PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A feasibility study to assess the delivery of a lifestyle intervention (TreatWELL) for colorectal cancer patients undergoing potentially curative treatment.
AUTHORS	Macleod, Maureen; Steele, Robert; O'carroll, Ronan; Wells, Mary; campbell, anna; Sugden, Jacqui; Rodger, Jackie; Stead, Martine; McKell, Jennifer; Anderson, Annie

VERSION 1 – REVIEW

REVIEWER	Tsuyoshi Ozawa, MD, PhD Sannno-Hospital, Tokyo, Japan
REVIEW RETURNED	30-Dec-2017

GENERAL COMMENTS	The authors evaluated the feasibility of a delivery of a life style intervention program in stage I-III colorectal cancer (CRC) patients. It is suggested that the life style change such as smoking cessation, increased physical activity, and improved dietary habit impact on cancer-related survival. The concept of this study is intriguing, however, I have several concerns in this study. 1) In Introduction, for P5 LINE15-16, citation is needed. 2) The manuscript is not summarized. For example, in Appendix 1, the intervention delivery plans are different between those who are introduced adjuvant chemotherapy and those who are not. However, it is hard to recognize what is the difference or the reason why they are different. The association between each intervention and achievement of its goal (outcome) is also not clear. 3) The outcomes are all not statistically evaluated, partially because of the small sample size. Although this study is feasibility evaluation for future prospective study, I can not see whether this is really feasible or what is the cause of un-feasibility from the present results.

REVIEWER	Daan Brandenbarg University Medical Center Groningen, Netherlands
REVIEW RETURNED	02-Jan-2018

GENERAL COMMENTS	This is an interesting paper which addresses relevant lessons for future lifestyle intervention trials or implementation of lifestyle protocols. I don't have major concerns regarding this paper. However, there are a few minor points which I believe should be addressed. Since most of the results in the manuscript are based on the

	outcomes of the qualitative interviews I believe the methods of these interviews could be more described. The authors state a thematic framework was used: in what sense was this used? How were the interviews conducted? By whom? How were they transcribed? How were they analysed (by 1 or 2 independent coders?) Etcetera. Furthermore it would be interesting to see the sampling strategy and whether or not the authors aimed for saturation and if it was reached. As to the results I feel that a majority of participants is male. The authors do not reflect on this in their discussion. Is the program more appealing to males? Were reasons for not participating assessed? And can the authors draw conclusions based on this information which would be helpful for future implementation or trials? Concerning the introduction and relevance: the authors state that PA has positive effects on fatigue. A recent systematic review (Brandenbarg D., Korsten, J. H. W. M., Berger, M. Y., Berendsen, A. J. (2017). The effect of physical activity on fatigue among survivors of colorectal cancer: a systematic review and meta-analysis. Support Care Cancer. Doi: 10.1007/s00520-017-3920-4. [Epub ahead of print]) showed no effect of PA on fatigue post treatment. I agree with the authors that there is some evidence it could still be effective in this patient group, but I think it is stated to definitively in this sense. I would like to point out that I do not mention this because I authored the publication, but because I believe there are some conclusions from this review (such as problems with participation and adherence, and no power to detect changes) that could be relevant.

VERSION 1 – AUTHOR RESPONSE

Response to reviewers

Reviewer 1

1. In Introduction, for P5 LINE 15-16, citation is needed.
Response Text has been changed as follows:
There is growing evidence for the impact of diet on CRC cancer outcomes [10]
(Van Blarigan EL & Meyerhardt JA (2015) Role of physical activity and diet after colorectal cancer. J Clin Oncol 1;33 (16) 1825-34)

2. The manuscript is not summarized. For example, in Appendix 1, the intervention delivery plans are different between those who are introduced adjuvant chemotherapy and those who are not. However, it is hard to recognize what is the difference or the reason why they are different. The association between each intervention and achievement of its goal (outcome) is also not clear.
Response Text has been changed as follows:
The total intervention period comprised 31 weeks although duration was flexible as it was based on the individual's treatment regimen. The delivery mode, consultation focus, resources and behaviour change techniques used in each phase are presented in Appendix 1. Decisions about phase completion (e.g. defining the end of post-surgical recovery) and progression was agreed in conjunction with the CNS. In summary, each phase of the programme comprised verbal educational approaches with written resources (e.g. booklets, resistance bands) and the use of behavioural techniques. Importantly, personalised, specific action goals were identified with a focus on two health behaviours that were selected as a priority for that individual (e.g. smoking, physical activity). All participants were invited to engage a support person (e.g. spouse) to assist in their adherence with

the programme. It should be noted that the protocol for phase 3 varied according to whether chemo therapy use. For patients with no adjuvant therapy, the progression to addressing body weight issues (over, under weight and weight loss) was addressed at the start of this phase. For participants undergoing chemotherapy the focus on diet and weight management was delayed to avoid any confusion which might arise with dietary issues related to treatment side effects (e.g. nausea).

