PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Exercise Programme in Endometrial Cancer; Protocol of the Feasibility and Acceptability Survivorship Trial (EPEC-FAST)
AUTHORS	Smits, Anke; Lopes, Alberto; Das, Nagindra; Bekkers, Ruud; Massuger, Leon; Galaal, Khadra

VERSION 1 - REVIEW

REVIEWER	Catherine Jankowski University of Colorado College of Nursing Aurora, Colorado, USA
REVIEW RETURNED	02-Aug-2015

GENERAL COMMENTS	4. The research design is not explained in sufficient detail. Inclusion criteria: In the introduction and discussion, emphasis is placed on the high prevalence of obesity in women with endometrial cancer yet there is no inclusion criterion for obesity. Either include this criterion or explain why there is no criterion based on body size. Exercise program: "Pillar strength" exercises should be explained. Ideally, images or drawings would be provided so that the protocol could be reproduced by another investigator. The relative intensity of the resistance exercises should be given (e.g., % 1-RM). Further, explain why a low intensity resistance protocol has been selected. If a participant can do 20-25 repetitions of an exercise, the intensity is low. The warm up activity is low intensity and the aerobic exercise is also low intensity (40-50% maximum HR). How will maximum heart rate be determined - directly in an exercise stress test or estimated using an appropriate validated equation? How will self-reported physical activity be determined? The methods used for items in the physical fitness assessment must be explained. For example, how will the percentage of body fat and muscle (lean mass is a more appropriate term) and resting metabolism be determined (e.g., indirect calorimetry under what set of conditions)? What method of the 6-minute walk will be used? Will one trainer be responsible for all training sessions? If not, what measures have been taken to confirm that multiple trainers are delivering the intervention in a consistent manner?

	6. Outcomes. In Figure 1, what will be collected at 6 months after the start of the intervention? The only follow-up measures stated in the text are at 3 months after the intervention. Regarding the qualitative evaluation, what are the outcomes and method of analysis; who will conduct the telephone interviews and will they be recorded for later transcription? In the data collection section (page 11), it is stated that data will be collected in an electronic database thus implying that the qualitative data will be saved. What software will be used to objectively identify themes in the interviews? How will the "selected subgroup" of participants (8-10) be decided? Are the outcomes for the quantitative data expected to be the changes in the questionnaire scores? What are the potential covariates to the questionnaire scores? 7. Statistical analyses are not included; there will be a mixture of nominal and interval-ratio data that will be summarized and presented descriptively. The QOL scores and other standardized questionnaire outcomes could be compared to normative values for similar patient populations. What are the CVs for the body composition and resting metabolic rate methods?

REVIEWER	David O. Garcia, PhD University of Arizona Mel and Enid Zuckerman College of Public Health United States
REVIEW RETURNED	03-Aug-2015

GENERAL COMMENTS	Abstract: According to BMJ Use these headings to provide brief descriptions of the following: • Purpose: describe why the cohort was set up • Participants: describe who is in the cohort • Findings to date: what data has been collected so far and any major results • Future plans: how will the cohort be used in future, including any date for completion of data collection • Please revisit your headings for the abstract. For instance, you can add the heading “Purpose” before stating the objective of the study. Methods and analysis: • This is a nice description of the study participants. • Please consider removing mortality as a secondary outcome measure given the study duration is only 10-weeks.

