PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Effectiveness of a digital dietary intervention program targeting young adults before parenthood: protocol for the PREPARED randomized controlled trial
AUTHORS	Overby, Nina Cecilie; Medin, Anine C.; Valen, Erlend Larsen; Salvesen, Lorentz; Wills, Andrew Keith; Engeset, Dagrun; Vik, Frøydis N.; Hillesund, Elisabet R.

VERSION 1 – REVIEW

REVIEWER	Portero de la Cruz, Silvia University of Cordoba
REVIEW RETURNED	27-Aug-2021

GENERAL COMMENTS	This is a well written paper about the evaluation of the potential effects of a dietary intervention among young adults. It is an interesting topic for readers. Lines 144-145: authors said that one of the recruitment strategies is through via postal mail. Do the authors have a census of the possible participants? Apart from SPIRIT guidance, I would recommend adding into the paper the circumstances under which blinding is permissible, and procedure for revealing a participant's allocated intervention during the trial. Could the authors please provide some information about the validated questionnaires used in this study (how many questions do they contain, how do you get the scores, how such scores are interpreted…). Line 272: What kind of statistical tests will the authors use? They should be more precise.

REVIEWER	Unicomb, Leanne International Centre for Diarrhoeal Disease Research, Infectious Disease Division
REVIEW RETURNED	30-Aug-2021

GENERAL COMMENTS	The protocol manuscript describes a study planned to evaluate a dietary intervention for the pre-conception period among Norwegian citizens. As it stands, the manuscript can benefit from further detail to increase clarity. Additionally, the RCT design includes a pilot period, for which I have some optional suggestions on further inclusions, that are based on my experience rolling out large behaviour change intervention trials and the value of a pilot

	period to test run pretty much every aspect of the broader trial. Specific comments are as follows: A) Improving manuscript clarity Line 34: secondly should replace secondary. Line 41: before 'birth ensues' insert 'for which' and replace 'collected' with 'study'. Introduction Line 77: Tighten the language here. It is obvious that the exact conception phase time period is unknown. Reframe the paragraph to read that since the period is hard to be fully inclusive, the study definition needs to be broad. Join with next paragraph. Essentially these two paragraphs are the basis for the study design. Line 91: change 'there is' to 'there are' and 'a lack of' to 'few'. Line 95: the HELTI project sounds very similar. If there are differences, other than country of intervention, please include these contrasts. Line 100: NCD is used for the first time here- spell out in full. Line 110: insert the word 'one's' prior to 'own health' and remove the word 'also' later in the sentence. Methods Line 118: refer to the SPIRIT checklist included in the table. Line 139: I am not clear on the partner participation. I am assuming that they will not be asked whether their partner will participate as that would break random recruitment and assignment. Is the objective here to obtain the Norwegian ID from the partner for future reference? Asking this each survey round seems like valuable data to collect. Line 144: in this section the sampling frame is not clear. The first sentence suggests, but doesn't state that all citizens with an ID number in the target age range forms the sampling frame. Line 152: how will the study handle Norwegians living outside the country? Will then be included? Line 158: there may be some who do not fully complete the questionnaire. How will this be handled? Consider this for the pilot: include these analyses to determine strategies. Use the pilot to better assess drop out types, rates, reasons. Line 164: I think that explaining control groups could introduce bias and increase drop out. I am not sure what was done for the previous study where the intervention was developed. I also recommend an intervention section in the methods. Line 173: it mentions that questionnaires will be sent. Presumably this is by email. Line 177: the authors state that they will make short animated films-. Will this be part of pilot? Line 180: use months rather than seasons; seasons differ by hemispheres and locations. Line 219 states that the intervention period is 6 months. What is the rationale for the 6-month intervention period? Line 221: Are there plans to provide feedback on dietary score? comparison of their diet to the recommendations? This can be a valuable incentive to participate, especially among controls and could be semi-automated. It may also further encourage improved diet. Line 225: again, there needs to be more precise description of the indicators rather than using terms like 'such as'. Possibly the authors have not decided on what indicators to include at this point. If that is the case, please make it clear.

