However, in a larger RCT this might involve many counsellors, and would like the authors to address how they would ensure equipoise. The evidence clearly supports weight and lifestyle modifications benefit patients in terms of The lifestyle programme offered involved face-to face and telephone/email contact, and the high intensity of this might have put some participants off? Wonder if authors had considered a lower intensity programme perhaps delivered remotely which could The recruits were overwhelmingly female, despite CRC being more prevalent in men. Perhaps the authors could comment on whether men are just not interested in lifestyle interventions of this kind or that the recruitment approach did not attract men.

	The predominately female recruits suggest that a more male targeted approach, either to recruitment or to tailoring of the intervention to attract more men is needed- or that the trial in its current form should concentrate on BC only (predominantly female) please comment on this. The secondary outcome was to collecting measurement to inform a power calculation. There is currently insufficient information to replicate this power calculation. This power calculation is currently based on detecting a 5% weight loss in the intervention group only, but presumably a full RCT will need to be powered to detect a difference between intervention and control (usual care) groups. As weight loss (presumably the primary outcome) will need to be superior in the intervention compared with the control for such a treatment to be considered for implementation (based on cost health economics). Some weight loss will be expected in the control group (particularly within the context of an RCT) Please comment or revise the power for the larger RCT- stating clearly the test (paired, unpaired, one or two tailed as well as any assumptions made (e.g. weight change in control)) Please also providing sufficient information so that power calculations can be replicated (SD of difference) or in each group. Additionally, it would be nice to see that based on the estimated sample size from the power calculation, how many patients would be needed to be contacted, agree to be contacted- and together with the numbers typically referred to these clinics, will allow readers to judge the scale and feasibility of a full RCT powered to detect difference between the groups.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Kevin Monahan
1. Abstract: 78 (40%) were randomised - perhaps it would be better to state the % of the total 480 patient approached rather than those who expressed interest as this reflects the feasibility of population intervention more accurately

Response: If all 480 patients were eligible then it would be more relevant to express the % of these randomised. A good compromise seems to be to present numbers and % thus we have expressed response as
Of 480 patients approached, 196 (41%) expressed interest in the study and of those 78 (40%) were randomised.
In the results section we have written this more fully as
A total of 78 people (40% of those who agreed to be contacted; 39% of BC and 42% of CRC FH approached; 16% of those who were potentially eligible for the study) were randomised.

2. Introduction paragraph 3: Although 45% of CRC risk may be attributable to these factors, the impact of intervention (i.e. healthy lifestyle) is not clear and may not be equivalent.

Response: In both colorectal and breast cancer the impact of lifestyle on risk reduction is unknown so we have returned to this point in the discussion and added the following text:
Whilst cancer preventability estimates suggest that healthful ways of life could significantly reduce cancer risk the impact of lifestyle interventions in this patient group is unknown and randomised controlled trial data is needed to examine the cost, benefits and harms.

3. Page 5: This sentence doesn't make sense, the phrase ' by increasing beliefs' is stated twice.... is this a typo?
Response: Text amended

4. Methods: Page 6 Intervention section paragraph 2: Why is the term 'LivingWELL' used? What does this mean?
Response ‘LivingWELL’ is the name given to the intervention as specified in the paper title. The text has been amended to clarify the intervention name with the addition of inverted commas.

5. Also in this paragraph the use of the term 'lifestyle coaches' is not clear to me, as such clinicians are not standard in England, and refer sometimes to unqualified independent practitioners. It may be worth clarifying this term.
Response: The text has been amended to
The ‘LivingWELL’ programme was delivered by lifestyle coaches (LC), personnel (with a nursing background) who received bespoke training on the delivery of the intervention programme.

6. Intervention outcome measurements - general comments: Is the ultimate outcome measure and clinic goal reduction in risk of colorectal cancer? I know this study doesn't ask this question but perhaps a longitudinal study would, perhaps with assessment of adenomas number/size/progression would be useful. It may be worth discussing in the conclusions.
Response: The text has been amended to:
In a fully powered trial the first stage would be to assess the magnitude of lifestyle change that can be achieved by this type of programme. In turn this fully powered trial would act as a “pilot” for a full trial of reduction in colorectal cancer markers. Adenomas (number and size) might be an appropriate end point depending on funding for the length of follow up.

