PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	BREAst Cancer Personalized NuTrition (BREACPNT) - dietary intervention in breast cancer survivors treated with endocrine therapy: A protocol for a randomized clinical trial
AUTHORS	Gal-Yam, Einav Nili; Rein, Michal; Dadiani, Maya; Godneva, Anastasia; Bakalenik-Gavry, Michal; Morzaev-Sulzbach, Dana; Vachnish, Yaeli; Kolobkov, Dmitry; Lotan-Pompan, maya; Weinberger, Adina; Segal, Eran

VERSION 1 – REVIEW

REVIEWER	Barratt, Alexandra University of Sydney, School of Public Health
REVIEW RETURNED	25-Apr-2022

GENERAL COMMENTS	This manuscript describes the rationale and study design of a phase 2 randomized controlled trial of a dietary intervention among women with breast cancer undergoing treatment with endocrine therapy. The intervention will be of wide interest given the commonness of the condition, and high frequency of weight gain on endocrine therapy. The manuscript is well written and provides a clear and detailed account of the rationale, aims, hypotheses and study design. There is a protocol and a completed SPIRIT checklist. Overall the investigators have done a very thorough and competent job. However I have some questions which could be addressed, and I have included some suggestions below (informed by CONSORT and SPIRIT statements) Questions Why is the study described as a phase 2 rather than phase 3 trial? It is describing the evaluation of the effectiveness of a well developed intervention against dietary standard care, with short and long term follow up and assessment of outcomes, so I would think it would warrant the label phase 3? Why is it described as single blind when patients and study team (presume including those people assessing outcomes) are blinded (see p11)? Why is Mediterranean diet chosen as the comparator? I'm sure there's a good reason, but I can't find it beyond a brief statement in the Abstract that it is the standard. A brief rationale and justification would be useful. When did the study start recruiting? I apologise if I have overlooked it, but I couldn't find it. Over half the anticipated sample size has already been recruited. However only 60 /120 participants

	recruited have completed the intervention and only 38 have completed the 12 month follow-up so far. This could be because insufficient time has elapsed? However, it does make me wonder whether the anticipated 10% loss to follow-up described in Statistical Considerations/ Sample Size is realistic and whether there have been difficulties in achieving the desired recruitment and follow-up rates? Suggestions for manuscript Consider adding words randomised trial to the title Add start date when study recruitment began Methods (page 5) – It may be useful to refer to the completed SPIRIT checklist (if it is to be published as supplementary material) If the protocol is to be published as a Supplementary file, please refer to it. The Intervention is generally well described, including the prediction algorithm with reference to its validation. I note that it may not be replicable by other investigators without access to the model. This might be added as a limitation? P9 Line 21 in Screening and profiling What is CBC? P11 Please give more details on the random allocation procedure including:- Who will do the consent and randomization? What happens to participants who fail the screening and profiling stage eg provide incomplete or unusable data? Confirm the computer randomization will provide allocation concealment Is it realistic to have 5 stratification factors with only 100 participants in each arm? Are these factors being used to minimize differences between groups in the allocation process rather than stratification on each? Outcome measurement and blinding – please clarify exactly who is blinded and/or reconsider use of the term single blind? Sample size and Statistical analysis – I think the sample size is sufficient for the primary outcome, but I'm not convinced it will be sufficient for analysing the secondary or exploratory outcomes. In particular I would be concerned about the ability to look at disease free survival. This may also need a multivariate analysis as the randomisation may not distribute all important confounders evenly given the relatively small sample size. Some discussion of these issues and limitations might be added to the Discussion. Discussion p 15-16 focuses on the dietary aspects of the study. I suggest adding some brief discussion of the methodological strengths and limitations of the study (eg see above).

REVIEWER	Knapp, Guido Technicsche Universitat Dortmund
REVIEW RETURNED	14-May-2022

GENERAL COMMENTS	This is a study protocol of an ongoing study. I have only some minor remarks/questions to the analysis/statistics: Caloric target calculation: ad 2. divided or muliplied by 0.7? I do not know the equation. Sample size determination: Which test / distributional assumption has been used for the calculation?

	Primary endpoint analysis: Which test should be used for the analysis of the primary endpoint?