	Table 1: improve the text alignment for variables, measures, instruments in each row. I don't think there is a need to footnote PO and SO, both are included in the title and then there is an abbreviation section in the footnote. Footnote numbers should appear in serial order however, there is one '6, 4'. The sample size column is a bit difficult to follow. It is not clear what indicator was used to develop the sample size in each instance, which is presumably in the text. Line 238: the variables outlined in this section are presumably potential confounders and effect modifiers. This section requires further detail. Are they all being collected from self-reports? How would a 35 year old report their birth weight or does this come from the national registry? Some other data collection needs some elaboration for example how will quality of life be measured (is there a scale for this), is there a standardized, validated measure for self-reported tobacco use (?scale). What is DOHaD-knowledge (spell out). How will the following be measured: sleep, physical activity, screen time? Potentially physical activity could be a secondary outcome. Line 244: This is an excellent section but it would be better if more precisely described indicators are included. Line 249: be more specific about methods here. Will the process evaluation be performed on a rolling basis? Will the data be analysed to affect course correction, in the event that fidelity is low for some aspects? Will this be piloted? Line 273: at what time point(s) will the analyses be performed? I am assuming that there will be examination of the data prior to 7000 enrolled subjects. What is the expected time frame for the study? Will the 1000 pilot participants' data be analysed in the same fashion as outlined in this section? Will the pilot data be combined with the broader study data or is the 7000 in addition to the 1000 in the pilot? Line 276: in the discussion it states that dietary quality will be assessed year by year. What methods will be employed (describe in the methods section)? Line 283: replace 'ingredients' with 'components'. Line 298: will the data entry fields include legal values to minimise errors and outliers? This may be as useful, if not more than validity and plausibility checks in some instances. Line 305: this sentence seems contradictory to the earlier sentence stating the inability to predict that the study will do no harm. I think this is an English expression issue Discussion Line 311: omit the word 'studies'. Line 316: also include that the intervention could be implemented in other settings. Line 320-339: Participant and public involvement in development of an intervention is considered a minimum by current standards so I don't see it as a study strength. In fact, the information here suggests that the intervention was piloted on a very small group and I think that further feedback on the intervention during the pilot period, to revise content and delivery would be warranted. It is a big leap from 34 participants and 57 university students to potentially 7000 (or 3500 intervention recipients). The information in paragraph starting from line 323 would fit better in the section Development and description of the dietary intervention'. Line 367: According to the instructions I received, there should be no conclusion section. Please check.

	References; there are some issues with formatting, some of which looks to be manually inserted. Figure 1: there is no timing given for follow up 1 and follow up 2 after the intervention is rolled out. B) Suggestions for inclusion in the pilot (just some thoughts based on my experience) Piloting is an opportunity to test run many aspects of the larger, long term study and pilot findings generate excellent insights and data that can often be published. Possibly the authors plan to pilot a range of study components, but little information is provided. Since the intervention has been tested on a small number of subjects, scaling this may reveal problems not previously detected. There is also little information on how the sample will be nationally representative. Do the authors plan to pilot their sampling and compare those recruited vs declined vs total population? The intervention itself has not been assessed for impact vs a control group. I did not find a reference for the intervention development other than the framework used for its development. If these data have not been published, this manuscript would be a useful place for inclusion. A pilot study would be useful for testing data collection instruments.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Silvia Portero de la Cruz, University of Cordoba Comments to the Author:
This is a well written paper about the evaluation of the potential effects of a dietary intervention among young adults. It is an interesting topic for readers.

Lines 144-145: authors said that one of the recruitment strategies is through via postal mail. Do the authors have a census of the possible participants?

AR: Thank you for this question and the opportunity to rephrase as we have started our pilot study. We have rephrased the recruitment strategy and the text regarding the pilot study, see lines 150-160 and 199-213.

Apart from SPIRIT guidance, I would recommend adding into the paper the circumstances under which blinding is permissible, and procedure for revealing a participant's allocated intervention during the trial.

AR: Thank you for your comment, which has led us to rephrase and include more details the SPIRIT-form and also in the manuscript. See text below and lines: 172-181.

In line with the nature of the intervention, this is an open-label study where participants are aware of their intervention status, but the statistician and all involved researchers only have access to anonymized datasets. The automatic recruitment system, which is a separate system from data collection and the intervention, is set up so that only one researcher (ELV) have access can see the email addresses of those who accept to participate. This is not connected to the entry of any data, however, one can see the e-mail-address and the group the person has been automatically drawn to. The list can only be accessed by two persons, one developer and ELV.