	Ethics and dissemination: • Please consider revising this heading to “Future Plans”. • Ethics approval can be placed in the methods section. Strengths and limitations of the study: • This is not necessary in the abstract and provides little value to the reader- please remove from the abstract. Introduction: • Very well written section. • Page 5 Line 58- consider word choice of “lifestyle intervention”- lifestyle includes diet, physical activity, and modifying thinking habits. Your intervention is an individualized exercise program. • Page 6 Lines 17-22- these statements do not appear necessary. The sentences in lines 8-17 support the need to evaluate the feasibility of this intervention strategy. Methods: Intervention: • Page 7-8: Is a 60 minute session/week for 10 weeks sufficient? Please clarify if participants have any recommendations for what they should do outside the gym setting. If there are no recommendations, how will you control for the individuals who do more than the one-time training session? • In addition to one-to-one training, do participants receive any “lifestyle” intervention training such as problem solving or relapse prevention? • While reviewing Table 1, it appears that participants will be doing aerobic exercise and strength training in a 40 minute period. How will you standardize this across participants? Is there a treatment fidelity plan in place? • Page 8, Lines 12-19 are not necessary as these measures should be described in the outcomes section. Outcomes: • Please clarify if outcome measures will be assessed at 6 months after the exercise program is completed as shown in Figure 1. Primary Outcome: • Please clarify how feasibility aspects will be obtained from hospital medical files. Is there a specific time period for recruitment and how will you quantify a clinicians willingness to recruit patients based on records? Secondary Outcomes: • One important measure missing is total Physical Activity. If you cannot quantify how much physical activity the

	participant is performing, it will be difficult to interpret if changes on QOL are a result of the intervention or the fact that the participant has become more active overall. • Page 10, lines 31-38. Please consider the wording lean muscle tissue in place of muscle percentage. In addition, please remove mortality as a secondary outcome measure- the study duration is not sufficient enough. Qualitative evaluation: • Please clarify if a moderator guide will be used and how data analysis will occur. Recruitment: • Please consider moving recruitment after study participants. The power calculation statement can be moved to data analysis. Data-collection: • It appears the qualitative evaluation was expanded in this section. Please consider removing the qualitative evaluation section as it does not seem necessary with this information. Discussion: • Again, very well written section. Particularly the sections based on the rationale for the study physical activity recommendations. • Page 14, paragraph 3 is focused heavily on survival. This appears tangential to your study given the focus is on improving QOL and feasibility of bringing participants into a supervised exercise program. Please consider removing.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name Catherine Jankowski
Institution and Country University of Colorado
College of Nursing
Aurora, Colorado, USA
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
4. The research design is not explained in sufficient detail.
• Inclusion criteria: In the introduction and discussion, emphasis is placed on the high prevalence of obesity in women with endometrial cancer yet there is no inclusion criterion for obesity. Either include this criterion or explain why there is no criterion based on body size.
Authors reply: Women with higher BMI are at higher risk of poorer QoL, however we believe that women with normal or overweight BMI may also benefit from an exercise intervention in terms of quality of life. In addition, even though obesity is associated with a sedentary lifestyle, non-obese women may also have a sedentary / inactive lifestyle and may benefit from an exercise intervention. A

recent study supports this, showing that non-obese women had significantly better outcomes in several quality of life domains compared to non-obese women after an exercise intervention*. Therefore we have chosen to include women with all BMI.
*: Basen-Engquist K, Carmack C, Brown J, Jhingran A, Baum G, Song J, et al. Response to an exercise intervention after endometrial cancer: differences between obese and non-obese survivors. Gynecologic oncology. 2014;133(1):48-55.

Exercise program:
• "Pillar strength" exercises should be explained. Ideally, images or drawings would be provided so that the protocol could be reproduced by another investigator.
Authors reply: we have explained the pillar strength exercises in Table 1. They comprise of exercises to improve stability and strength of the hip and core which has also been briefly mentioned in the text. We have included the individual exercises in Table 1 (hip flexion/extension/adduction/abduction and crunch, back extension, arm and leg raise). We have used standard exercises to improve reproducibility of the programme, therefore we do not believe additional images are necessary.

