Author’s response to reviews

Title: Pilot randomised controlled trial of Weight Watchers® referral with or without dietitian-led group support for weight loss in women treated for breast cancer: the BRIGHT (BReast cancer weIGHT loss) trial.

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Version: 1 Date: 15 Aug 2018

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Author’s response to reviews:

Many thanks for considering our manuscript for publication and for providing us with a set of extremely helpful comments. We would like to thank all four reviewers for their comments, questions and suggestions on this manuscript. We found their suggestions very useful in clarifying our thinking and improving the manuscript. We have responded to each comment in turn below and reference specific portions of the revised manuscript where the reviewers’ comments are addressed. Changes in the revised text have been made using the track changes mode.

We look forward to hearing from you.

Yours sincerely,

Dr Rumana Newlands
(On behalf of all authors)

Reviewer #1: The BRIGHT Study was a pilot randomized controlled trial (RCT) that assessed the feasibility of implementing a breast cancer-tailored dietetic support with generic Weight Watchers (WW) referral as compared to generic WW referral or a control. Participants were randomized to receive a 12 session WW referral plus five breast cancer-tailored dietitian led group support (WW Plus group), a WW referral (WW group) or a WW referral after three months (Controls). At two time points (3 and 12 months) the authors measured change in body weight and QoL using the FACT-B questionnaire. I thought that this feasibility study protocol explored a very interesting clinical question and addresses the lack of research investigating weight loss among women with breast cancer. However, I do have a few comments:

Major Limitations

1. In the Abstract it states that: "This article reports the feasibility of the procedures and the outcomes of changes in body weight and quality of life in a parallel group-based intervention for women treated for breast cancer." I would suggest rewording this sentence because I feel that it does not truly capture the objective of your trial.
Our response: The ‘Background’ section has been edited to address this suggestion. Please see Page 2.

2. I found the discussion of weight gain in women with breast intriguing. It would be interesting if you could add a point on the factors that contribute to weight gain in women with breast cancer.

Our response: A sentence has been added under Background, 1st paragraph. Please see Page 3, line 17-22.

3. (line 25, page 3) "…teachable moment…” One could also argue that cancer patients could be more motivated to engage in healthy behaviors (ie healthy volunteer bias). This could be mentioned in the Background section.

Our response: A sentence has been added to address this suggestion. Please see Page 4, line 13-14.

4. I found that the primary and secondary objectives of the trial were not clearly outlined within the Manuscript. To provide more clarity, I would suggest that the authors incorporate the following sentences from the Methods section into the Background section:

(line 27, page 4) "The research question asked was: Is additional breast cancer-tailored dietetic support with generic WW referral.."

(line 32, page 4) "…The primary outcome assessed was feasibility of the trial procedures from recruitment till trial exit. The secondary outcomes assessed were changes in body weight and quality of life (QoL) (trial outcomes)."

Our response: These sentences are now moved as suggested, under Background section. Please see Page 5, line 18-22.

5. It was stated that: (line 7, page 5): "Formal sample size power calculations were not required… programmes and possibility of pregnancy, to assess their eligibility." What was the authors rationale for recruiting 30 patients per arm? Furthermore, 45 patients were enrolled in the trial, which is about half of what the authors expected (N = 90). It would be helpful if the authors could discuss this point and implications for future RCTS.
Our response: We have clarified the sampling process of our study further to address this comment. Please see Page 6, line 28-34.

We have also edited the Discussion section. Please see Page 26, line 23-27; Page 31, line 34-35 and Page 33, line 3-12.

6. Although it was stated that women were recruited from a breast clinic at ARI, I am unclear of how and when patients consented to join the pilot trial. Furthermore, I am unclear of why baseline measurements were taken prior to randomization. Since this was an open-label trial, there may be a disproportional rate of drop-outs.

Our responses: Thank you for this query. Women were recruited from a breast clinic at the local hospital, ARI by sending out an invitation letter. Then women who were interested in taking part in the trial sent the opt-in form back to the researcher. Based on this opt in form eligible participants were contacted to attend the Maggie’s centre for a baseline meeting. At this meeting, women were asked to give their written informed consent (see Page 7, line 10-11) and then, for consenting participants, their height and weight were measured.

We decided to use these methods to avoid recruiting participants with a ≤healthy BMI and/or to minimise differences between groups. We learned from previous work that often patients could not remember their current height and weight or reported a weight and/or height that were taken a long time ago. Please see Page 7, line 12-13.

In relation to drop-outs our overall retention rate was 84% (WW plus= 93%, WW group= 81% and control= 80%) in this small sample. Participants seemed satisfied otherwise it is unlikely that they would have continued and consequently the study would have had a poor retention rate. Please see Page 19, line 32-33.