REVIEWER	Lin, Pao-Hwa Duke University Medical Center, Department of Medicine
REVIEW RETURNED	14-May-2022

GENERAL COMMENTS	This manuscript describes the rationale and design of a randomized trial comparing an algorithm-based diet intervention to a Mediterranean diet for 6 months on weight and glycemic control. The study design is very innovative and is based on the authors' previous experience and evidence. The manuscript is relatively well written, except for some unclear areas. 1. Though the algorithm was previous developed, this manuscript should include a very brief summary of the algorithm including the goal of the algorithm. 2. The study timing, especially for the key steps (profiling, randomization, intervention and follow up) is unclearly described in the abstract and Methods. Figure 1 is very helpful. 3. Box 1-secondary endpoint is unclear. What is the glycemic response that will be used, average of all data during the two weeks period? Exploratory endpoints are also unclear regarding timing. 4. Page 10 of 61, line 10-11, what is the target for the personal dietary recommendations? 5. Page 14 of 61, lines 30-35, the sample calculation of the grade is unclear. How were the 600 kcal and 1000 kcal of meals included in the formula? 6. Page 14 of 61, line 50, what is the recommended amount of fiber? Is there a fiber target for Med arm and another personalized target for the algorithm arm?

VERSION 1 – AUTHOR RESPONSE

Reviewer# 1
Prof. Alexandra Barratt, University of Sydney

We thank Prof. Alexandra Barratt, for her appreciation of our work and its importance.

Comments to the Author:
This manuscript describes the rationale and study design of a phase 2 randomized controlled trial of a dietary intervention among women with breast cancer undergoing treatment with endocrine therapy. The intervention will be of wide interest given the commonness of the condition, and high frequency of weight gain on endocrine therapy.
The manuscript is well written and provides a clear and detailed account of the rationale, aims, hypotheses and study design. There is a protocol and a completed SPIRIT checklist. Overall the investigators have done a very thorough and competent job. However I have some questions which could be addressed, and I have included some suggestions below (informed by CONSORT and SPIRIT statements)

Questions
Why is the study described as a phase 2 rather than phase 3 trial? It is describing the evaluation of the effectiveness of a well developed intervention against dietary standard care, with short and long term follow up and assessment of outcomes, so I would think it would warrant the label phase 3?

A- Phase 2 randomized trial design was chosen to allow recruitment of a relatively small cohort (N=200) with a larger type I error rate than usually used in a phase III design. While long term follow up will be performed – due to the cohort size we do not expect a statistically significant survival difference between the groups. If results are positive in this trial it will pave the way to a larger phase 3 trial.

Why is it described as single blind when patients and study team (presume including those people assessing outcomes) are blinded (see p11)?

A- This study is defined as single blind since the dietitians, part of the study team, are aware of the study arm of the participants and provide dietary recommendations accordingly. In addition, although anthropometric measurements (including weight as part of the primary outcome), are measured by the study coordinator which is blinded to the study arm , the study dietitians are aware of the participants weight changes and discuss them during the monthly meetings.
Importantly, the study participants, study coordinators and the clinical staff from the breast cancer clinic in Sheba medical center are blinded to the study arm, assigned for each participant.
We added a clarification to the methods section, randomization, page 9:
“Patients and part of the study team (oncologists and study coordinators), excluding the dietitian, will be blinded to the study arm assigned. At the end of intervention, dietary assignment was revealed, and participants were asked to continue following their respective diets for 6 additional months.”

Why is the Mediterranean diet chosen as the comparator? I’m sure there’s a good reason, but I can’t find it beyond a brief statement in the Abstract that it is the standard. A brief rationale and justification would be useful.

A- Dietary guidelines for breast cancer survivors aim to induce weight loss and to improve metabolic health in the short term and further to decrease the risk of disease recurrence(1,2). As a control diet, compared to the PPT dietary approach, we chose the Mediterranean (MED) diet because it is commonly recommended in national guidelines of different countries including Israel (3) and was suggested to improve metabolic health in the general population as well as within breast cancer survivors (4–6).
We added this additional explanation to the revised manuscript, introduction section, page 4: “… We chose the Mediterranean (MED) diet as a control diet because it is commonly recommended in different countries including Israel and was suggested to improve metabolic health in the general population as well as within breast cancer survivors”.

