PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	ObesiStress: Stress Management in Obesity during a thermal spa residential programme – a protocol for a randomised controlled trial study
AUTHORS	DUTHEIL, Frédéric; CHAPLAIS, Elodie; VILMANT, Audrey; COURTEIX, Daniel; DUCHE, Pascale; ABERGEL, Armand; PFABIGAN, Daniela M.; HAN, Shihui; MONDILLON, Laurie; VALLET, Guillaume T.; Mermillod, Martial; BOUDET, Gil; Obert, Philippe; Izem, Omar; MIOLANNE-DEBOUIT, Magalie; Farigon, Nicolas; Pereira, Bruno; Boirie, Yves

VERSION 1 – REVIEW

REVIEWER	Rolando Giovanni Díaz Zavala Universidad de Sonora, Department of Chemical and Biological Sciences
REVIEW RETURNED	19-Dec-2018

GENERAL COMMENTS	Observations: - Page 5 of 26, row 32. Add the primary objective - Page 8 of 26, 35. Ad reference (using minimization approach). - Page 8 of 26, row 40. Are there no drugs or medical conditions that significantly affect the primary outcome (heart rate variability) of the study that could be considered as exclusion criteria? - -Page 10 of 26, (measurements). Perhaps it would be appropriate to measure (even if by self-report) the use of psychological techniques by the participants once the intensive phase of the study is finished (after 21 days) in order to have an indicator of adherence to the intervention. - Page 10 of 26, row 18. Describe in more detail the psychological intervention to allow replication. - Page 12 of 26, row 26, 31. “85” I think it's a mistake. - Page 13 of 26, row 3 (Endocrine assays) add the basic methodology (without much detail) for its determination or references. - Page 13 of 26, row 21. (Complementary measures). Consider adding references (unless there are restrictions) that support the validity of the questionnaires used. - Page 18. Carefully review all references, for example the 4 is not complete (it has no page number, volume, etc.), the same as 6. Some journals are abbreviated (Int J Obes) and others are not (Biological Psychiatry). - - Add in the appropriate section that neither the participants, care providers, data analyst and outcome assessors will be blinded to the participants' allocation group. - You can add other points of the SPIRIT guidelines, although they will not be done. For example, other works in the area put in the Harms section (“Harms: This section was not considered in the

	protocol, but this kind of intervention is considered as very low risk.") - Add the section (confidentiality point #27).

REVIEWER	Phillip Brantley Pennington Biomedical Research Center, Behavioral Medicine
REVIEW RETURNED	11-Mar-2019

GENERAL COMMENTS	The paper fits the criteria for inclusion in BMJ Open. This study is a randomized clinical trial currently in the recruitment phase. It studies overweight and obese adults attending a 21 day spa program. It compares one group receiving a usual care program and another group receiving usual care plus stress management. This is a messy manuscript with many typos. The hypothesis in the introduction (paragraph one page 6) needs rewriting. It does not reflect the group comparison proposed by the clinical trial. The exclusion criteria are vague/absent. What about a history of recent weight loss or bariatric surgery? Any medication restrictions? Since you are restricting participation to "usual participants of the spa" consider describing the demographics of this group and discussing potential generalizability of your expected results. The stress management intervention is poorly described. Please include data on the use of the protocol to assure readers you are using a tested/credible/definable intervention. Does your intervention work? Can it be replicated based on your description? The methods sound like you are just throwing together techniques from a variety of therapies. If you do not get group differences will it be due to a poor intervention? Impressive outcome measures but it would strengthen the paper to document that the measures have been sensitive to stress management interventions in previous studies. Why do you need a pediatric nurse to collect blood samples? (Page 11 first sentence). Good luck. Wish I could be a participant.