• The relative intensity of the resistance exercises should be given (e.g., % 1-RM). Further, explain why a low intensity resistance protocol has been selected. If a participant can do 20-25 repetitions of an exercise, the intensity is low.
Authors reply: The intensity of the resistance exercise will 40-60% of 1 RM (one repetition maximum) for high repetitions (<15), using short rest periods (< 90 seconds), as this is the recommendation of the American College of Sports Medicine (ACSM)*. This has been clarified in the methods and Table 1.
A low intensity protocol has been selected because this is the recommendation of the ACSM for local muscular endurance training* and because of the expected study population. The majority of the endometrial cancer patients is over the age of 65, are overweight or obese and do not engage in an active lifestyle. In addition, they may have several comorbidities. We wanted to device an exercise intervention to which women can easily adhere to, which we hope will result in long-term sustainability of lifestyle changes.
*: American College of Sports Medicine. American College of Sports Medicine position stand. Progression models in resistance training for healthy adults. Med Sci Sports Exerc. 2009 Mar;41(3):687-708.

• The warm up activity is low intensity and the aerobic exercise is also low intensity (40-50% maximum HR). How will maximum heart rate be determined - directly in an exercise stress test or estimated using an appropriate validated equation?
Authors reply: heart rate will be measured using a Polar Heart Rate monitor, and maximum heart rate will be estimated using the age-predicted maximal heart rate (MHR) equation: MHR = 220 - age. The Karvonen method will be used for calculating the target heart rate interval.

• How will self-reported physical activity be determined?
Authors reply: self-reported physical will not be determined. Physical activity levels will be assessed during the health assessment using the 6-minute walk test. We agree that this is an important outcome measure which is missing from our study. We have included this as a limitation of the study protocol in the discussion. In a more definitive trial, this should be incorporated as an outcome measure, as we recognise this may influence quality of life.

• The methods used for items in the physical fitness assessment must be explained. For example, how will the percentage of body fat and muscle (lean mass is a more appropriate term) and resting metabolism be determined (e.g., indirect calorimetry under what set of conditions)? What method of the 6-minute walk will be used?
Authors reply: Percentage of body fat and muscle percentage, and resting metabolism will be

determined using a Omron Body Composition Monitor and Scale, Model HBF-514C, which has been validated clinically*.
*: Bosy-Westphal A1, Later W, Hitze B et al. Accuracy of bioelectrical impedance consumer devices for measurement of body composition in comparison to whole body magnetic resonance imaging and dual X-ray absorptiometry. Obes Facts. 2008;1(6):319-24.

The 6-minute walk test will be performed on a treadmill with a heart monitor attached, and uses an adaptation of the American Thoracic Society guidelines*.
*: American Thoracic Society. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166:111-117

• Will one trainer be responsible for all training sessions? If not, what measures have been taken to confirm that multiple trainers are delivering the intervention in a consistent manner?
Authors reply: one trainer will be responsible for all training sessions. We have clarified this in the text.

6. Outcomes.
• In Figure 1, what will be collected at 6 months after the start of the intervention? The only follow-up measures stated in the text are at 3 months after the intervention.
Authors reply: outcome measures including quality of life, psychological distress, fatigue and pain are assessed at baseline, 3 months and 6 months. The physical fitness assessments are collected at baseline and 3 months (post-intervention). Weight and BMI are also collected at 6 months. We have further clarified this in the text.

• Regarding the qualitative evaluation, what are the outcomes and method of analysis; who will conduct the telephone interviews and will they be recorded for later transcription? In the data collection section (page 11), it is stated that data will be collected in an electronic database thus implying that the qualitative data will be saved. What software will be used to objectively identify themes in the interviews? How will the "selected subgroup" of participants (8-10) be decided?
Authors reply: the outcomes of the interviews will be to evaluate taking part in the research exploring the recruitment, information and potential (hypothetical) to be randomized to an allocated treatment group, and the exercise component experience of the exercise intervention, in particular:
• How patients experienced the exercise programme and its individual components
• How patients valued the exercise programme and its individual components
• How patients tolerated the exercise programme and its individual components
• Possible barriers to taking part and attending the exercise programme
• Motivators and facilitator for taking part
Method of analysis: the transcripts will be manually coded. Simple descriptive thematic analyses will be performed*. All transcripts will be read a minimum of three times prior to coding. Extracts of the transcripts will be coded; codes with similar meaning will be allocated categories before final descriptive themes are identified. Quotes to illustrate findings will be extracted.
Analysis will be conducted independently by a researcher independent of the research delivery team. The coding will be checked by another independent senior qualitative researcher where agreement of findings will be reached through discussion.
*: Braun, V. and V. Clark, Using thematic analysis in psychology. Qualitative Research in Psychology, 2006. 2: p. 77-101.
Conduct of interviews: the interviews will be conducted by an independent researcher by telephone. The interview will be recorded as an audio file using an Olympus DM-650 recording device, anonymised and then transcribed by an administrator of the research team. The anonymised transcripts will be in Word format.
Subgroup selection: the selected subgroup of 8-10 participants will be a purposively selected population with maximum variation in terms of age, BMI, adherence and adverse events. We have further clarified this in the test.