7a. The main drawback of this study is low uptake amongst the potential patient population, especially amongst those of lower social classes.
Response: The socio-demographic profile relates to patients who attend the family history clinics which tend to be from a less deprived population.

7b. It would be good to know how this could be enhanced.
Response: Text added in discussion:
It would be desirable to increase patient recruitment and the current findings suggest that overall uptake could be increased with better training, support and endorsement from the genetic counsellors and other clinical staff. This area of study was almost entirely new and met with scepticism from staff and indeed patients. Our earlier work suggests ambiguous attitudes about the importance of lifestyle with little evidence that these topics have been previously discussed with clinicians17.

7c. Was this related to the intensity required on the intervention (which meant that the LCs deviated from protocol due to time constraints)?
Response: The intervention intensity is considerably less than that of a slimming group or series of dietetic consultations. The intervention was also less intense that our previous study (BeWEL)12 for people who had previously been diagnosed with adenomas. However, in that study recruitment involved written endorsements from lead clinicians which would be desirable in future work.

7d. Is greater justification required before developing a RCT?
Response: This is something of a chicken and egg situation. We cannot demonstrate the impact of lifestyle intervention on cancer risk (convincing level intervention evidence) unless we can complete a trial. The justification for lifestyle intervention is well made in the literature but this has not been widely communicated to the genetic community. More work is needed to endorse the need for the study and clinical support.

8. Overall it is also important to understand why clinician uptake, for example amongst genetic counsellors, is not higher - is this related to training or other issues?
Response: In discussion we note that:
This pilot study has highlighted a number of perceived challenges for NHS staff discussing lifestyle issues amongst patients with a family history of breast and colorectal cancer.
During the course of the study our discussions with genetic counsellors indicated a number of relevant issues – we intend to report this in a paper (under preparation) on gate keeping by health service staff which combines the finding of the current study with several other similar lifestyle intervention studies. Given the word limit we have not expanded on this topic here and would welcome editors advise on this.

Reviewer: 2
Reviewer Name: Dr Nerys M Astbury
1. It would be nice to know the number of patients referred to these genetic counsellors (per clinic), so that the reader can judge whether these clinics are best placed to identify this patient population– and whether there are sufficient number of patients referred to these clinics to conduct a full RCT.
Response: In the results section '600 patients were identified as potentially eligible for the study (364 BC and 236 CRC FH) over the 8 month recruitment period'. In a full trial it would be preferable to extend this to several sites. There is no doubt that these clinics would be the best place to identify people with increased risk although recruitment could be extended through patients groups (e.g. Lynch Syndrome Association).

2a Generally recruitment was lower than expected. I am surprised that no new patients contacted by letter did not go on to be randomised, thus the face-to face contact was preferred method of identification.
Response: Face to face recruitment is generally considered a more effective recruitment method. Additionally, people who were contacted by letter (new referrals) were more likely to be at population risk and not invited for clinic visits thus may have perceived the study as less relevant.

2b However, in a larger RCT this might involve many counsellors, and would like the authors to address how they would ensure equipoise.
Response: In our previous and current trials we train all counsellors/ NHS staff involved in highlighting studies to a recruitment protocol, providing certificates and feedback. Additionally, we have recently started providing regular newsletters for NHS personnel who are introducing the study to their clients to maintain study engagement and provide reminders about study requirements.

3. The evidence clearly supports weight and lifestyle modifications benefit patients in terms of the lifestyle programme offered involved face-to face and telephone/email contact, and the high intensity of this might have put some participants off? Wonder if authors had considered a lower intensity programme perhaps delivered remotely
Response: See response above to reviewer 1. Clearly our approach does attract people at high risk of cancer and can produce effective lifestyle change. There is little support for effectiveness of less intensive methods in people within the older age range. E- communications are less acceptable amongst older people and previous work offering skype communications on breast cancer and lifestyle produced no interest. The low response to the study by letter (versus face to face information) also highlights the importance of direct contact communications.