When did the study start recruiting? I apologise if I have overlooked it, but I couldn’t find it. Over half the anticipated sample size has already been recruited. However only 60 /120 participants recruited have completed the intervention and only 38 have completed the 12 month follow-up so far. This could be because insufficient time has elapsed? However, it does make me wonder whether the anticipated 10% loss to follow-up described in Statistical Considerations/ Sample Size is realistic and whether there have been difficulties in achieving the desired recruitment and follow-up rates?

A- The study recruitment was initiated in July 2019 and the study is ongoing. The numbers reported represent the number of participants that have already reached the mentioned stages (either 6m time point or 12m - long term follow-up - time point). Re recruitment rate, there was an expected slow down in recruitment due to the COVID-19 epidemic but after the initial months of the epidemics recruitment has caught up and has been going on well. We added the following information:

"...Enrollment and recruitment initiated in July 2019" to the revised manuscript, current status section, page 16.

Suggestions for manuscript

A- Consider adding words randomized trial to the title
We have changed the title according to the suggestion. The revised title is: BREAst Cancer Personalized NuTrition (BREACPNT) - dietary intervention in breast cancer survivors treated with endocrine therapy: Protocol for a randomized clinical trial

Add start date when study recruitment began
A- Done. See the revised manuscript, current status section, page 16

Methods (page 5) – It may be useful to refer to the completed SPIRIT checklist (if it is to be published as supplementary material) If the protocol is to be published as a Supplementary file, please refer to it.
A- Done for both SPIRIT checklist and study protocol, revised manuscript, methods section page 5.

The Intervention is generally well described, including the prediction algorithm with reference to its validation. I note that it may not be replicable by other investigators without access to the model. This might be added as a limitation?
A- We understand the need to point out this limitation. We added the following to the revised manuscript, discussion section, page 17.
" …Another limitation of using a home-developed algorithm is that it is not available for general use which may make it difficult to replicate the intervention, although we do publish the full list of features we use to generate the menus based on personal and microbiome data".

P9 Line 21 in Screening and profiling What is CBC?
A- CBC refers to Complete blood count. We changed the abbreviation into the full phrase which appears in the revised manuscript, page 8

P11 Please give more details on the random allocation procedure including:-
Who will do the consent and randomization? What happens to participants who fail the screening and profiling stage eg provide incomplete or unusable data?
Confirm the computer randomization will provide allocation concealment
A- The randomization is performed by one programmer from the trial personnel who has no contact with participants. Patients who can not complete the screening or profiling stage and provide the mandatory data such as stool sample are excluded from the study. However, participants who had only partial CGM data during profiling will not be excluded.
Lastly, the menus are being generated in the Segal lab in Weizmann institute of science and provided to participants without the study arm allocation.
We added the following to the revised manuscript, page 9:
"...by one programmer from the trial personnel who had no contact with participants".

Is it realistic to have 5 stratification factors with only 100 participants in each arm? Are these factors being used to minimize differences between groups in the allocation process rather than stratification on each?
We agree with the comment and would like to clarify.

A- We used the five stratification factors to minimize differences between groups in the allocation process and will not analyze the data according to the stratification factors. Data analysis will include only two stratification factors, BMI and Menopausal status, which result in only 4 strata, allowing sufficient number of patients per stratum, given the proposed sample size. We added this clarification to the revised manuscriptת Methods section, Randomization paragraph page 9 as well.

Outcome measurement and blinding – please clarify exactly who is blinded and/or reconsider use of the term single blind?
A- Please see our answer to the question above. Added a clarification to the methods section, randomization, page 9.