• Are the outcomes for the quantitative data expected to be the changes in the questionnaire scores? What are the potential covariates to the questionnaire scores?
Authors reply: yes, the outcomes for the quantitative data will be the changes in the questionnaire scores. Potential covariates will be baseline and clinical characteristics such as age, ethnicity, performance status, comorbidities, treatment and other clinical characteristics.

7. Statistical analyses are not included; there will be a mixture of nominal and interval-ratio data that will be summarized and presented descriptively. The QOL scores and other standardized questionnaire outcomes could be compared to normative values for similar patient populations. What are the CVs for the body composition and resting metabolic rate methods?
Authors reply: we had addressed statistical analysis in the data-analysis section. In addition we have replaced ''data-analysis'' with ''statistical analysis'' and removed the sub-heading ''quantitative data''. We assume that CVs is meant as covariates. Covariates for body compositions and resting metabolism will be baseline and clinical characteristics including age, gender, height and weight. The Bioelectrical Impedance Method is used to estimate body composition and resting metabolism using the Omron Full Body Sensor Body Composition Monitor and Scale.

Reviewer: 2
Reviewer Name David O. Garcia, PhD
Institution and Country University of Arizona
Mel and Enid Zuckerman College of Public Health
United States
Please state any competing interests or state 'None declared': None declared.

Please leave your comments for the authors below
This manuscript would benefit from the addition of more detail to provide clarity for the reader with regards to the study methodology. Specific concerns are related to physical activity recommendations outside of the one-to-one training sessions. In addition, the abstract structure should be revisited. Revisions for each section of the manuscript are provided.
Abstract: According to BMJ Use these headings to provide brief descriptions of the following:
• Purpose: describe why the cohort was set up
• Participants: describe who is in the cohort
• Findings to date: what data has been collected so far and any major results
• Future plans: how will the cohort be used in future, including any date for completion of data collection
• Please revisit your headings for the abstract. For instance, you can add the heading "Purpose" before stating the objective of the study.
Authors reply: we have made amendments to the abstract and added the heding ''Purpose''.
Methods and analysis:
• This is a nice description of the study participants.
• Please consider removing mortality as a secondary outcome measure given the study duration is only 10-weeks.
Authors reply: we have removed this from the text.
Ethics and dissemination:
• Please consider revising this heading to "Future Plans".
• Ethics approval can be placed in the methods section.
Authors reply: following the editorial comments, we have not altered this section.
Strengths and limitations of the study:
• This is not necessary in the abstract and provides little value to the reader- please remove from the abstract.
Authors reply: we have removed this paragraph.

Introduction:
• Very well written section.
• Page 5 Line 58- consider word choice of “lifestyle intervention”- lifestyle includes diet, physical activity, and modifying thinking habits. Your intervention is an individualized exercise program.
Authors reply: we have replaced ‘’lifestyle intervention’’ with ‘’exercise intervention’’.

• Page 6 Lines 17-22- these statements do not appear necessary. The sentences in lines 8-17 support the need to evaluate the feasibility of this intervention strategy.
Authors reply: we have removed the last two statements (lines 17-22) from the background.

