PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effects of photobiomodulation therapy combined to static magnetic field in strength training and detraining in humans: protocol for a randomised placebo-controlled trial
AUTHORS	de Paiva, Paulo Roberto; Casalechi, Heliodora; Tomazoni, Shaiane; Machado, Caroline; Vanin, Adriane; Baroni, Bruno; de Carvalho, Paulo de Tarso; Leal-Junior, Ernesto Cesar

VERSION 1 – REVIEW

REVIEWER	Nathaniel Jenkins Oklahoma State University
REVIEW RETURNED	07-Apr-2019

GENERAL COMMENTS	Overall, the authors have provided a strong rationale and have clearly described the protocol for their clinical trial investigating the effects of photobiomodulation therapy on muscle strength and architecture following 12 weeks of strength training and 4 weeks of detraining. I would suggest that the authors provide a clear overview of the primary outcome variables and when these will be measured in the Materials and Methods section (this should compliment figure 1). I have no other major comments or concerns.

REVIEWER	Lilach Gavish The Hebrew University of Jerusalem, Jerusalem, Israel
REVIEW RETURNED	20-Jul-2019

GENERAL COMMENTS	This study protocol is planned to evaluate the effect of Photobiomodulation (PBM) in strength training and detraining in humans using an RCT factorial design (placebo/active over training/detraining phases). The authors give a good introduction about PBMT and its known ergogenic effects and describe the study rational clearly. The group conducting the study produced previous central high-quality studies on this subject and therefore experienced in the methods used to conduct such studies. The subject is important and the scientific question novel. Several issues should be corrected before publication: 1. The explanation about detraining should be centralized since the protocol revolves around this issue. 2. Typo - Page 4 line 47, please remove the word “is” from the sentence - “which is represents a challenging…” 3. Please add an explanation why volunteers of different skin colors can be recruited (page 4, line 50-15)

	4. Patient and public involvement statement - it is not clear why this statement is required. patient and public are seldomly involved in the design, recruitment, or conduct of RCTs. 5. Page 6 line 8-10 - “and who completed at least 80% of the study procedures will be included in the study” - maybe you are referring to “included in the analysis”? if so, this is not an inclusion criterion. Otherwise, please explain how a volunteer can complete 80% of the procedures and not be included in the study. 6. Please detail the block randomization scheme - how big is the block, based on what categories of MVC? 7. In the Procedure section (page 6), please begin with a statement of the number of planned evaluation visits - for example - “The protocol includes 5 planned evaluation visits: baseline, 4, 8, 12, and 16 weeks. Evaluations will include….” 8. Photobiomodulation therapy (page 8) - please explain how you plan to keep the blinding when you use wavelength of 640nm (visible red). 9. Statistical analysis: • Please detail what you mean by ”the intention-to-treat analysis will be followed a priori”. How does this refer to those “who completed at least 80% of the study procedures”. • The effect size is commonly related to the baseline measurements and therefore, all analysis on absolute data should adjusted to baseline measurements. • How are you taking the stratification into account? Are you planning additional analysis? • Consider using additional statistical methods to take the repeated measures design into account such as area under curve etc. 10. Discussion (page 9): please add a separate “limitation” section within the discussion.

REVIEWER	Justin Rigby The University of Utah, Salt Lake City, UT The United States of America
REVIEW RETURNED	28-Jul-2019

GENERAL COMMENTS	General Comments: The manuscript provides a logical study in the next step of understanding photobiomodulation therapy’s (PBMT) role in muscle performance and protection. The study methods use established protocols from previous publish literature. Additional details or better operational definitions may enhance the study protocol. Specific Comments: Introduction The introduction highlights previous studies related to PBMT effects on muscle performance (ergogenic effects) during strength training. Clarification and additional information regarding the protective effects of PBMT on skeletal muscle may enhance the need for the study. Specifically, I wonder if the effects of PBMT during detraining, if found positive, are truely ergogenic since there is no performance during detraining. Instead, potential effects may be protective. Page 3, lines 51-60: I find the description of the study by Nakano et al to be misleading. The study is presented in a way that