REVIEWER	Mohammed Hudda St George\'s, University of London, Population Health Research Institute
REVIEW RETURNED	08-Apr-2019

GENERAL COMMENTS	This manuscript and the proposed RCT is very interesting in its concept of assessing how stress management could help in the treatment of obesity for those attending a spa resort in France. However there are some concerns with the protocol, largely due to lack of detail where required. Specific Comments: Methods (page 6): - Randomisation strategy is not explained in enough detail. What was the rationale for the stratification groupings for level of stress? Furthermore, would it not be more appropriate to assess baseline measures prior to randomisation? Who will conduct the randomisation and how? Exclusion criteria (page 7): - this section does not provide sufficient information. What are specific criteria for exclusion? Will this be based on any baseline measures?

	Power Analysis (page 7): - Please define HRV, LF and HF at first use. - Reference 3 is cited as a pilot study for this trial and as the basis for the difference in effect size. However, it is very unclear where these effect differences were ascertained from the cited paper. - Whilst the calculation seems fine, the expected difference between gorups is very unclear. - Participants: Will the study include 18 year olds or only those above 18 years? - Recruitment details provided are not sufficient. More is needed to ascertain how you will recruit participants from the Spa Resort. - Follow-up (page 8): Will this at-home visit be done at 6 months also? - Measurements: Will any demongraphic information be collected from participants? Statistical Analysis (Page 12): - Please state on which basis you intend to analyse the data? Presumably intention-to-treat? - There needs to be more detail regarding the covariate adjustments within models - The justification for the primary analysis model is not clear. Will baseline measures be adjusted for? - The intensity of the intervention will vary per individual as mentioned by the authors. However, how will this be reflected within the analysis? - Will any of the study team be blinded? - How will the level of bias be reduced? Blinding participants to the randomisation group may not be an option, however will they be blind to the primary aims of the study? - How will missing data be tackled in the analysis? - Reporting checklist: Many relevant items are not complete which is reflected in the lack of details provided in the manuscript. The checklist manuscript by Chan et al. need also be cited within the manuscript.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Reviewer Name: Rolando Giovanni Díaz Zavala
Institution and Country: Full time professor. Departamento de Ciencias Químico Biológicas, Universidad de Sonora, Hermosillo, México

Observations:
- Page 5 of 26, row 32. Add the primary objective
[REPLY] Thank you for your comment. We added both primary and secondary objectives.

- Page 8 of 26, 35. Add reference (using minimization approach).
[REPLY] We added the following reference (Dutheil F, Lac G, Lesourd B et al. Different modalities of exercise to reduce visceral fat mass and cardiovascular risk in metabolic syndrome: The resolve randomized trial. Int. J. Cardiol. 2013;168:3634-42) where details on inclusion criteria where given (see also supplementary file of the added reference)

- Page 8 of 26, row 40. Are there no drugs or medical conditions that significantly affect the primary outcome (heart rate variability) of the study that could be considered as exclusion criteria?
[REPLY] We added a reference from another study on heart rate variability during a spa intervention program (Boudet G, Walther G, Courteix D et al. Paradoxical dissociation between heart rate and heart rate variability following different modalities of exercise in individuals with metabolic syndrome: The resolve study. European journal of preventive cardiology. 2017;24:281-96) and the following reference "Elghozi JL, Girard A, Laude D. Effects of drugs on the autonomic control of short-term heart rate variability. Auton Neurosci. 2001;90:116-21". We also added the following sentence: "Drugs and medical conditions that significantly affect the primary outcome (heart rate variability) will also be exclusion criteria (e.g. alpha or beta-blockers; arrhythmias or conduction disorders such as bundle branch block, atrioventricular heart block)."

- Page 10 of 26, (measurements). Perhaps it would be appropriate to measure (even if by self-report) the use of psychological techniques by the participants once the intensive phase of the study is finished (after 21 days) in order to have an indicator of adherence to the intervention.
[REPLY] Thank you very much for your relevant comment. Yes of course, we planned to follow the adherence to the intervention and also physical activity and food intake. We did not see that this information was missing. We added the following sentence: "Observance with physical activity, nutrition, and psychological techniques will be retrieved. Physical activity will be assessed with the use of RPAQ at M6 and M12. Nutrition will be assessed by using three days self-report questionnaire with a face-to-face validation with a dietitian at M6 and M12. The use of psychological techniques will be measured by monthly self-report questionnaires (number of use per month for each technique)." We also added the following sentence within the statistics section: "This primary analysis will be completed by multivariable analysis (linear regression with logarithmic transformation of dependent outcome if necessary) considering an adjustment on covariates fixed according to univariate results, clinical and epidemiological relevance (notably age, gender, baseline BMI and baseline stress levels) and observance to physical activity, nutrition, and the use of psychological techniques."