Methods: Intervention:
• Page 7-8: Is a 60 minute session/week for 10 weeks sufficient? Please clarify if participants have any recommendations for what they should do outside the gym setting. If there are no recommendations, how will you control for the individuals who do more than the one-time training session?
Authors reply: the duration and frequency of the sessions was largely based on input from patient groups. In addition, general health recommendations physical activity are given (moderate-intensity exercise for 150 minutes/week) as part of standard care. We have included this statement in the ‘’intervention’’ section.
This question coheres with another issue raised regarding the assessment of total physical activity (down below under secondary outcomes). We do not assess the physical activity women perform outside of the programme, which precludes controlling for physical activity people do outside of the programme. However, as this is a feasibility study, the study will be limited in conclusions drawn regarding the effect of the intervention on QoL. We do believe this should be assessed in a more definitive trial. This issue is addressed more in detail below.

• In addition to one-to-one training, do participants receive any “lifestyle” intervention training such as problem solving or relapse prevention?
Authors reply: no, participants will not receive any other training besides the exercise training.

• While reviewing Table 1, it appears that participants will be doing aerobic exercise and strength training in a 40 minute period. How will you standardize this across participants? Is there a treatment fidelity plan in place?
Authors reply: we have allocated 20 minutes to aerobic training, 10 minutes to pillar strength training and 10 minutes to resistance training. We have amended this in Table 1 to be more explicit.
A treatment fidelity plan is in place; the personal trainer will document duration of total exercise session, time spent on each component of the training (aerobic/pillar/resistance), mentioning specific exercise performed (e.g. walking/cycling/hip flexion) and the number of repetitions. In this way we will assess the degree to which the programme is implemented as intended, and identify any problems/improvements which need to be made.

• Page 8, Lines 12-19 are not necessary as these measures should be described in the outcomes section.
Authors reply: we have removed this from the intervention section and described it within the outcomes section.

Outcomes:
• Please clarify if outcome measures will be assessed at 6 months after the exercise program is completed as shown in Figure 1.
Authors reply: The outcome measures including quality of life, psychological distress, fatigue and pain are assessed at baseline, 3 months and 6 months. The physical fitness assessments are collected at

baseline and 3 months (post-intervention). Weight and BMI are also collected at 6 months. We have further clarified this in the text.

Primary Outcome:
• Please clarify how feasibility aspects will be obtained from hospital medical files. Is there a specific time period for recruitment and how will you quantify a clinicians willingness to recruit patients based on records?
Authors reply: we have further clarified how feasibility aspects will be obtained from medical files. A clinicians willingness to recruit will be assessed through interviews with the clinical team, we have changed this in the text. The recruitment will be 12 months, which is mentioned in the ''Recruitment'' paragraph.

Secondary Outcomes:
• One important measure missing is total Physical Activity. If you cannot quantify how much physical activity the participant is performing, it will be difficult to interpret if changes on QOL are a result of the intervention or the fact that the participant has become more active overall.
Authors reply: we agree that this is an important outcome measure which is missing from our study. We have included this as a limitation of the study protocol in the discussion. However, as this is a feasibility study, limited conclusions will be drawn from changes in QoL, as our primary focus is to assess feasibility. Ideally, we would have liked to assess this with accurate measures such as an accelerometer, but unfortunately this was not possible within the study budget. In a more definitive trial, this will be incorporated as an outcome measure, as we recognise this may influence quality of life.

• Page 10, lines 31-38. Please consider the wording lean muscle tissue in place of muscle percentage. In addition, please remove mortality as a secondary outcome measure- the study duration is not sufficient enough.
Authors reply: we have replaced muscle percentage with lean muscle tissue and we have removed mortality as a secondary outcome.

Qualitative evaluation:
• Please clarify if a moderator guide will be used and how data analysis will occur.
Authors reply: a moderator guide will be used to allow structured interview. In addition, a content analysis will be performed, using simple descriptive thematic analyses by a researcher independent of the research delivery team*. We have clarified this in the text.
*: Braun, V. and V. Clark, Using thematic analysis in psychology. Qualitative Research in Psychology, 2006. 2: p. 77-101.