	indicates PBMT minimized disuse atrophy during the disuse phase in the study. However, PBMT in Nakano et al was only used during the active recovery phased of the study from the passive disuse. This would make PBMT effects ergogenic in nature during this active phase of the study, which activity is important for the physiological effects of satellite cell proliferation and angiogenesis. Currently, I am unaware of a study, animal or human, that represents PBMT effects during a passive phase. Thus, the physiological mechanism of PBMT may be completely different during activity and inactivity since the muscle signaling effects are different. Page 4, lines 10-12: Consider updating the wording of the study aim. Instead of “assess the ergogenic effects” the outcomes of the study suggest you are assessing the ability of PBMT to aid in maintaining strength during detraining. Materials and Methods Page 4, lines 30-36: The beginning of the sentence of the "Subject and sample size" sub-heading should be revising for conciseness and clarity. Page 4, lines 47: For consistency and clarity, please include “n of 12 per group” after the indication that 48 total participants will be recruited. Page 5, line 10: Where volunteers who presented with any musculoskeletal injury, for example, only an upper extremity injury, excluded from the study or just lower extremity? Page 5, line 11: For those that sustained an injury during the study time frame, was it any reported injury? For example, could it be a self-reported injury or did it have to be a diagnosis from a medical provider? Page 5, Randomization and blinding: Please clarify randomization procedures with more details. First, how are balanced block randomization procedures performed based on the primary outcome measures? Are participants randomized into groups before baseline measures? Second, initial procedures state balanced block randomization occurred; however, at lines 31-34, the description of using random.org and numbered envelopes describes simple randomization procedures instead of block randomization procedures. Page 6, Procedures: Somewhere in the procedures section an operational definition of detraining for this study and procedures to ensure that participants are equally detrained (or inactive during the 4-weeks) in all groups need to be included. Page 6, line 32: Should the wording be “in-line” to indicate the axis of rotation of the dynamometer will be “in-line” to the knee joint line. Page 6 lines 43-44: Did MVC outcome testing days occur on non-PBMT days. The treatment could have an ergogenic effect on the outcome for those assigned to PBMT groups. Research also indicates that there may be a lasting effect of PBMT. At least a 24 h time should pass between PBMT and outcome measures.

	Page 6, line 56: How many sets and reps occurred during the familiarization procedures? Page 7, line 5: Where the leg-extension and leg-press procedures performed unilateral or bilaterally? Previous research indicates unilateral, but it is unclear here. Discussion Page 9, lines 71-24: It may be beneficial to discuss the likelihood that the PBMT group during the strength training phased will create higher strength gains. I think it is a strength of the study that everybody does the same strength training program, but I don't see how focusing on the detraining period will be adjusted. This may be a limitation. Will there be an analysis of percent change from the peak strength training period to the end of the detraining period? Page 9, lines 37-44: Only assessing 4 weeks may not be a large limitation. I would assume most sports injuries, if that is the target population of this study, would be 3-4 weeks of time loss. Major injuries would obviously be longer. Epidemiology data would need to confirm.

REVIEWER	Jeri-Anne Lyons University of Wisconsin-Milwaukee, USA
REVIEW RETURNED	05-Aug-2019

GENERAL COMMENTS	1. Justify why only male subjects will be recruited. 2. I did not find the dates of the study in the manuscript. Your instructions indicate this is required. 3. The authors did not detail "placebo" treatment. Only the parameters for "active" treatment are provided.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Reviewer Name: Nathaniel Jenkins
Institution and Country: Oklahoma State University
Please state any competing interests or state 'None declared': None declared

Reviewer: Overall, the authors have provided a strong rationale and have clearly described the protocol for their clinical trial investigating the effects of photobiomodulation therapy on muscle strength and architecture following 12 weeks of strength training and 4 weeks of detraining.
Authors' response: Thanks for your kind comments about our manuscript.

Reviewer: I would suggest that the authors provide a clear overview of the primary outcome variables and when these will be measured in the Materials and Methods section (this should compliment figure 1). I have no other major comments or concerns.
Authors' response: We have added these details in manuscript text. Thank you!

Reviewer 2

Reviewer Name: Lilach Gavish
Institution and Country: The Hebrew University of Jerusalem, Jerusalem, Israel
Please state any competing interests or state 'None declared': None declared

Reviewer: This study protocol is planned to evaluate the effect of Photobiomodulation (PBM) in strength training and detraining in humans using an RCT factorial design (placebo/active over training/detraining phases).The authors give a good introduction about PBMT and its known ergogenic effects and describe the study rational clearly. The group conducting the study produced previous central high-quality studies on this subject and therefore experienced in the methods used to conduct such studies. The subject is important and the scientific question novel.
Authors' response: Thanks for your kind comments about our manuscript.