Sample size and Statistical analysis – I think the sample size is sufficient for the primary outcome, but I'm not convinced it will be sufficient for analysing the secondary or exploratory outcomes. In particular I would be concerned about the ability to look at disease free survival. This may also need a multivariate analysis as the randomisation may not distribute all important confounders evenly given the relatively small sample size. Some discussion of these issues and limitations might be added to the Discussion.
A- We understand the concerns and would like to clarify.
The sample size was calculated in order to support the primary outcome while the exploratory outcomes will be followed during the intervention period and for a period of 5 years following the intervention. We are aware that for disease recurrence differences the sample size is not large enough, however we aim for a rich dataset including deep phenotyping of each patient that may allow us to deeply investigate associations between clinical and Omic data to DFS in breast cancer patients. As mentioned above if a positive signal is obtained this will pave the way for a phase 3 trial.

Discussion p 15-16 focuses on the dietary aspects of the study. I suggest adding some brief discussion of the methodological strengths and limitations of the study (eg see above).
A- We added some of the points that were discussed above into the discussion section, pages 16-17, including the possibility to replicate the intervention using the PPT diet and the limitation of our relatively small sample size when assessing exploratory outcomes.

Reviewer# 2
Dr. Guido Knapp, Technicsche Universitat Dortmund
Comments to the Author:
This is a study protocol of an ongoing study.
I have only some minor remarks/questions to the analysis/statistics:

We thank Dr. Guido Knapp for his important comments .

Caloric target calculation: ad 2. divided or muliplied by 0.7? I do not know the equation.
A- For the caloric target we calculate the average between 3 caloric calculations. One of them is the Basal Metabolic Rate (BMR) measured by the TANITA (a body composition analyzer bought especially for the study and located in the clinic). Since BMR represents ~70% of total energy expenditure, we divide the result by 0.7 to get the total estimation of Energy Expenditure Rate (EER). The mentioned equation is done by the TANITA and takes into account gender, age and physical activity level.

Sample size determination: Which test / distributional assumption has been used for the calculation?
A- For sample size calculation we used an unpaired t-test assuming normal distribution of the primary outcome (weight change). Mentioned in page 14.

Primary endpoint analysis: Which test should be used for the analysis of the primary endpoint?
A- We elaborated the statistical plan on the manuscript page 15.
In order to compare the primary endpoint, which is the weight change (mean difference) between the study arms, a paired-samples t-test will be performed (or Wilcoxson test in case of non-normally distributed). P values < 0.05 will be considered significant.

Reviewer# 3
Prof. Pao-Hwa Lin, Duke University Medical Center
Comments to the Author:
This manuscript describes the rationale and design of a randomized trial comparing an algorithm-based diet intervention to a Mediterranean diet for 6 months on weight and glycemic control. The study design is very innovative and is based on the authors' previous experience and evidence. The manuscript is relatively well written, except for some unclear areas.

We thank Prof. Pao-Hwa Lin for her comments and appreciation of the manuscript.

1. Though the algorithm was previous developed, this manuscript should include a very brief summary of the algorithm including the goal of the algorithm.

A- We accepted the comment raised by Prof. Pao-Hwa and added to the method section a brief description of the algorithm (revised manuscript page 12), attached also below.
"…Personalized Postprandial-glucose-response Targeting (PPT) diet
In this arm, dietary recommendations will be based on the algorithm predictions of the postprandial glucose responses (7), shown to improve glycemic control and metabolic health in healthy individuals or in individuals with prediabetes and diabetes (8,9). Notably, these interventions were not caloric restricted as in the current study. Among the features used to predict PPGR to meals were anthropometrics, blood tests (FPG, HbA1c% and Hemoglobin), lifestyle features derived from questionnaires, microbiome (abundances of species estimated by MetaPhlAn2 and meal features (macro- and micronutrient composition) were used (see Supplementary table 1 for the full list). Since no events around the meal were used for prediction, trained predictor could predict response for any profiled participant to any given meal.
All logged meals will be scored from 1-5 based on a unique scoring method that we developed and tested in previous studies, and study participants will be asked to consume only meals with score 1 or 2. Importantly, the PPT diet, by definition, was not aimed to have a predetermined macronutrient distribution, In contrast to the Med-diet".

2. The study timing, especially for the key steps (profiling, randomization, intervention and follow up) is unclearly described in the abstract and Methods. Figure 1 is very helpful.
A- We thank Prof. Pao-Hwa for her comment. In order to allow better understanding of the design both from the text and the figure we slightly changed the titles and order of the study methods in the manuscript, so it will fit the order in Figure1.
The revised manuscript includes the changes we implemented in the method section, pages 8-10. In order to allow a continuation of the study design description we moved the part of menus construction to page 11, method section in the revised manuscript.