Blinding of data will only be reversed in the case that a participant withdraws his/her consent for participation. In such cases, data withdrawal will be performed by a project worker and still be anonymized for the researchers performing the analysis.

Could the authors please provide some information about the validated questionnaires used in this study (how many questions do they contain, how do you get the scores, how such scores are interpreted…).

AR: Thank you for suggesting this. Information and links to the questionnaires are provided in table 1, and we have also included some more information in the text on outcome measurements, lines 156-186. We have not yet developed the diet score, but we plan to do so and publish the results in a separate paper.

Line 272: What kind of statistical tests will the authors use? They should be more precise.

AR: We have included more details on the statistical tests in the manuscript. See lines 336-346.

Dear Reviewer 2: Thank you for your detailed, well-thought-through comments which improve the manuscript as well as our study. Thank you for sharing your valuable experience. That is highly appreciated. We have responded to and changed according to your suggestions, as you see below. The pilot study is already ongoing; however, we will explore more details than what was commented on at first, also inspired by your comments.

Reviewer: 2
Dr. Leanne Unicomb, International Centre for Diarrhoeal Disease Research Comments to the Author:
The protocol manuscript describes a study planned to evaluate a dietary intervention for the pre-conception period among Norwegian citizens. As it stands, the manuscript can benefit from further detail to increase clarity. Additionally, the RCT design includes a pilot period, for which I have some optional suggestions on further inclusions, that are based on my experience rolling out large behaviour change intervention trials and the value of a pilot period to test run pretty much every aspect of the broader trial.

Specific comments are as follows:

A) Improving manuscript clarity
Line 34: secondly should replace secondary.
AR: As this refers to our secondary aim, we have rephrased it to make it clearer. Thank you for highlighting this.

Line 41: before 'birth ensues' insert 'for which' and replace 'collected' with 'study'.
AR: This is edited accordingly.

Introduction
Line 77: Tighten the language here. It is obvious that the exact conception phase time period is unknown. Reframe the paragraph to read that since the period is hard to be fully inclusive, the study definition needs to be broad. Join with next paragraph. Essentially these two paragraphs are the basis for the study design.

AR: Language is tightened, and we have deleted some overlap and merged the two paragraphs as you suggest.

Line 91: change 'there is' to 'there are' and 'a lack of' to 'few'.
AR: changed accordingly

Line 95: the HELTI project sounds very similar. If there are differences, other than country of intervention, please include these contrasts.

AR: We have included more information about HELTI, it is a consortium where most projects recruit only women, some also partners, and women who are planning to have a child within 3 years. See lines 94-96.

Line 100: NCD is used for the first time here- spell out in full.
AR: Changed accordingly

Line 110: insert the word 'one's' prior to 'own health' and remove the word 'also' later in the sentence.
AR: Thank you! Changed accordingly.

Methods
Line 118: refer to the SPIRIT checklist included in the table. [NOTE FROM THE EDITORS: there is no need to refer to the SPIRIT checklist in the manuscript, as this is generally not part of the final published paper [as we ask authors to indicate page numbers on the checklist, this would not be accurate in the final published version of the manuscript, so it is best to avoid citing the checklist in the manuscript to avoid the need to include it with the publication.]
AR: We have included page numbers in the checklists in line with editor comments. Lines refer to clear text copy.

Line 139: I am not clear on the partner participation. I am assuming that they will not be asked whether their partner will participate as that would break random recruitment and assignment. Is the objective here to obtain the Norwegian ID from the partner for future reference? Asking this each survey round seems like valuable data to collect.

AR: Thank you for this comment and the possibility to clarify this. Partners will not be invited to participate in this study. However, if a participant becomes a parent, we will ask for permission from both the participant and her/his partner to use registry data. To take into account any potential contamination of data (e.i. both persons in a couple participate and they are in separate groups), we will assess whether a participant is in a relationship with another participant. This enables us to analyze data excluding those in such a relationship from the analyses in sensitivity analyses. We have commented on this in lines 144-148

Line 144: in this section the sampling frame is not clear. The first sentence suggests, but doesn't state that all citizens with an ID number in the target age range forms the sampling frame.

AR: We have clarified this in line with your suggestion, see lines 150-151

Line 152: how will the study handle Norwegians living outside the country? Will then be included?
AR: This is clarified, see lines 158-160

Line 158: there may be some who do not fully complete the questionnaire. How will this be handled? Consider this for the pilot: include these analyses to determine strategies. Use the pilot to better assess drop out types, rates, reasons.