Reviewer: The explanation about detraining should be centralized since the protocol revolves around this issue.
Authors' response: In current version of our manuscript we gave focus on detraining as suggested. Thanks for your comment.

Reviewer: Typo - Page 4 line 47, please remove the word "is" from the sentence - "which is represents a challenging…"
Authors' response: We have corrected the sentence. Thank you.

Reviewer: Please add an explanation why volunteers of different skin colors can be recruited (page 4, line 50-15)
Authors' response: We have added this information in our manuscript as requested. Thanks for your comment.

Reviewer: Patient and public involvement statement - it is not clear why this statement is required. patient and public are seldomly involved in the design, recruitment, or conduct of RCTs.
Authors' response: This statement is mandatory in this journal, even if there isn't any patient or public involvement. Thanks for your comment.

Reviewer: Page 6 line 8-10 - "and who completed at least 80% of the study procedures will be included in the study" - maybe you are referring to "included in the analysis"? if so, this is not an inclusion criterion. Otherwise, please explain how a volunteer can complete 80% of the procedures and not be included in the study.
Authors' response: This information was wrong in first version of our manuscript, and it was corrected in current version. Thank you!

Reviewer: Please detail the block randomization scheme - how big is the block, based on what categories of MVC?
Authors' response: This information was also wrong in first version of our manuscript, and it was corrected in current version. Thank you.

Reviewer: In the Procedure section (page 6), please begin with a statement of the number of planned evaluation visits - for example - "The protocol includes 5 planned evaluation visits: baseline, 4, 8, 12, and 16 weeks. Evaluations will include…."
Authors' response: We have changed the sentence as suggested. Thanks for your comment.

Reviewer: Photobiomodulation therapy (page 8) - please explain how you plan to keep the blinding when you use wavelength of 640nm (visible red).
Authors' response: We have added this explanation. In summary the power output of red diodes will be decreased to minimum to keep the visual aspect of red light, but to do not deliver an effective therapeutic or considerable dose according the current available evidence. Thank you.

Reviewer: Statistical analysis:
- Please detail what you mean by "the intention-to-treat analysis will be followed a priori". How does this refer to those "who completed at least 80% of the study procedures".
- The effect size is commonly related to the baseline measurements and therefore, all analysis on absolute data should adjusted to baseline measurements.
- How are you taking the stratification into account? Are you planning additional analysis?
- Consider using additional statistical methods to take the repeated measures design into account such as area under curve etc.

Authors' response: The "who completed at least 80% of the study procedures" was wrong and excluded, we have included effect sizes analysis as suggested, and we are not considering using additional analysis in this study. Thanks for your valuable comments.

Reviewer: Discussion (page 9): please add a separate "limitation" section within the discussion.
Authors' response: We have added the limitation section as requested.

Reviewer 3

Reviewer Name: Justin Rigby
Institution and Country: The University of Utah, Salt Lake City, UT, The United States of America
Please state any competing interests or state 'None declared': None declared

Reviewer: The manuscript provides a logical study in the next step of understanding photobiomodulation therapy's (PBMT) role in muscle performance and protection. The study methods use established protocols from previous publish literature. Additional details or better operational definitions may enhance the study protocol.
Authors' response: Thanks for your kind comments about our manuscript.

Reviewer: The introduction highlights previous studies related to PBMT effects on muscle performance (ergogenic effects) during strength training. Clarification and additional information regarding the protective effects of PBMT on skeletal muscle may enhance the need for the study. Specifically, I wonder if the effects of PBMT during detraining, if found positive, are truely ergogenic since there is no performance during detraining. Instead, potential effects may be protective.
Authors' response: We appreciate reviewer's comment. In current version of our manuscript we tried to highlight the protective effects of PBMT as well.