Recruitment:
• Please consider moving recruitment after study participants. The power calculation statement can be moved to data analysis.
Authors reply: we have implemented the suggested changes.

Data-collection:
• It appears the qualitative evaluation was expanded in this section. Please consider removing the qualitative evaluation section as it does not seem necessary with this information.
Authors reply: we have removed this from the data-collection and added a part to the description of the qualitative evaluation.

Discussion:
• Again, very well written section. Particularly the sections based on the rationale for the study physical activity recommendations.

• Page 14, paragraph 3 is focused heavily on survival. This appears tangential to your study given the focus is on improving QOL and feasibility of bringing participants into a supervised exercise program. Please consider removing.
Authors reply: we agree and we have removed this paragraph from the discussion.

VERSION 2 – REVIEW

REVIEWER	David O. Garcia University of Arizona Mel and Enid Zuckerman College of Public Health Department of Health Promotion Sciences
REVIEW RETURNED	08-Sep-2015

GENERAL COMMENTS	Authors are to be commended for addressing many concerns/comments regarding their initial submission. In your responses to reviewer #1, it appears you cited manuscripts to support your use of the 6-minute walk test but did not cite it within your manuscript. Please update this. In addition, if you are performing the walk test on a treadmill you must state this- however, it is strongly advised that you do not as advised by your reference. You will also need to add the references for your qualitative analysis. In addition, while a power analysis was not performed, you should include a target enrollment. Lastly, the study limitations need to be reworked as it is disjointed. Minimally, you may consider adding a self-reported physical activity questionnaire in the future as this will likely limit your ability to determine if your intervention increased activity. Particularly if you are going to recommend 150 minutes of moderate-intensity PA/wk. This is standard practice within intervention trials regardless if the outcomes are largely related to feasibility and is low-cost.

VERSION 2 – AUTHOR RESPONSE

Reviewer Name

David O. Garcia

Institution and Country

University of Arizona
Mel and Enid Zuckerman College of Public Health
Department of Health Promotion Sciences

Please state any competing interests or state 'None declared':
None Declared

Please leave your comments for the authors below
Authors are to be commended for addressing many concerns/comments regarding their initial submission.
2. In your responses to reviewer #1, it appears you cited manuscripts to support your use of the 6-minute walk test but did not cite it within your manuscript. Please update this.
Author's reply: we have added this reference to the text

3. In addition, if you are performing the walk test on a treadmill you must state this- however, it is strongly advised that you do not as advised by your reference.
Author's reply: we agree completely with this suggestion and recognise the limitation of performing the 6 minute walk test on a treadmill as has been outlined by the American Thoracic Society. However, we did not have access to the required 30 meter straight corridor (or 20 meter corridor) at the local gym facility. We therefore chose to assess participant's functional exercise capacity on the treadmill. In addition, our primary aim was to assess its feasibility within the protocol. In a definitive trial we aim to execute the 6 minute walk test as outlined by the American Thoracic Society.
We have amended the text to specify that a treadmill is used.

4. You will also need to add the references for your qualitative analysis.
Author's reply: we have added this reference to the text.

5. In addition, while a power analysis was not performed, you should include a target enrollment.
Author's reply: we have added this to the Recruitment section of the Methods.

6. Lastly, the study limitations need to be reworked as it is disjointed. Minimally, you may consider adding a self-reported physical activity questionnaire in the future as this will likely limit your ability to determine if your intervention increased activity. Particularly if you are going to recommend 150 minutes of moderate-intensity PA/wk. This is standard practice within intervention trials regardless if the outcomes are largely related to feasibility and is low-cost.
Author's reply: we agree with this and we will consider adding a self-reported physical activity questionnaires (most likely the Godin Leisure Time Questionnaire) to the protocol.
We have amended the study limitations to reflect this.