7. Although the authors did a good job at explaining the treatment arms of the trial, the manuscript would benefit from a small section describing the trial design and including a statement on when the primary and secondary outcomes were measured (i.e. baseline, trial exit). For instance, the trial exit is introduced on (Line 31, page 7) and (line 33, page 7) yet there is not a clear description in the Methods Section. Also it would be beneficial if the authors could discuss the protocol amendment to extend follow-up to 12 months in this section and what happened to patients after the trial exit.

Our Response: Thank you for the suggestions. A new sub-heading has now been added under Methods called ‘Trial Design’. Please see Page 5, line 26.

Text has been moved as suggested under ‘Trial Design’. Please see Page 6, line 13-17.
8. If the information is available, please provide more details on the patient characteristics (Table 3), including: "..completed initial treatment (surgery, chemotherapy and/or radiotherapy) for breast cancer…" was done in the neoadjuvant or adjuvant setting, stage of cancer and how many patients had ongoing treatment during the trial.

Our response: No other data were collected other than those are reported in the Table 3. In a future trial, we would consider collecting additional data as suggested.

All participants completed their initial treatments which was one of the inclusion criteria for the BRGHT trial.

9. There appears to be an imbalance in Table 1 for the "Menopausal status at diagnosis". Please comment.

Our response: In Table 3 (Page 20) age, BMI and Time since diagnosis were used for the purpose of minimising differences across groups in the randomisation process. Menopausal status could be used as minimisation factor in the future RCT to ensure better balance between groups.

10. It would be interesting if the authors could also discuss RCTs that have assessed the effect of the Mediterranean diet in patients with breast cancer.

Our response: We have added a sentence under Background to address this suggestion. Please see Page 3 line 33.

11. What is the minimally important difference of the FACT-B questionnaire for this patient population? Also please provide the completion rates for the QoL questionnaire.

Our response: The suggested minimally important differences (MID) for this scale: BCS = 2–3 points, TOI = 5–6 points, FACT-G total = 5–6 points, and FACT-Breast total = 7–8 points.

The section Changes in QoL has been edited and sentences added explaining MID, the suggested MID for FACT-B and also findings of the BRIGHT trial in relation to MID. Please see Page 26, line 7.

Table 5 has been edited. Please see Page 28 and added footnotes.

In relation to completion rates for QoL Q, it was same as the data available at each time point, as already stated under Retention (Page 19, line 32).
It should be noted that we performed Intention to treat analysis for both secondary outcomes.

12. (line 15, page 6) "The trial was run in two batches: Batch 1 (November 2013- February 2013) and Batch 2 (March-June 16 2014) to avoid a long interval between recruitment, baseline meeting and trial entry." Did recruitment, baseline measurements and randomization occur at these different times? Would future RCTs use this approach?

Our response: Yes, recruitment, baseline measurements and randomisation occurred at two different time points for Batch 1 & 2 to reduce the ‘waiting time’ and ‘disappointments’ between recruitment, baseline meeting (taken consent and measured height and weight) and trial entry and also to incorporate the ‘current/baseline weight/QoL scores soon after measuring at baseline to capture any true changes at trial exit.

Depending on how many hospitals/sites get involved and based on sample size required, this approach could be modified in the future trials.

13. It was stated that (line 13, page 9) "the proportion of patients who had lost 5% or more...." and that (line 28, page 16) "...WW Plus group achieved clinically important >5% loss...". Although it was described in the Discussion section, it would be helpful if the authors could mention the clinical relevance of a ≥ 5% weight loss in the Methods section.

Our response: A sentence that explains the clinical relevance of ≥ 5% weight loss has been moved to ‘Data collection, management and analysis’ from the Discussion section. Please see Page 11, line 31-33.

14. For the paragraph (line 17, page 17) "Participants from the WW group (46%, 5/11) reported having attended WW meetings more often than … vegetables and reduction of the amount of "fattening" foods following trial exit." I feel that this section should be moved to the "Adherence" Results section.

Our response: As suggested, we have added a new sub-section called ‘Adherence’ under Results and the sentences are moved here. Please see Page 22, line 1.

15. The authors should also mention in the Limitations section that a long-term weight loss intervention may be required to observe a difference in weight-loss and an impact on survival.
Our response: A sentence has been added under Strengths and limitations. Please see Page 32, line 6-8.

Minor Limitations

1. Please provide the allocation ratio.

Our response: It has been added now. Please see Page 8, line 2.