- Page 10 of 26, row 18. Describe in more detail the psychological intervention to allow replication.
[REPLY] Thank you for your relevant comment. The section now reads: "Participants randomized to the intervention group will benefit from psychological interventions based on validated approaches of stress (3 x 1h30 per week i.e. 9 sessions in total). Participants will attend psychological sessions by group of less than 10 individuals. Individual meeting with the psychologist will occur at least twice: at the beginning of the residential program and at the end. Psychological interventions will include various validated approaches of work-related stress: physical 18 and psychoanalytic 19 approaches, cognitive behavioral therapy,20 acceptance and commitment therapy,22 33 mindfulness,23 24 etc. Participants

will have to acquire techniques in order to be autonomous and pursue at-home psychological training. The 9 psychological sessions will be the following: 1) Stress management and lack of self-confidence, 2) cognitive behavioral therapy, 3) Body-centered approach: body language, 4) Management of emotions, 5) Identity approach: concept and self-image, 6) Cognitive approach (information processing), 7) Sophrology – relaxation, 8) Food and addictive behavior, and 9) Psychopathological approach and anxiety disorders. Each session will be constructed and validated by a psychologist specialized in the field of the session and already working in the management of obese individuals. The aim is to build a psychological program that can be easily replicated for long term used after evidence based medicine proof of success of our program."

- Page 12 of 26, row 26, 31. "85" I think it's a mistake.
[REPLY] Yes sure, thank you. 85 was the number of a reference that was not taking into account using Endnote. We now added the following reference instead of 85: "Nagueh SF, Smiseth OA, Appleton CP et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: An update from the american society of echocardiography and the european association of cardiovascular imaging. European heart journal cardiovascular Imaging. 2016;17:1321-60."

- Page 13 of 26, row 3 (Endocrine assays) add the basic methodology (without much detail) for its determination or references.
[REPLY] Thank you for you relevant comment. We added references on methodology for each parameters measured and we also added references linking all parameters measured with stress outcomes. We also added Table 1 with all outcomes measured, modalities of measurements, and references.

- Page 13 of 26, row 21. (Complementary measures). Consider adding references (unless there are restrictions) that support the validity of the questionnaires used.
[REPLY] Thank you for you relevant comment. We added references on methodology for each parameters measured and we also added references linking all parameters measured with stress outcomes. We also added Table 1 with all outcomes measured, modalities of measurements, and references.

- Page 18. Carefully review all references, for example the 4 is not complete (it has no page number, volume, etc.), the same as 6. Some journals are abbreviated (Int J Obes) and others are not (Biological Psychiatry).
[REPLY] Thank you for you relevant comment. We amended several references. Despite the use of a software to manage references, there were some incomplete references. All should be fine now.

- Add in the appropriate section that neither the participants, care providers, data analyst and outcome assessors will be blinded to the participants' allocation group.
[REPLY] Thank you for your relevant comment. We added a "Confidentiality and blind assessments" section that reads: "Despite the participants and care providers will not be blinded to the participants' allocation group, in order to reduce the level of bias, assessors for most outcomes will be blinded to the assignment group of each participant, such as for HRV, biological measures, or bone parameters. All outcome data will remain blinded until the end of the study. Patient's data will be deidentified and all data will be treated anonymously."

- You can add other points of the SPIRIT guidelines, although they will not be done. For example, other works in the area put in the Harms section ("Harms: This section was not considered in the protocol, but this kind of intervention is considered as very low risk.")
[REPLY] Thank you for you relevant comment. We added the following sentence "A Harms section was not considered in the protocol, but this kind of intervention was considered as very low risk by the ethics committee".