3. The outcomes are all not statistically evaluated, partially because of the small sample size. Although this study is feasibility evaluation for future prospective study, I cannot see whether this is really feasible or what is the cause of un-feasibility from the present results.
Response
The main outcomes of this study are to examine feasibility namely recruitment, retention, programme implementation, achieved measures, fidelity, factors affecting protocol adherence and acceptability. These outcomes are not subjected (and indeed in many cases cannot be subject) to statistical analysis. In the conclusions we highlight four areas that need to be addressed before the feasibility of progression to a full trial can be assessed. No specific achievement points were assessed (e.g. 50% of people approached should be recruited or 75% retained etc.). We have now set out specific challenges in terms of feasibility for progressing to a full trial as follows (This text is in the abstract and manuscript conclusions).
To make this intervention feasible for testing as a full trial, further research is required on a) recruitment optimization b) appropriate assessment tools c) protocols for phase 2 and 3 which can build in flexibility and d) ways for NHS staff to facilitate the programme.

Reviewer: 2

1. Since most of the results in the manuscript are based on the outcomes of the qualitative interviews I believe the methods of these interviews could be more described. The authors state a thematic framework was used: in what sense was this used? How were the interviews conducted? By whom? How were they transcribed? How were they analysed (by 1 or 2 independent coders?) Etcetera.
Response
Methods section: The following has been added re method
Participants' views on acceptability of the intervention and factors influencing adherence were explored in in-depth qualitative interviews conducted by MS and JMcK. Interviews lasted around 45-60 minutes and were conducted either face to face or by telephone. Interviews were digitally recorded with participants' consent, and transcribed verbatim for analysis.

Analysis section: The following has been added
Data from the transcripts were coded by MS and JMcK using a framework approach [Gale], with an initial framework developed around different aspects of engagement in the study and intervention: recruitment and delivery acceptability, engagement with lifestyle change, facilitators and barriers to lifestyle change, and any issues which would need to be considered if conducting a full RCT. The framework was revised to incorporate additional themes which emerged from the transcripts (for example, concerning PA goals and conflicting advice given by other health professionals).

2. Furthermore it would be interesting to see the sampling strategy and whether or not the authors aimed for saturation and if it was reached.
Response
The following has been added to the methods section
The original intention was to interview a random sample of one in three participants at the end of phase 2 and another at the end of phase 3. However, because of the low number of participants all participants were invited to take part in an interview towards the end of their journey through the intervention programme and eleven agreed to do so.

3. As to the results I feel that a majority of participants is male. The authors do not reflect on this in their discussion. Is the program more appealing to males? Were reasons for not participating assessed? And can the authors draw conclusions based on this information which would be helpful for future implementation or trials?
Response The gender difference is notable and we have added some text on this
In results
Of the 22 who were recruited, the mean age was 67 years and 77% were male.
In discussion
It is notable that a high proportion of participants were male (77%) and whilst national data reports [43] that more men are diagnosed with colorectal cancer compared to women (54% versus 46%), the proportion in this study is higher than anticipated. The reason for this is not clear but does indicate the need to explore this in future work.

4. Concerning the introduction and relevance: the authors state that PA has positive effects on fatigue. A recent systematic review (Brandenbarg D., Korsten, J. H. W. M., Berger, M. Y., Berendsen, A. J. (2017). The effect of physical activity on fatigue among survivors of colorectal cancer: a systematic review and meta-analysis. Support Care Cancer. Doi: 10.1007/s00520-017-3920-4. [Epub ahead of print]) showed no effect of PA on fatigue post treatment. I agree with the authors that there is some evidence it could still be effective in this patient group, but I think it is stated too definitively in this sense. I would like to point out that I do not mention this because I authored the publication, but because I believe there are some conclusions from this review (such as problems with participation and adherence, and no power to detect changes) that could be relevant.

Response A very useful point –thank you
The following text has been added
A number of studies have reported that higher levels of physical activity are associated with better physical functioning [3] and reduced fatigue [4] although further work is needed in these areas [5].

