Title: Can physical activity help to maintain cognitive functioning and psychosocial well-being among breast cancer patients treated with chemotherapy? A Randomised Controlled Trial: Study Protocol.

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Author’s response to reviews: see over
Dear Sir/Madam

Please find enclosed the manuscript entitled ‘Can physical activity help to maintain cognitive functioning and psychosocial well-being among breast cancer patients treated with chemotherapy? A Randomised Controlled Trial: Study Protocol.’ by Kajal Gokal, Fehmidah Munir, Deborah Wallis, Samreen Ahmed, Ion Boiangu and Kiran Kancherla to be considered for an original article publication in BMC Cancer. We have no conflicts of interest to report and certify that the submission is original work and is not under review at any other publication.

The manuscript is 26 pages long and includes 1 figure and 1 table. The manuscript is a protocol for a randomised controlled trial comparing a physical activity intervention to usual care alone in adjuvant and neo adjuvant breast cancer patients receiving chemotherapy. The clinical trial aims to investigate the effects of a moderate intensity walking intervention on the cognitive and emotional functioning of female breast cancer patients receiving chemotherapy. The intervention has been designed and reported using behavior change taxonomies to enable accurate, reliable replication.

We believe the protocol would be of interest to readers of BMC cancer as it provides evidence for the need of an intervention to address cognitive and emotional side effects commonly experienced by breast cancer patients. The manuscript discusses the feasibility of the study and provides a detailed account of the home based, moderate intensity walking intervention. The study is funded by Loughborough University and has been given a favorable opinion by the NHS Research Ethics Committee in Leicestershire.

We hope that the editorial board and the reviewers will agree on the interest of this study.

Please see below for responses to reviewer’s comments:

Reviewer: Norelee Kennedy

Pg 3 Paragraph 2 – first sentence – revise this sentence to make it clearer what the argument is – do you mean frequently reported by patients as opposed to frequently reported as in a research finding? Include refs for last two sentences in this paragraph
3rd paragraph – first sentence reads like a reference to specific study findings – please give more detail on the study and situate the study better ie with an introduction to this paragraph and relate it more to breast cancer and chemotherapy

Argument for evidence of cognitive decline in breast cancer patients treated with chemotherapy needs to be better made. Introduction starts with a general introduction to cognitive issues post chemotherapy. It is not clear the magnitude of the problem in breast cancer to make a case for why an intervention is needed.

The above comments have been addressed and the literature review/background information has been modified to include a clearer argument for the need of an intervention to address chemotherapy induced cognitive difficulties.

Benefits of PA are well described – however it is assumed that cognition responses will be similar in this population to healthy individuals, children and the elderly. Can it be assumed that cognitive functioning will respond to PA in a similar way in people undergoing chemotherapy?

This section of the literature review has been supported with references from previous intervention addressing cognitive function in other populations-it is fair to assume similar benefits in managing cognitive function will be demonstrated in chemotherapy patients.

Why is a home based programme proposed as opposed to a lab based study to explore effects followed by a home based study to explore further practicalities, feasibility, acceptability?

The choice of a home-based study has now been justified within the literature review

On what basis is the judgment re suitability to participate in moderate exercise being made? Will any objective measurement of fitness be used in that decision making?

Additional information has been provided to clearly show that the oncologists will subjectively judge suitable participants- no objective measures will be used

Who will invite the participants to the study?

This information has been made clearer- the researcher will invite participants to take part in the study following initial recommendations from the oncologists.

Change grammar tense to “will be assessed” and will complete”

These concerns regarding tense have been addressed.

Age range of participants is wide – how will natural differences in cognitive function associated with age be accounted for?

Natural differences in cognitive function will be addressed by including age as a covariate in mixed measures analysis.

Add – receiving chemotherapy as an inclusion criterion. Add not meeting PA guidelines as a criterion

These criterion have now been added.
Who will determine the exclusion criteria?

It has now been made clearer that the researcher will conduct all stages of the study including recruitment, data collection and delivery of the intervention.

Explain why pseudo randomisation is being done. How will it be done? Why is not possible to blind the allocation and the research team?

The method of randomisation has been changed to block randomisation as opposed to pseudo randomisation and this choice has been justified. Due to the nature of the study it is not possible to blind the allocation as participants need to complete the PA intervention. The researcher will carry out all stages of the study including recruitment, randomisation and delivery of the intervention and therefore it is not possible to blind the researcher.