3. Box 1-secondary endpoint is unclear. What is the glycemic response that will be used, average of all data during the two weeks period? Exploratory endpoints are also unclear regarding timing.

A- We accepted the comment raised by Prof. Pao-Hwa and added a clarification to the secondary and exploratory points in the revised manuscript, BOX-1. As BOX-1 summarizes the study endpoints, the full description is also available in the study protocol (supplemental material 2).

The additions to the revised protocol include:
1. The glycemic control, i.e. secondary endpoint will be assessed by the AUC of the glycemic graph during the connection to CGM. We will compare glycemic control during profiling as compared to glycemic control during the intervention. Notably, participants are connected to CGM at profiling and at +3m and +6m meetings (middle and end of intervention) as written in the protocol of the study (supplemental material 2).
2. We clarified the timing of tests within the exploratory endpoints as detailed:
a. Second end point refers to the microbiome and metabolites modulation during the intervention. We will compare the samples taken at profiling and +6m timepoints.
b. The 4th endpoint refers to dietary compliance will be assessed using monthly compliance questionnaire
In addition, please see the revised BOX-1 attached in the PBP file.

4. Page 10 of 61, line 10-11, what is the target for the personal dietary recommendations?

We thank Prof. Pao-Hwa for this important question. By definition, the PPT diet was not generated according to a predetermined macronutrient distribution, In contrast to the MED-style diet. Hence, meals in the PPT approach are based on the algorithm prediction of the postprandial glucose response and are recommended accordingly. We added a clarification regarding this point into the revised manuscript method section, page 12 as well.

5. Page 14 of 61, lines 30-35, the sample calculation of the grade is unclear. How were the 600 kcal and 1000 kcal of meals included in the formula?

A- We accepted the comment and would like to explain. In order to be able to give a feedback report on logged meals we generated a systematic scoring system for each arm. When calculating the score within the PPT intervention we considered meals with less than 500 calories as 100 calories and meals with more than 500 calories as 500 in order to give a total score taking into account that larger meals have a greater influence on the score (i.e the predicted glycemic response). Specifically in the example on page 14, lines 30-35, the meal including 600 calories that got the score 4 is being represented in the equation as 500*4, the meal with 1000 calories, score 5 is being represented in the equation as 500*5, and the smaller meals including 80 kilocalories, with the score 1 score 4 is being represented in the equation as 100*1

6. Page 14 of 61, line 50, what is the recommended amount of fiber? Is there a fiber target for Med arm and another personalized target for the algorithm arm?

A- The amount of dietary fiber intake was set to 14 gram for every 1000 kcal/day as recommended for healthy dietary patterns (10). We set this goal for both arms since dietary fiber intake is highly recommended for breast cancer survivors (11) and may have a role in reduction of glycemic response as we previously showed in healthy population (7). Notably, this score was mainly discussed during the monthly meetings with the study participants as an additional parameter to estimate their compliance to the diet. Mentioned in the revised manuscript, page 14.

Reviewer: 1
Competing interests of Reviewer: None to declare.

Reviewer: 2
Competing interests of Reviewer: None declared!

Reviewer: 3
Competing interests of Reviewer: None

Editor(s)' Comments to Author (if any):

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VERSION 2 – REVIEW

REVIEWER	Barratt, Alexandra University of Sydney, School of Public Health
REVIEW RETURNED	11-Sep-2022

GENERAL COMMENTS	I thank the authors for their clarifications and changes to the manuscript. I am satisfied with the responses, and have no further comments.

REVIEWER	Knapp, Guido Technicsche Universitat Dortmund
REVIEW RETURNED	08-Aug-2022

GENERAL COMMENTS	No further comments. Thank you!

REVIEWER	Lin, Pao-Hwa Duke University Medical Center, Department of Medicine
REVIEW RETURNED	13-Sep-2022

GENERAL COMMENTS	The authors have addressed the previous comments adequately. There is no further comments from this reviewer.