2. It would be helpful if the authors could indicate in the Methods section if any study personal, participants, statisticians were blinded during the trial. This information is scattered throughout the manuscript.

Our response: to address this suggestion a sentence has been added under ‘Trial Design’, Page 6, line 17-19.

3. A period needs to be added (line 15, page 17): "… finishing the BRIGHT trial Finally…”

Our response: a ‘full stop’ has been inserted as suggested. This section has been moved under ‘Adherence’, Page 22, line 6.

Reviewer #2: The study describes a feasibility randomised controlled trial with women treated for breast cancer (age ≥18 years) comparing Weight Watchers® referral plus five breast cancer-tailored dietitian led group support sessions or Weight Watchers® referral only with Control. Overall I thought that the paper was well laid out and the intervention of sound concept. I do however think that more details could be included to make the study clearer to the reader. Nevertheless, I feel that these changes are minor and would recommend publication of the manuscript once the comments presented below have been addressed.

1. The authors refer to the study as both a "feasibility" and "pilot" study/trial, the introduction section could be enhanced by the addition of some further details on the terminology used. See article: Eldridge et al. (2016) Defining Feasibility and Pilot Studies in Preparation for Randomised Controlled Trials: Development of a Conceptual Framework. PLoS ONE 11(3): e0150205.
Our response: A great suggestion, thank you. This study is now called a ‘pilot trial’ based on the suggested literature. A sentence has been added under Background section. Please see Page 5, line 11.

The title of the study has been edited accordingly. Please see Page 1.

2. The authors aimed to recruit 30 participants per arm, stating that a formal sample size calculation was not required. Some additional details on how 30 was set would be of use (i.e. was this based on previous research in similar populations)

Our response: This section regarding sample size has been edited for further clarification. Please see Page 6, line 28.

3. The authors state that one of the exclusion criteria was "Participated in Weight Watchers programme within the previous three months" - why was the cut-off of 3 months used?

Our response: It was one of the criteria set by the Weight Watchers research programme in order to be eligible for membership via WW referral system.

A footnote under Table 1 has been added and superscript used to highlight the criteria set by WW (Page. 7, line 4).

4. Apart from the fidelity checklist for adherence to content etc. little detail is given as to how the primary outcomes were recorded (i.e. all primary outcome data (quantitative and qualitative) were documented from beginning until trial exit in the form of field notes) more details would be useful in the primary outcomes and data collection, management … sections.

Our response: Data collection, management and analysis section (pg. 10-12) has been edited now and more information has provided as requested. Please see Page 10, line 32.

5. The authors state that "other lifestyle changes such as dietary habit and physical activity" were recorded - more details on how this was done would be useful.

Our response: This section under Secondary outcomes has been edited and expanded to address this comment. Please see Page 10, line 27.
6. The authors elaborate on how the quantitative data was analysed but not the qualitative. Some details should be given on this.

Our response: Thank you for this suggestion. We have edited the section under Data collection management and analysis to address this comment. Please see Page 11, line 18.

7. In the recruitment section: "Recruitment by one researcher (RN) at one hospital breast cancer out-patient clinic took four months." Is this what was expected? Ability to successfully reach target recruitment numbers within a set time would be an interesting discussion point.

Our response:

We did not set any time frame in the BRIGHT trial protocol as the purpose was to check the feasibility of this process. However, we aimed to recruit n= 90 in the trial and we could not reach this target within the resources available.

Please see response to Reviewer 1, comment 5 (Page 3) above.

A sentence has been added under Results/Recruitment to show how long it took to screen patient notes at the clinic). Please see Page 12, line 15. Also the Discussion section has been edited to address this comment. Please see Page 26, line 23-27; Page 31, line 34-35 and Page 33, line 3-12.

8. It is unclear what "No modification was done in the dietitian-led session contents or delivery during the course of the study" (Pg.15; Ln. 19) means.

Our response: We have edited the sentence. Please see Page 22, line 29.

General comments

1. Pg. 4 Ln. 20 "This article reports the feasibility of the trial procedures and the outcomes relate to participants in the feasibility trial." Should relate be related?

Our response: This sentence has been edited now as suggested. Please see Page 5, line 10.

2. Double check the spacing before and after full stops.

Our response: Thank you. This has been done as suggested.
3. The wording "face-to-face" and "one-to-one" is used interchangeably, this should be consistent when referring to the same follow-up meeting.

Our response: Face-to-face has been deleted and replaced with one-to-one under the section Retention (Page 20, line 10).

4. Double check the quality of the figures.

Our response: A new version of the flowchart figure has been uploaded. Thank you.