- Add the section (confidentiality point #27).
[REPLY] Thank you for your relevant comment. We added a "Confidentiality and blind assessments" section that reads: "Despite the participants and care providers will not be blinded to the participants' allocation group, in order to reduce the level of bias, assessors for most outcomes will be blinded to the assignment group of each participant, such as for HRV, biological measures, or bone parameters. All outcome data will remain blinded until the end of the study. Patient's data will be deidentified and all data will be treated anonymously."

Reviewer 2
Reviewer Name: Phillip Brantley
Institution and Country: Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, Louisiana, USA

The paper fits the criteria for inclusion in BMJ Open. This study is a randomized clinical trial currently in the recruitment phase. It studies overweight and obese adults attending a 21 day spa program. It compares one group receiving a usual care program and another group receiving usual care plus stress management.
[REPLY] Thank you for your positive comment.

This is a messy manuscript with many typos.
[REPLY] Thank you for your relevant comments. Several of coauthors are native English. We carefully revised the manuscript and all typos should have now been corrected.

The hypothesis in the introduction (paragraph one page 6) needs rewriting. It does not reflect the group comparison proposed by the clinical trial.
[REPLY] The hypothesis now reads: "The main hypothesis of this project is that a thermal spa residential program (21 days) of stress management in obesity will exhibit its efficacy through objective measures of well-being and cardiovascular morbidity, via a randomised controlled design comparing a group with stress management and a group without stress management (both groups will benefit from the same spa treatments, physical activity, and diet)."

The exclusion criteria are vague/absent. What about a history of recent weight loss or bariatric surgery? Any medication restrictions?
[REPLY] Thank you for your comment. The section now reads: "Inclusion criteria: Volunteers will be overweight or obese participants aged over 18 years, who wish to follow a spa thermal residential program for the treatment of obesity. Participants must have a stable weight during the last three months, with no cardiac, hepatic, renal or endocrine diseases uncontrolled.[29] Stress at baseline will not be an inclusion criteria but an explanatory/independent variable. In compliance with Human Ethics

guidelines, participants will have to be covered by a social health insurance and will have to sign consent forms.
Exclusion criteria: Volunteers participating in the study will be excluded if major treatment and/or protocol deviations are observed.[30] Drugs and medical conditions that significantly affect the primary outcome (heart rate variability) will also be exclusion criteria (e.g. alpha or beta-blockers; arrhythmias or conduction disorders such as bundle branch block, atrioventricular heart block).[31] Bariatric surgery is also an exclusion criteria."

Since you are restricting participation to "usual participants of the spa" consider describing the demographics of this group and discussing potential generalizability of your expected results.
[REPLY] Thank you for your comment. As stated in our manuscript: "Patients will be recruited through the usual participants of the spa resort of Vichy, through health-care workers (physicians, dieticians, physiotherapist, etc.), or through advertisements. Inclusions will be realized at the CHU Clermont-Ferrand or at the thermal spa resort of Vichy." Therefore, only some patients will be recruited through the usual participants of the spa resort. We added in the discussion section the following sentence: "In order to avoid generalizability of our expected results, we will pay a particular attention at the demographics of included participants (particularly between participants recruited from the "usual clients of the spa", and other participants). Secondary and sensitivity analyses will take into account provenance of participants."