AR: Thank you for this kind suggestion. We have included your suggestions and will use our pilot more broadly than what we had originally included in the text, lines 200-2013.

Line 164: I think that explaining control groups could introduce bias and increase drop out. I am not sure what was done for the previous study where the intervention was developed. I also recommend an intervention section in the methods.

AR: Thank you for suggesting this. To clarify we have changed the wording: The control group will receive an email informing about group allocation, highlighting the importance of control groups in research and the value of their continued responses to questionnaires. See lines 183-185. We originally wrote we would “explain the control group”, but that was not our intention. We believe it is important to highlight the need for and importance of control groups for the participants, as this is just as important for the study aim as the intervention group.
We have included text about the intervention in the methods section, lines 216-246

Line 173: it mentions that questionnaires will be sent. Presumably this is by email.
AR: We have clarified this- it is by e-mail.

Line 177: the authors state that they will make short animated films-. Will this be part of pilot?

AR: These will not be sent to the pilot participants.

Line 180: use months rather than seasons; seasons differ by hemispheres and locations.

AR: Thank you for this. We have changed this.

Line 219 states that the intervention period is 6 months. What is the rationale for the 6-month intervention period?

AR: The rationale for six months is decided based on two principles: 1) study time frame limitations and cost and 2) information from stakeholders and 3) general perception that 6 months is the shortest relevant duration, lines 237-241. We have mentioned this in the discussion as a limitation, lines 463-466.

Line 221: Are there plans to provide feedback on dietary score? comparison of their diet to the recommendations? This can be a valuable incentive to participate, especially among controls and could be semi-automated. It may also further encourage improved diet.

AR: This is a good idea and we have discussed this in our group previously. And we have decided that we will not provide feedback on dietary quality. We believe this would complicate the interpretation of our results as having such information might be regarded as a part of the intervention and we want to test if an easy-access intervention can work to improve diet. We have included that feedback will not be given, lines 251-252.

Line 225: again, there needs to be more precise description of the indicators rather than using terms like 'such as'. Possibly the authors have not decided on what indicators to include at this point. If that is the case, please make it clear.

AR: Thank you for this comment. All outcomes are listed in table 1 and we have now presented them in the text as well. And we have deleted such as etc. See lines 256-286.

Table 1: improve the text alignment for variables, measures, instruments in each row. I don't think there is a need to footnote PO and SO, both are included in the title and then there is an abbreviation section in the footnote. Footnote numbers should appear in serial order however, there is one '6, 4'. The sample size column is a bit difficult to follow. It is not clear what indicator was used to develop the sample size in each instance, which is presumably in the text.

AR: Thank you for this comment. We have improved table 1 accordingly.

Line 238: the variables outlined in this section are presumably potential confounders and effect modifiers. This section requires further detail. Are they all being collected from self-reports? How would a 35 year old report their birth weight or does this come from the national registry? Some other data collection needs some elaboration for example how will quality of life be measured (is there a scale for this), is there a standardized, validated measure for self-reported tobacco use (?scale). What is DOHaD-knowledge (spell out). How will the following be measured: sleep, physical activity, screen time? Potentially physical activity could be a secondary outcome.

AR: Thank you for these comments. We have included more details about all data that are being collected, see also comment from reviewer 1, lines 256-277. As we do not address physical activity in the intervention we have not included this as a secondary outcome.

Line 244: This is an excellent section but it would be better if more precisely described indicators are included.

AR: We have included more details on this, lines 299-312.

Line 249: be more specific about methods here. Will the process evaluation be performed on a rolling basis? Will the data be analysed to affect course correction, in the event that fidelity is low for some aspects? Will this be piloted?

AR: We have included more details on the methods in the manuscript. We will not perform a full-scale process evaluation of the pilot study, but assess fidelity and dose. We will also not perform any qualitative assessment in the pilot. We have included fidelity when describing per-protocol analyses, line 347.

Line 273: at what time point(s) will the analyses be performed? I am assuming that there will be examination of the data prior to 7000 enrolled subjects. What is the expected time frame for the study? Will the 1000 pilot participants' data be analysed in the same fashion as outlined in this section? Will the pilot data be combined with the broader study data or is the 7000 in addition to the 1000 in the pilot?