5. Baseline meeting: Potential participants were invited to attend a one-to-one baseline meeting with RN at the Maggie's… Suggest putting meeting with the researcher then (RN). My first thought was that this was a one-to-one baseline meeting with a registered nutritionist

Our response: Thank you, this has been edited throughout the manuscript as suggested. Please see. Page 6, line 19; Page 7, line 6; Page 8, line 1, 6, 19; Page 9, line 27; Page 10, line 17, 20; Page 11, line 10, 20, 25; Page 19, line 6; Page 23, line 20.

6. Full stop missing after BRIGHT trail (Pg. 17; Ln. 15).

Our response: Thank you for spotting this error. This section has moved now under ‘Adherence’ and a ‘full stop’ has inserted. Please see Page 22, line 6.

Reviewer #3: An interesting study. Well written. I have listed a few queries below.

TITLE

Perhaps modify to be: Feasibility "of a" randomised….  

Our response: The title has been edited. Please see Page 1 and also comments from Reviewer 2 (comment 1, Page 7 in this document)

ABSTRACT

* Method doesn't mention 12 month follow-up
Our response: The last sentence in the Methods has mentioned of 12 months follow-up as: Outcomes were measured at 0, 3 (‘trial exit’) and 12 months post intervention (please see Page 2, line 19).

* Results do not report all feasibility criteria mentioned in the abstract. For example, recruitment rate suggests that it is about recruiting a certain number of participants within a time frame but these data are not presented.

Our response: The Results section has been edited to report findings related to feasibility criteria. Please see Page 2, line 24.

* Line 22 - direction of the difference between the groups?

Our response: This sentence has been edited. Please see Page 2, line 33.

* Line 23 - is % weight loss at 12 months a key criteria to report if it was not part of the original study design? (Method - page 8). Participants were unaware that there would be follow-up…were they told to keep losing weight at trial exit?

Our response: A target weight loss of ≥5% from baseline weight within six months for weight loss programmes is recommended by weight management guidelines. This section has been edited under Data collection, management and analysis to reflect the importance of assessing this 5% weight loss changes. Please see Page 11, line 31 (also see comments from reviewer 1, comment 13, Page 6 of this document).

This section has been edited under Trial Design to clarify this query further. Please see Page 6, line 16.

* Line 26 - I don't feel that you have presented enough data in your results to support your statement that the trial procedures were feasible.

Our response: The Results section has been edited to address this comment. Please see Page 2.

The sentence has been edited under Conclusion. Please see Page 3, line 4
INTRODUCTION

* Page 3 Line 20 - perhaps include a couple of examples of breast-cancer related outcomes
   
   Our response: Two examples are added. Please see Page 4, line 6.

* Page 3 Line 34 - consider changing to "evaluate the feasibility of a weight loss RCT"
   
   Our response: This sentence has been edited as suggested. Please see Page 4, line 23.

   Please also see Reviewer 2, comment 1 (Page 7 of this document) as this trial is called a ‘pilot’ trial now.

* I think the introduction could be strengthened by including a list of specific objectives of the study
   
   Our response: The last paragraph of the Background has been edited to add primary and secondary objectives. Please see Page 5, line 18.

   These objectives are explained further under Methods-Outcomes-Primary (Page 9, line 33) and secondary outcome (Page 10, line 16) and Data collection, management and analysis (Page 10, line 31).

METHODS

* Table 1 - can you clarify - how long was it since they had completed treatment?
   
   Our response: Previous systematic reviews and our preliminary work suggested a wide range of timing that would suit cancer survivors joining a weight loss programme. Therefore, we decided not to set any time gap between women finishing treatment and trial entry and instead, we wanted to observe at what time point women were interested to take part in a weight loss intervention.

* Page 6 line 15: perhaps "cohort" would be a better descriptor than "batches"
   
   Our response: The sentence has been edited as suggested. Please see Page 6, line 6.

   Other sentences with ‘batch’ are also edited: Page 19, line 5 and 29, 30.
Page 8 - I cannot seem to find a clear list of objectives and associated criteria which were used to determine feasibility. This should be included.

Our response: The Primary outcomes section has been edited. Please see Page 9, line 33

Further information on what data was collected and how are discussed under Data collection, management and analysis (Page 10, line 31).

RESULTS

* Related to the comment above about listing objectives and specific criteria that were used to determine feasibility- this limited interpretation of table 2. For instance, how did you determine that your invite letter was "feasible" and "acceptable". This table should be revised to include the criteria so that it is possible to see whether they were met or not. The text may also need to be update to reflect these changes.