4. The recruits were overwhelmingly female, despite CRC being more prevalent in men.

Response: Fundamentally, recruitment is limited by the clients referred to the family history clinics which may not reflect the gender balance in disease incidence of CRC. We were not permitted to collect details (including gender) about individual clients who said they were not interested in the study.
The following sentence has been added to discussion
The response from men (33% of CRC risk patients) was lower than anticipated (given the incidence of the disease in men) and lower than that attained in our fully powered trial of people at high risk of CRC due to an adenoma diagnosis12 which suggests that it is unlikely to be the intervention approach per se that is a problem and is more likely to reflect the gender balance of clinic attendees (data unavailable).

5. Perhaps the authors could comment on whether men are just not interested in lifestyle interventions of this kind or that the recruitment approach did not attract men. The predominately female recruits suggest that a more male targeted approach, either to recruitment or to tailoring of the intervention to attract more men is needed- or that the trial in its current form should concentrate on BC only (predominantly female) please comment on this.
Response: Our previous study 12 of a more intensive lifestyle intervention of 997 people at high risk of CRC (they had a CRC adenoma diagnosis) reported a 49% expression of interest and recruitment with 329 meeting eligibility criterion (BMI >25) and being randomised to a lifestyle intervention of 3 face to face visits plus monthly phone calls. Overall, 74% of the participants were men, and 35% lived in the two most deprived Scottish index of multiple deprivation fifths.

In this study fewer men presented through the genetics clinics (357 women vs 64 men) so the pool from which to recruit was limited. We do however acknowledge that recruitment rates for men (26.6%) was lower than for women (42.3%) and this is something that should be considered in the design of future work.

6. The secondary outcome was to collecting measurement to inform a power calculation. There is currently insufficient information to replicate this power calculation. This power calculation is currently based on detecting a 5% weight loss in the intervention group only, but presumably a full RCT will need to be powered to detect a difference between intervention and control (usual care) groups. As weight loss (presumably the primary outcome) will need to be superior in the intervention compared with the control for such a treatment to be considered for implementation (based on cost health economics). Some weight loss will be expected in the control group (particularly within the context of an RCT). Please comment or revise the power for the larger RCT- stating clearly the test (paired, unpaired, one or two tailed as well as any assumptions made (e.g. weight change in control)) Please also providing sufficient information so that power calculations can be replicated (SD of difference) or in each group.

Response: We have revised the calculation (checking the power calculation can be replicated) and expanded the text as follows:
Using the data from the current study, where we observed a mean body weight of 89.5kg (+/- SD 13.3), a total of 187 participants per group would be needed to detect a between group difference of a 5% weight change (4.47 kg) at follow up at 90% power and 5% alpha based on a 2-tailed unpaired t-test . Allowing for an assumed 25% drop out this would mean recruiting 250 participants per group.

7. Additionally, it would be nice to see that based on the estimated sample size from the power calculation, how many patients would be needed to be contacted, agree to be contacted- and together with the numbers typically referred to these clinics, will allow readers to judge the scale and feasibility of a full RCT powered to detect difference between the groups.
Response: The following text has now been added

Based on the current figures: to recruit 500 people, 1250 would need to express an interest (40% of those who express an interest were recruited). For 1250 to express an interest, 3048 would require to be approached (based on 41% of people approached were interested). If all clinics recruited similar numbers to the two in the current study (240 in an 8 month period/360 per year) then 9 centres would be needed for a 12 month recruitment period.

VERSION 2 – REVIEW

REVIEWER	Kevin Monahan Imperial College, London
REVIEW RETURNED	30-Nov-2017

GENERAL COMMENTS	My previous comments have been fully addressed, and I strongly recommend this paper for publication as it answers an important clinical question