FORMATTING AMENDMENTS (if any)
Required amendments will be listed here; please include these changes in your revised version:
1. Please include Figure legends at the end of your main manuscript.
Response
Completed

VERSION 2 – REVIEW

REVIEWER	Daan Brandenbarg University Medical Center Groningen
REVIEW RETURNED	27-Feb-2018

GENERAL COMMENTS	I believe the authors have sufficiently incorporated the comments of the reviewers in their updated manuscript.

REVIEWER	Tsuyoshi Ozawa, MD, PhD Sanno Hospital, International University of Health and Welfare, Tokyo, Japan
REVIEW RETURNED	01-Mar-2018

GENERAL COMMENTS	1. As the authors mention, this is feasibility study, therefore, the authors should evaluate the factors which objectively show that the study is really feasible and why the authors think so, and if not what is the cause of un-feasibility. Otherwise, it does not make any sense to show the present study. From that respect, the authors just show

	the result in un-summarized fashion, therefore, it is very hard to evaluate the feasibility of this study. Seventy percent of the recruited patients completed the study, however, I am not sure this 70% means feasible or not. 2. The authors mention in method section that recruited patients had stage I-III CRC, however, in table 1, those who had metastases were included. 3. The TreatWELL aims to behavior changes including physical activity and calorie intake (and alcohol intake), therefore, baseline information of these should be shown in table 1.

VERSION 2 – AUTHOR RESPONSE

Response to Editor and reviewers comments

Editor

1. Please clarify how this study relates to your recently published paper: “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”. Related work should be cited/ discussed in the introduction section.

The work under review does not really directly relate to the LivingWELL study in so much that the participants in that study were people at high risk of breast and colorectal cancer but had not been diagnosed with the disease and had not received any treatments. We have added the following sentence to highlight LivingWELL as an example of lifestyle feasibility work.

Discussion para 3

Whilst our recent intervention study has tested the feasibility of undertaking lifestyle interventions in people at high risk of colorectal (and breast) cancer, this study (to the best of our knowledge) is the first to have offered a comprehensive lifestyle intervention at diagnosis with support before, during and after treatment in patients with colorectal cancer.

2. Along with your revised manuscript, please provide a completed copy of the CONSORT extension for feasibility trials. See: http://www.consort-statement.org/extensions/overview/pilotandfeasibility

An update on our previous CONSORT extension has now been completed and accompanies our submission

Reviewer

1. As the authors mention, this is feasibility study, therefore, the authors should evaluate the factors which objectively show that the study is really feasible and why the authors think so, and if not what is the cause of un-feasibility.

We have added the following text

It is important to note that no specific progression criteria were identified (or agreed) for trial progression in the current study, but each of the parameters identified are relevant in decisions around future progression (recruitment, retention, programme implementation, achieved measures, fidelity, factors affecting protocol adherence and acceptability). The findings show that the recruitment was too low (both due to eligibility, people approached and willingness to participate), too many participants failed to complete because of major health problems, the intervention delivery varied

widely from the protocol (in terms of timing and approaches) and the number of achieved measures (notably at end of phase 1) would be inadequate to provide any indication of impact.

In accordance with Thabane et al [45] there are four possible progression outcomes as follows (i) Stop - main study not feasible; (ii) Continue, but modify protocol - feasible with modifications; (iii) Continue without modifications, but monitor closely - feasible with close monitoring and (iv) Continue without modifications - feasible as is.
Our results suggest that it would be plausible to continue but that the protocol should be modified and further feasibility testing undertaken prior to a full trial.

It should be noted that there are no “standard” values for recruitment, retention etc. and that pre-specified criteria agreed with funders need to be flexible as described by Avery et al.
(Avery et al, (2016) http://bmjopen.bmj.com/content/7/2/e013537#block-system-main)

2. The authors mention in method section that recruited patients had stage I-III CRC, however, in table 1, those who had metastases were included.

In our text we have described the eligibility criterion as follows:
Eligible patients were adults aged >18 years , capable of giving informed consent, considered to have stage I to III colorectal cancer, eligible for potentially curative treatment (had to be fit for major surgery).

We have now added the following sentence to the results text
It should be noted that because of the short window for intervention, some participants were recruited before CT Scans were complete. In one case, lung metastases were diagnosed after CT staging. Surgery was still undertaken for this patient on the clinical basis that it had the potential to improve survivorship.

3. The TreatWELL study aims to behaviour changes including physical activity and calorie intake (and alcohol intake), therefore, baseline information of these should be shown in table 1.

The data on physical activity, alcohol and dietary scores have now been added to Table 1. No data on caloric intake is available.

The following text has been added
Baseline data on Body Mass Index (BMI) and key health behaviours (smoking, physical activity, alcohol and diet score) indicate significant potential for health gain.