Our response: Table 2 has been edited as suggested (Page 15)

* Page 16. Changes in body weight are listed in the text, and the table, and shown in a figure. Need to pick one…

Our response: This section has been edited under Changes in body weight to address this comment. Please see Page 24, line 4.

* Page 18 Line 6: what was the time frame for the improvement in the QoL parameters in this statement - 3 months?

Our response: This sentence has been edited to add both trial exit and 12 months follow-up. Please see Page 25, line 17. We have also clarified throughout paragraph.

DISCUSSION

* Page 18, Line 23 - check grammar

Our response: The Discussion has been edited. Please see Page 26, line 16-19.
* Page 21, line 1. Suggest symptoms were less severe than closer to diagnosis. Can you include a statement around how severe they are, or a comparison to levels in general population?

Our response: Sentences have been added to address this comment. Please see Page 30, line 35.

Reviewer #4: This is an interesting paper that fully describes the protocol and related feasibility considerations.

A limitation of the study is that it takes place in a single centre and has been coordinated by an individual with great enthusiasm for the project. There is little discussion of the impact of this dedicated coordinator on the feasibility of the trial and considerations for a possible future larger multi-site trial. Likewise, the time taken to recruit could be alleviated by having more than one site. The paper would benefit from a discussion of considerations for a multi-site study and the impact that this might have on time to recruit. For example, a sample size estimate could be made together with an estimate of the time needed to recruit this number with a single or multi-site.

Our response: The manuscript has been edited in several sections to address this comment.

- Please see Page 26, line 24
- Please see Page 31, line 22
- Please see Page 31, line 34.

We have also included sample size estimates for a larger trial (see page 33 & Appendix 4)

The paper describes the participants of the study in terms of age, menopausal status and body weight/BMI. However, it may be pertinent to also discuss the ethnicity of the participants and how the WW intervention can be adapted to different cultural and religious dietary behaviours. If all participants in the study were of a single ethnicity then this is something that may need to be considered in a future trial.

Our response: A sentence under Results/Baseline Characteristic has been added (Page 19, line 23).

Sentences have been added under ‘Overview of the Weight Watchers Programme’ to highlight that this programme is suitable for a wide range people with different cultural/dietary restrictions. Please see Page 9, line 1 and Page 32, line 31 to address the comment on whether any adaptations required in future trial.
Although not designed to assess the recurrence rate of breast cancer is there published data on recurrence rates at varying timepoints? The follow up duration of a future study together with the length of WW or control intervention may need to be considered as a 12 week program may not be sufficient in a follow up of, for example, 5 years.

Our response: Data related to survival/mortality prediction is available (Breast cancer survival statistics, available at https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/mortality). Based on these data (post diagnosis follow-up, between 5-10 years) and other literature related to lifestyle interventions/Weight loss RCTs in cancer survivors (between 5-10 years), in future RCTs, the follow up period could be set as 10 years or over to assess any relapse free survival and/or overall mortality.

The sentence Under Conclusions has been edited. Please see Page 33, line 31.

Aside from those points it was an interesting read and a well written paper.

Thank you.

Other additional changes made by the author:

1. We have edited the Title page, some institutional details of the co-authors. Please see Page 1.

2. We have changed the Version number and date. Please see Page 1.

3. We have edited the ‘Methods’ section under Abstract to maintain the same order of feasibility components as discussed under Results (e.g. retention has moved earlier in the sentence). Please see Page 2.

4. The caption of figure 1 changed (pilot inserted), see Page 18.

5. We have edited the section to remove ‘randomised controlled trial’ which has been mentioned earlier on; please see Page 4, line 23.

6. We have edited the section under Trial design to remove ‘feasibility’ and insert ‘pilot’. Please see Page 5, line 27. We have also edited a sentence under this section for further clarity. Please see Page 5, line 31.
7. Under Trial Arms- Control Group (Page 9, line 30) ‘3 months’ following randomisation’ edited and changed to ‘12 weeks’ to be consistent as we stated duration in ‘weeks’ in other places.

8. A sentence deleted under Primary Outcome to avoid repetition. Please see Page 9, line 34.

9. A complete new section has been added ‘Possible Next Steps’ to explain the contents and mechanisms of the future trial procedures based on the BRIGHT trial findings. I believe this section was missing in our previous version of the manuscript. Please see Page 32, line 18.

10. A sentence has moved to Secondary outcomes and expanded for further clarification (Page 10, line 21).

11. Deleted ‘recruited’ and inserted ‘invited’ as it’s the correct wording in this context (Page 29, line 35).

12. Added Appendix 4 (sample size calculation).

13. Additional minor changes to correct spellings, grammar or for clarity.