

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The PREHAB Study: A protocol for a prospective randomized clinical trial of exercise therapy for people living with frailty having cancer surgery
AUTHORS	Mclsaac, Daniel; Saunders, Chelsey; Hladkowitz, Emily; Bryson, Gregory; Forster, Alan; Gagne, Sylvain; Huang, Allen; Lalu, Manoj; Lavalley, Luke; Moloo, Husein; Nantel, Julie; Power, Barbara; Scheede-Bergdahl, Celena; Taljaard, Monica; van Walraven, Carl; McCartney, Colin

VERSION 1 – REVIEW

REVIEWER	Jonathan Moran Trinity College, The University of Dublin, Ireland
REVIEW RETURNED	15-Feb-2018

GENERAL COMMENTS	<p>The authors should be congratulated for a well designed study, and well written protocol. My comments to the authors are only minor and mostly are with the discussion.</p> <p>Minor Comments:</p> <ol style="list-style-type: none"> 1. I would use the specific term 'exercise prehabilitation' instead of only prehabilitation. Some institutions describe prehabilitation as a multi-modal treatment and although exercise is most commonly associated with prehab, I think we should be specific as to the type of prehab. 2. Pg 16, Ethics will be notified of an adverse event within 15 days (7 days if serious adverse event). Can you confirm if this is standard? It seems quite long to me. 3. Pg 17, lines 22-25. Can you provide more details of studies that have focused on younger cohorts (i.e. references and results) 4. Pg 17, line 26-36. This sentence is very long, please break it up. 5. Pg 18, line 14-17. Please provide a reference 6. More references to current prehabilitation material are needed. Current references are quite restricted.
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REVIEWER	Laura Lorenzo-López University of A Coruña
REVIEW RETURNED	27-Feb-2018

GENERAL COMMENTS	<p>The authors present the protocol of an ongoing interventional research study using home-based physical exercise and nutritional advice before surgery (prehabilitation) to improve postoperative patient function in frail people with intraabdominal or thoracic cancer. The study design and methodology seem correct. Authors should describe in more detail the specific instrument employed to diagnose frailty (briefly describing the items or methods used to explore the</p>
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	domains of mobility, energy, physical activity, and function), and adequately justify the variable duration of the intervention (≥ 3 weeks). In the literature, exercise interventions have demonstrated improvement in different outcome measurements in frail older adults, with multicomponent exercise intervention reversing frailty in some research studies. This literature should be cited in the protocol.
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

1. I would use the specific term 'exercise prehabilitation' instead of only prehabilitation. Some institutions describe prehabilitation as a multi-modal treatment and although exercise is most commonly associated with prehab, I think we should be specific as to the type of prehab.

Response:

Thank you for your suggestion. We have applied this change throughout.

2. Pg 16, Ethics will be notified of an adverse event within 15 days (7 days if serious adverse event). Can you confirm if this is standard? It seems quite long to me.

Response:

Thanks for your query. We have re-checked with our REB and re-verified the local standard operating procedures and can confirm that serious AEs must be reported within 7 days. However, we have clarified the process in the manuscript. In brief, if an AE is deemed to be serious and potentially study-related the event is reported to the REB as soon as possible, and within 7 days at most.

3. Pg 17, lines 22-25. Can you provide more details of studies that have focused on younger cohorts (i.e. references and results)

Response:

Thanks for your comment. We have added references and discussion contrasting findings from exercise prehabilitation studies in younger people with more recent examples of studies in older people that have demonstrated significantly improved outcomes with exercise prehabilitation.

4. Pg 17, line 26-36. This sentence is very long, please break it up.

Response:

Thanks for picking that up. It is now communicated in 3 sentences.

5. Pg 18, line 14-17. Please provide a reference

Response:

We now provide reference to ACC/AHA guidelines that specify 4 metabolic equivalents as a screening criterion for surgery.

6. More references to current prehabilitation material are needed. Current references are quite restricted.

Response:

Thank you for your comment. We now include the recent (2018) Barberan-Garcia et al paper, which is a key comparator study to ours. Additionally, we reference a systematic review which has also been published since our initial submission (Marmelo and colleagues).

Reviewer: 2

1. Authors should describe in more detail the specific instrument employed to diagnose frailty (briefly describing the items or methods used to explore the domains of mobility, energy, physical activity, and function)

Response:

We have added description of the CFS, including referring to the fact that it is also highly correlated with the CSHA frailty index.

2. ...and adequately justify the variable duration of the intervention (≥ 3 weeks).

Response:

Thank you for requesting clarification. We have added description of why we have chosen the 3-week time frame (a balance between exposure periods with proven efficacy balanced with wait time standards), as well as the reality that some people will require neoadjuvant therapy that may lead to a longer exposure period. The prespecified analysis will adjust for neoadjuvant therapy.

3. In the literature, exercise interventions have demonstrated improvement in different outcome measurements in frail older adults, with multicomponent exercise intervention reversing frailty in some research studies. This literature should be cited in the protocol.

Response:

Thank you, we have expanded upon this in the introduction, and in particular include Barberan Garcia and colleagues randomized trial which is now available ahead of print. We have additionally added discussion and references to Tarazona and colleagues randomized trial of a multicomponent exercise program which demonstrated a reduction in frailty in the intervention group. Finally, we directly refer to findings from Theou and colleagues which indicate that multicomponent structured programs are likely to be the most effective means to improve outcomes.

VERSION 2 – REVIEW

REVIEWER	Laura Lorenzo-López University of A Coruña. Spain
REVIEW RETURNED	12-Apr-2018
GENERAL COMMENTS	The manuscript is adequately revised and the comments are adequately considered.
REVIEWER	Jonathan Moran Trinity College Dublin, Ireland
REVIEW RETURNED	17-Apr-2018
GENERAL COMMENTS	The authors should be congratulated for a well designed study, and well written protocol. The authors have addressed my previous comments.