Reviewer: Page 3, lines 51-60: I find the description of the study by Nakano et al to be misleading. The study is presented in a way that indicates PBMT minimized disuse atrophy during the disuse phase in the study. However, PBMT in Nakano et al was only used during the active recovery phased of the study from the passive disuse. This would make PBMT effects ergogenic in nature during this active phase of the study, which activity is important for the physiological effects of satellite cell proliferation and angiogenesis. Currently, I am unaware of a study, animal or human, that represents PBMT effects during a passive phase. Thus, the physiological mechanism of PBMT may be completely different during activity and inactivity since the muscle signaling effects are different.
Authors' response: For clarification and to avoid any misleading we added to the sentence that PBMT in Nakano et al was only used during the active recovery phase of the study from the passive disuse, and that since during the detraining the muscles wouldn't be in complete inactivity nor immobilized,

PBMT could work in delaying strength loss. We appreciate your suggestion and we hope that now the sentence is clear.

Reviewer: Page 4, lines 10-12: Consider updating the wording of the study aim. Instead of “assess the ergogenic effects” the outcomes of the study suggest you are assessing the ability of PBMT to aid in maintaining strength during detraining.
Authors’ response: We agree with the reviewer, and we changed the sentence as suggested.

Reviewer: Page 4, lines 30-36: The beginning of the sentence of the "Subject and sample size" sub-heading should be revising for conciseness and clarity.
Authors’ response: We agree with the reviewer, and we changed the sentence as suggested.

Reviewer: Page 4, lines 47: For consistency and clarity, please include “n of 12 per group” after the indication that 48 total participants will be recruited.
Authors’ response: We have added this information as requested by reviewer. Thank you.

Reviewer: Page 5, line 10: Where volunteers who presented with any musculoskeletal injury, for example, only an upper extremity injury, excluded from the study or just lower extremity?
Authors’ response: The volunteers were excluded if they present musculoskeletal injuries that limit or preclude performing the exercises in the strength training protocol. We have added this information in manuscript. Thanks for your comment.

Reviewer: Page 5, line 11: For those that sustained an injury during the study time frame, was it any reported injury? For example, could it be a self-reported injury or did it have to be a diagnosis from a medical provider?
Authors’ response: It could be a self-reported injury or an injury diagnosed by a medical doctor. We have added this information in manuscript as well. Thanks.

Reviewer: Page 5, Randomization and blinding: Please clarify randomization procedures with more details. First, how are balanced block randomization procedures performed based on the primary outcome measures? Are participants randomized into groups before baseline measures? Second, initial procedures state balanced block randomization occurred; however, at lines 31-34, the description of using random.org and numbered envelopes describes simple randomization procedures instead of block randomization procedures.
Authors’ response: We have corrected this aspect in current version of manuscript. Actually, randomization labels will be created through the random.org website, and a series of sealed, opaque, and numbered envelopes will be used to ensure confidentiality and will determine to which experimental group each volunteer will be allocated. We have corrected this section in our manuscript. Thank you.

Reviewer: Page 6, Procedures: Somewhere in the procedures section an operational definition of detraining for this study and procedures to ensure that participants are equally detrained (or inactive during the 4-weeks) in all groups need to be included.
Authors’ response: We have included this information in current version of manuscript. Thanks for your comment.

Reviewer: Page 6, line 32: Should the wording be “in-line” to indicate the axis of rotation of the dynamometer will be “in-line” to the knee joint line.
Authors’ response: This exactly what we meant. We have corrected this in manuscript text, thank you.

Reviewer: Page 6 lines 43-44: Did MVC outcome testing days occur on non-PBMT days. The treatment could have an ergogenic effect on the outcome for those assigned to PBMT groups. Research also indicates that there may be a lasting effect of PBMT. At least a 24 h time should pass between PBMT and outcome measures.
Authors' response: All assessments will be performed at least 24 hours before or after any kind of intervention (PBMT, placebo or strength training). We have added this information in manuscript. Thank you!

Reviewer: Page 6, line 56: How many sets and reps occurred during the familiarization procedures?
Authors' response: We added this information in manuscript. Thank you.

Reviewer: Page 7, line 5: Where the leg-extension and leg-press procedures performed unilateral or bilaterally? Previous research indicates unilateral, but it is unclear here.
Authors' response: It was performed unilaterally. We have included this information in manuscript. Thanks for your comment.