Justify why 12 weeks for the intervention.

The choice of a 12 week intervention has now been justified.

Will the period of time to get to 30 mins activity per week be part of the 12 week intervention?

Increasing PA to get to 30 mins of activity will not be part of the intervention.

Measures of PA – what accelerometer will be used to measure PA?

ActiGraph GT3X+ accelerometers will be used- this is now stated in the manuscript.

Pedometers are not accelerometers and will not measure intensity.

Pedometers are not used to measure intensity but to monitor steps and motivate participants to walk.

Why 10 hours wear time for the monitor?

This decision was based on previous literature and has been included to justify the decision.

In what order will the questionnaires be completed?

The order of questionnaire completion has now been stated.

What previously published data was used for the sample size calculations? What is the primary outcome measure?

Previously published data to calculate sample size have been referenced and the the primary outcome measure (memory- measured using digit span) is clearly stated.

Review No.2
Reviewer: Christine Friedenreich
Reviewer's report:
General Comments:

The authors present a novel physical activity intervention that they are proposing in breast cancer patients undergoing chemotherapy that is aimed at improving
their emotional and cognitive functioning after treatment. This area has not been adequately researched to date, hence, this study will be a welcome addition to the scientific literature.

Some specific comments are provided for consideration by the authors.

1. The authors are proposing a pseudo-randomization in this study which is not justified or explained in any detail. This study design decision is crucial and could severely limit the results from this study. Hence, more detail and justification are needed, or, better yet the authors should consider using a proper randomized controlled exercise intervention trial design.

As mentioned above, this concern has now been altered and block randomisation is explained and justified.

2. The home-based walking intervention appears to have one weakness. The authors suggest that the participants will be asked to "reflect upon their achievements or shortfalls from the previous week and to take these into consideration by modifying their goals to ensure they are realistic and achievable". The goals for an intervention should be set out by the study design and the investigators rather than allowing participants to decide what they will be doing in any given week of the trial. There should be a clear protocol of increasing intensity, frequency and duration of activity in the ramp-up period and then a maintenance of the exercise prescription for the duration of the intervention. Hence, this section needs either further clarification or some modification to ensure that there is some standardization in the exercise prescription for all study participants in this trial.

The intervention is self-prescribed allowing patients to take control and manage their own walking schedules.

3. It is unclear why the exercise intervention starts mid-way through treatment rather than at the outset. It is commonly understood that there is a cumulative effect of chemotherapy on patients' wellbeing and physical function. Hence, it would increase the likelihood of success of this trial, if the exercise intervention were to begin before treatment or at least at the same time as treatment onset. In so doing, the participants would have the opportunity to begin exercising whilst they are still feeling relatively good and before the effects of chemotherapy become more severe.

The intervention is implemented mid treatment following suggestions from oncologists regarding feasibility and adherence to walking. This is now explained in the manuscript.

4. Further to point #2, the walking schedules are self-prescribed - does this point mean that the participants are allowed to walk whenever they wish? If so, that is fine. However, if it means that the actual weekly exercise prescription can be modified by the participants, there could be problems with exercise adherence and achieving the full exercise prescription.

The intervention is self-prescribed and patients are allowed to walk whenever they wish.

5. The statistical analysis does not include any discussion of an ITT or per protocol approach, nor is there any inclusion of mixed linear regression models. Indeed, the statistical analysis section could be enhanced and more detailed throughout with more explanation of what will be undertaken to address all the main questions being examined in this trial.
The statistical section has now been modified, more detail is given and ITT is also referred to.

6. The authors need to ensure that they have provided all of the details of their study methods as required for the CONSORT guidelines. It is recommended that they consult the checklist to ensure that all details are presented here.

The CONSORT checklist has been used to ensure all details are presented in the manuscript.

7. The manuscript could use some revision to improve the overall English writing style. Some problems that were encountered included long sentences, difficult grammar, split infinitives, the use of "this" without a noun after it, the use of "upon" instead of "on" in several instances. The language throughout could be tightened and made more precise.

The manuscript has been checked and proof read again.

8. The paper would be enhanced if a flow chart of study methods was included.

A flow chart has now been included.

Yours faithfully,
Miss Kajal Gokal on behalf of the authors

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