The stress management intervention is poorly described. Please include data on the use of the protocol to assure readers you are using a tested/credible/definable intervention. Does your intervention work? Can it be replicated based on your description? The methods sound like you are just throwing together techniques from a variety of therapies. If you do not get group differences will it be due to a poor intervention?
[REPLY] The methods section – psychological interventions now reads: "Participants randomized to the intervention group will benefit from psychological interventions based on validated approaches of stress (3 x 1h30 per week i.e. 9 sessions in total). Participants will attend psychological sessions by group of less than 10 individuals. Individual meeting with the psychologist will occur at least twice: at the beginning of the residential program and at the end. Psychological interventions will include various validated approaches of work-related stress: physical [REF] and psychoanalytic [REF] approaches, cognitive behavioral therapy,[REF] acceptance and commitment therapy,[REF] mindfulness,[REF] etc. Participants will have to acquire techniques in order to be autonomous and pursue at-home psychological training. The 9 psychological sessions will be the following: 1) Stress management and lack of self-confidence, 2) cognitive behavioral therapy, 3) Body-centered approach: body language, 4) Management of emotions, 5) Identity approach: concept and self-image, 6) Cognitive approach (information processing), 7) Sophrology – relaxation, 8) Food and addictive behavior, and 9) Psychopathological approach and anxiety disorders. Each session will be constructed and validated by a psychologist specialized in the field of the session and already working in the management of obese individuals. The aim is to build a psychological program that can be easily replicated for long term used after evidence based medicine proof of success of our program."

Impressive outcome measures but it would strengthen the paper to document that the measures have been sensitive to stress management interventions in previous studies. Why do you need a pediatric nurse to collect blood samples? (Page 11 first sentence).

[REPLY] Thank you for you relevant comment. We added references linking all parameters measured with stress outcomes. We also added Table 1 with all outcomes measured, modalities of measurements, and references.
We do not need a pediatric nurse. It was a wrong cut and paste. We removed “pediatric”.

Good luck. Wish I could be a participant.
[REPLY] Thank you :)

Reviewer 3
Reviewer Name: Mohammed Hudda
Institution and Country: St George's, University of London, England, UK

This manuscript and the proposed RCT is very interesting in its concept of assessing how stress management could help in the treatment of obesity for those attending a spa resort in France.
[REPLY] Thank you for your positive comment.

However there are some concerns with the protocol, largely due to lack of detail where required.
[REPLY] We hope to have clarified all points by adding much more details on each of the concerns raised.

Specific Comments:
Methods (page 6):
- Randomisation strategy is not explained in enough detail. What was the rationale for the stratification groupings for level of stress? Furthermore, would it not be more appropriate to assess baseline measures prior to randomisation? Who will conduct the randomisation and how?
[REPLY] We thank the reviewer for the relevant comment. As the protocol is based on a stress management program, it appeared interesting to take into account the baseline level of stress in our analysis. We clarified the use of baseline assessments within analysis in several sections. We added a “Randomisation” section which now gives more details on the randomization process. The Randomisation section reads as follow: Randomization will be stratified by BMI category (25-30, 30-35, >35), sex, and level of stress (visual analog scale of stress <50, between 50 and 80, >80), using minimization approach. A permuted-block randomization (i.e. random block sizes) will be conducted using a computer-generated random allocation (Stata software, version 13, StataCorp, College Station, US), with a 1:1 ratio allocation, ensuring complete randomness of the assignment of a participant to each randomized group. To guarantee concealment of allocation, the participants will be randomized after it is clear that they have met the inclusion criteria and have provided written consent.”

Exclusion criteria (page 7):
- this section does not provide sufficient information. What are specific criteria for exclusion? Will this be based on any baseline measures?
[REPLY] Thank you for your relevant comment. We added several references within the inclusion and exclusion criteria sections. The Exclusion criteria section now reads: “Volunteers participating in the study will be excluded if major treatment and/or protocol deviations are observed.[30] Drugs and medical conditions that significantly affect the primary outcome (heart rate variability) will also be exclusion criteria (e.g. alpha or beta-blockers; arrhythmias or conduction disorders such as bundle branch block, atrioventricular heart block).[31] Bariatric surgery is also an exclusion criteria.”

Power Analysis (page 7):
- Please define HRV, LF and HF at first use.
[REPLY] Amended.