AR: Baseline characteristics will be analyzed when we have stopped recruiting participants. Evaluation of primary outcome will be evaluated when participants have been given enough time to respond after reminders (about 3 months after the last participant should have responded). As we will keep following the population until they get children, or up to the year 2040, the time frame is difficult to describe.
However, the timeframe relating to the intervention and the two follow-ups are now described in more detail in figure 1 and 2. The pilot study will not be included in the main study, and we will test our analyses on the data from the pilot study, however, this will not be published.

Line 276: in the discussion it states that dietary quality will be assessed year by year. What methods will be employed (describe in the methods section)?

AR: Thank you- this is now included under the primary outcome section.

Line 283: replace 'ingredients' with 'components'.

AR: Thank you. We have changed this.

Line 298: will the data entry fields include legal values to minimise errors and outliers? This may be as useful, if not more than validity and plausibility checks in some instances.

AR: This is commented- under data management. And, yes, there are legal fields for continuous measurements, lines 363-365.

Line 305: this sentence seems contradictory to the earlier sentence stating the inability to predict that the study will do no harm. I think this is an English expression issue
AR: Thank you- this is changed.

Discussion
Line 311: omit the word 'studies'.
Line 316: also include that the intervention could be implemented in other settings.

AR: Thank you- valuable suggestions and text is changed accordingly.

Line 320-339: Participant and public involvement in development of an intervention is considered a minimum by current standards so I don't see it as a study strength. In fact, the information here suggests that the intervention was piloted on a very small group and I think that further feedback on the intervention during the pilot period, to revise content and delivery would be warranted. It is a big leap from 34 participants and 57 university students to potentially 7000 (or 3500 intervention recipients). The information in paragraph starting from line 323 would fit better in the section Development and description of the dietary intervention'.

AR: Thank you for these comments. We have deleted the sentence about participant involvement as being a strength. As the editor has suggested, we have removed this passage of public involvement after Data monitoring. We have also mentioned this in the intervention development, as you suggest.

Line 367: According to the instructions I received, there should be no conclusion section. Please check.

AR: This is right- we have changed this. Thank you.

References; there are some issues with formatting, some of which looks to be manually inserted.

AR: We have edited the references.

Figure 1: there is no timing given for follow up 1 and follow up 2 after the intervention is rolled out.

AR: Thank you for commenting this. Follow up 1 is immediately after the intervention (6 months after the start), while follow up 2 is 6 months after follow up 1. This is included i figure 1.

B) Suggestions for inclusion in the pilot (just some thoughts based on my experience)
Piloting is an opportunity to test run many aspects of the larger, long term study and pilot findings generate excellent insights and data that can often be published. Possibly the authors plan to pilot a range of study components, but little information is provided. Since the intervention has been tested

on a small number of subjects, scaling this may reveal problems not previously detected. There is also little information on how the sample will be nationally representative. Do the authors plan to pilot their sampling and compare those recruited vs declined vs total population? The intervention itself has not been assessed for impact vs a control group. I did not find a reference for the intervention development other than the framework used for its development. If these data have not been published, this manuscript would be a useful place for inclusion. A pilot study would be useful for testing data collection instruments.

AR: Thank you for suggesting and pointing out the importance of the pilot study.

1) We have included more details on your previous suggestions on how we are to use pilot data. In addition to your suggestions, we want to test the automated flow created for the data collection.
2) The description of the study being nationally representative relates to the pilot study, as we recruited for this by mail. Statistics Norway has drawn a representative sample of the age group, from different parts of Norway and both genders being represented equally. We have highlighted that this relates to the pilot study.
3) Unfortunately, we are not able to analyze the pilot study regarding differences between those who are recruited vs non-recruited. We can explore who are responding, the numbers of women vs men, which age groups are responding, where they are from (county). We have included information about this in the pilot study section.
4) We are working on a paper on the intervention development which will be published separately from the protocol.

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COI statements:

Reviewer: 1
Competing interests of Reviewer: None declared.

Reviewer: 2
Competing interests of Reviewer: I have no competing interests.

VERSION 2 – REVIEW

REVIEWER	Portero de la Cruz, Silvia University of Cordoba
REVIEW RETURNED	28-Oct-2021

GENERAL COMMENTS	The authors have satisfactorily responded to all my questions and made the necessary changes to the manuscript.