Reviewer: Page 9, lines 71-24: It may be beneficial to discuss the likelihood that the PBMT group during the strength training phased will create higher strength gains.
I think it is a strength of the study that everybody does the same strength training program, but I don't see how focusing on the detraining period will be adjusted. This may be a limitation. Will there be an analysis of percent change from the peak strength training period to the end of the detraining period?
Authors' response: We totally agree with your comment. This is why we have planned statistical analysis of both absolute values and percentage of change in our protocol, which will provide a clearer understanding regarding the outcomes of this project. Additionally, we have added a paragraph in discussion section regarding the likelihood that the PBMT group during the strength training phased will create higher strength gains as suggested.

Reviewer: Page 9, lines 37-44: Only assessing 4 weeks may not be a large limitation. I would assume most sports injuries, if that is the target population of this study, would be 3-4 weeks of time loss. Major injuries would obviously be longer. Epidemiology data would need to confirm.
Authors' response: In fact, it is an important aspect, we have added a brief discussion about this in our manuscript. Thank you.

Reviewer 4

Reviewer Name: Jeri-Anne Lyons
Institution and Country: University of Wisconsin-Milwaukee, USA
Please state any competing interests or state 'None declared': None declared

Reviewer: Justify why only male subjects will be recruited.
Authors' response: The choice to recruit only male volunteers is to allow direct comparison with a previous study carried out by our research group. This information was included in current version of our manuscript. Thank you.

Reviewer: I did not find the dates of the study in the manuscript. Your instructions indicate this is required.
Authors' response: We have added it as suggested. Thank you.

Reviewer: The authors did not detail "placebo" treatment. Only the parameters for "active" treatment are provided.

Authors' response: We have detailed the parameters for placebo treatment in current version of our manuscript. Thank you.

VERSION 2 – REVIEW

REVIEWER	Lilach Gavish Institute for Research in Military Medicine, Faculty of Medicine, The Hebrew University of Jerusalem, Israel
REVIEW RETURNED	05-Sep-2019

GENERAL COMMENTS	The authors have responded to all of my concerns in the previous review. Two minor points in the new text should be corrected: 1. Page 3, line 12: Please see the following manuscript that suggests evidence for a substance that may decrease the effect of detraining - Hüttemann et al: "(-)-Epicatechin maintains endurance training adaptation in mice after 14 days of detraining" FASEB J. 2012 Apr;26(4):1413-22. Please consider modifying the sentence to include the word "clinical" - "To the best of our knowledge, currently there is no CLINICAL evidence or consensus on any particular resource or method". 2. Page 8, line 55: Please correct a typo - replace "but to do not deliver" with "but not to deliver" Good luck in the completion of the study.

REVIEWER	Justin Rigby The University of Utah, USA
REVIEW RETURNED	13-Sep-2019

GENERAL COMMENTS	The manuscript has been significantly updated. I have one minor comment. The first paragraph of the introduction was added to this version of the manuscript. It should be edited as it lacks a clear focus and is difficult to read.

VERSION 2 – AUTHOR RESPONSE

Reviewer 2

Reviewer Name: Lilach Gavish

Institution and Country: Institute for Research in Military Medicine, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel

Please state any competing interests or state 'None declared': None declared

Reviewer: The authors have responded to all of my concerns in the previous review. Two minor points in the new text should be corrected:

1. Page 3, line 12: Please see the following manuscript that suggests evidence for a substance that may decrease the effect of detraining - Hüttemann et al: "(-)-Epicatechin maintains endurance training adaptation in mice after 14 days of detraining" FASEB J. 2012 Apr;26(4):1413-22. Please consider modifying the sentence to include the word "clinical" - "To the best of our knowledge, currently there is no CLINICAL evidence or consensus on any particular resource or method".

Authors' response: Thanks for your heads up. We changed the sentence as suggested.

2. Page 8, line 55: Please correct a typo - replace "but to do not deliver" with "but not to deliver"

Authors' response: We have corrected the sentence as suggested. Thanks.

Good luck in the completion of the study.

Authors' response: We really appreciate your constructive comments about our manuscript. Thank you!

Reviewer 3

Reviewer Name: Justin Rigby

Institution and Country: The University of Utah, Salt Lake City, UT, The United States of America

Please state any competing interests or state 'None declared': None declared

Reviewer: The manuscript has been significantly updated. I have one minor comment. The first paragraph of the introduction was added to this version of the manuscript. It should be edited as it lacks a clear focus and is difficult to read.

Authors' response: We have edited the paragraph as suggested. Thanks for your comment.