- Reference 3 is cited as a pilot study for this trial and as the basis for the difference in effect size. However, it is very unclear where these effect differences were ascertained from the cited paper.
[REPLY] Reference 3 is a randomized study that gives more than 15 articles published and indexed in PubMed. Please see the following link: https://www.ncbi.nlm.nih.gov/pubmed/?term=dutheil+AND+obert+AND+courteix+AND+chapier+AND+vinet+AND+lesourd+AND+walther. Among the numerous data available (the cost of this large RCT was >1 million euros, i.e. tremendous quantity of data), some are linking stress and HRV parameters, and we based our calculation of the sample size on these parameters. However, those data are not published yet. We added the following information in the section: "According to our results from a pilot study (data not published),[3] […]."

- Whilst the calculation seems fine, the expected difference between groups is very unclear.
[REPLY] We thank the reviewer to give us the opportunity to clarify the sample size estimation. We now define all parameters of HRV in the primary outcome section. We also added more details in the power analysis section. The section now reads: "The rationale for the sample size calculation is based on HRV which is a biomarker of both stress and morbidity/mortality.11 30 32 In particular, within multiple parameters of HRV, we considered the log Low-Frequency/High-Frequency (LF/HF) for sample size calculation because it is the parameter that traditionally represents sympathovagal balance (see description of LF/HF below in the description of the primary outcome section).11 30 The log LF/HF with low values associated with a good adaptation of the autonomic nervous system. According to our results from a pilot study (data not published),[3] we hope to highlight an absolute difference of 12% between groups concerning the decrease of log LF/HF at one year after the stress management program. For a standard-deviation at 20%, the expected size will be around 0.60. For a two-sided type I error of 5%, we need to include 59 participants by group to achieve a statistical power equals 90%. Finally, to take into account lost to follow-up, it is proposed to recruit 70 patients per arm."

- Participants: Will the study include 18 year olds or only those above 18 years?
[REPLY] We will include adults. However, the probability of including young adults within the study is very low. Usually people undergoing a spa program are over 40 years old.

- Recruitment details provided are not sufficient. More is needed to ascertain how you will recruit participants from the Spa Resort.
[REPLY] The section now reads: "Volunteers will be overweight or obese participants aged over 18 years, who wish to follow a spa thermal residential program for the treatment of obesity. We will also promote the study by advertisements in local newspaper and on radio. Volunteers will be screened by phone interview or directly by spa physicians. Participants must have a stable weight during the last three months, with no cardiac, hepatic, renal or endocrine diseases uncontrolled.[2] Stress at baseline will not be an inclusion criteria but an explanatory/independent variable."

- Follow-up (page 8): Will this at-home visit be done at 6 months also?
[REPLY] In order to avoid any confusion, the Follow-up section now reads: "After the intervention phase of the study, participants will undergo a one-year at-home follow-up with measures at 6 and 12 months."

We also added the time of measurements again in the Measurements section which now reads: “Data collection will be performed 5 times as previously described (inclusion, at the start, at the end of the spa program, at 6 and 12 months), […].”

- Measurements: Will any demongraphic information be collected from participants?
[REPLY] Thank you for your relevant comment. Of course, demographics will be assessed at each measurements time. We added demographics within the complementary measures section. We also added Table 1 with all outcomes measured, modalities of measurements, and references.

Statistical Analysis (Page 12):
- Please state on which basis you intend to analyse the data? Presumably intention-to-treat?
[REPLY] We thank the reviewer for the comment. We agree that the statistics will be analyzed in intention-to-treat. The statistics section has been modified accordingly.

- There needs to be more detail regarding the covariate adjustments within models
[REPLY] The section now reads: “This primary analysis will be completed by multivariable analysis (linear regression with logarithmic transformation of dependent outcome if necessary) considering an adjustment on covariates fixed according to univariate results, clinical and epidemiological relevance (notably, age, gender, baseline BMI and baseline stress levels) and observance to physical activity, nutrition, and the use of psychological techniques. The results will be expressed as regression coefficients and 95% confidence intervals.”

- The justification for the primary analysis model is not clear. Will baseline measures be adjusted for?
[REPLY] The section now reads: “This primary analysis will be completed by multivariable analysis (linear regression with logarithmic transformation of dependent outcome if necessary) considering an adjustment on covariates fixed according to univariate results, clinical and epidemiological relevance (notably, age, gender, baseline BMI and baseline stress levels) and observance to physical activity, nutrition, and the use of psychological techniques. The results will be expressed as regression coefficients and 95% confidence intervals.” We also added the following sentences: “In addition to previous analyses, to study differences during follow-up (end of the spa program, 6 and 12 months), these analyses will be completed using ANCOVA considering values at baseline.[REF: Vickers AJ, Altman DG. Analysing controlled trials with baseline and follow up measurements. BMJ. 2001 Nov 10;323(7321):1123-4]. Normality of residuals will be verified.”

- The intensity of the intervention will vary per individual as mentioned by the authors. However, how will this be reflected within the analysis?
[REPLY] We thank the reviewer for the interesting comment. According to this remark, we added to the statistical analyses an approach based on random-effects model, useful to take into account between and within patient variability, studying the following fixed effect: group, time-point evaluation and their interaction.

- Will any of the study team be blinded?
[REPLY] Thank you for your relevant comment. We added a “Confidentiality and blind assessments” section that reads: “Despite the participants and care providers will not be blinded to the participants' allocation group, in order to reduce the level of bias, assessors for most outcomes will be blinded to the assignment group of each participant, such as for HRV, biological measures, or bone parameters. All

outcome data will remain blinded until the end of the study. Patient's data will be deidentified and all data will be treated anonymously."

- How will the level of bias be reduced? Blinding participants to the randomisation group may not be an option, however will they be blind to the primary aims of the study?
[REPLY] Thank you for your relevant comment. We added a "Confidentiality and blind assessments" section that reads: "Despite the participants and care providers will not be blinded to the participants' allocation group, in order to reduce the level of bias, assessors for most outcomes will be blinded to the assignment group of each participant, such as for HRV, biological measures, or bone parameters. All outcome data will remain blinded until the end of the study. Patient's data will be deidentified and all data will be treated anonymously."

- How will missing data be tackled in the analysis?
[REPLY] We thank the reviewer for the relevant comment. We added the following sentence: "A sensitivity analysis will be realized to study the statistical nature of missing data (at random or not) and then, to apply the most appropriate imputation data method (multiple imputation data, last observation carried out). Baseline characteristics of participants who will have a complete follow-up and those who will be lost to follow-up will be compared with statistical tests aforementioned."

- Reporting checklist: Many relevant items are not complete which is reflected in the lack of details provided in the manuscript. The checklist manuscript by Chan et al. need also be cited within the manuscript.
[REPLY] We added several sections and several references. We also added Table 1 with all outcomes measured, modalities of measurements, and references. We hope all changes made were statisfactory.

VERSION 2 – REVIEW

REVIEWER	Phillip J. Brantley, PhD Pennington Biomedical Research Center, Behavioral Medicine
REVIEW RETURNED	10-Jun-2019

GENERAL COMMENTS	The authors were highly responsive to reviewer comments. The description of the stress management program is much improved but still lacks the specifics for anyone to replicate. The authors promise more detail after the study

REVIEWER	Mohammed Hudda St George\'s, University of London, Population Health Research Institute
REVIEW RETURNED	07-Jun-2019

GENERAL COMMENTS	I am now satisfied that the level of detail in this revised version is improved from the previous version.

VERSION 2 – AUTHOR RESPONSE

Reviewer 2

Reviewer Name: Phillip Brantley

Institution and Country: Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, Louisiana, USA

The authors were highly responsive to reviewer comments. The description of the stress management program is much improved but still lacks the specifics for anyone to replicate. The authors promise more detail after the study

[REPLY] Thank you for your comment.

Reviewer 3

Reviewer Name: Mohammed Hudda

Institution and Country: St George's, University of London, England, UK

I am now satisfied that the level of detail in this revised version is improved from the previous version.
[REPLY] Thank you for your comment.