Reviewer’s report

Title: The effects of prehabilitation versus usual care to reduce postoperative complications in high-risk patients with colorectal cancer or dysplasia scheduled for elective colorectal resection: study protocol of a randomized controlled trial

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Reviewer: Emer Guinan

Reviewer’s report:

This manuscript describes the protocol for a prehabilitative exercise intervention for patients scheduled for colorectal surgery which aims to reduce incidence of postoperative complications. The topic of the manuscript is extremely important in an era of enhanced recovery after surgery and increasing focus on the role of exercise prehabilitation to optimise postoperative outcomes.

Introduction:

The authors provide a nice overview of the purpose of exercise prehabilitation and cite various literature. It would be useful for the authors to describe the challenges of exercise prehabilitation, typically related to the short timeframe between diagnosis and surgery and how the intervention that they propose fits with the current clinical pathway in the Netherlands. The introduction should be reviewed for grammatical errors and correct use of terms. For example in paragraph 1, line 11 the authors use the term 'psychophysiological' which I do not think was intended here.

Methods:

The authors aim to reduce incidence of postoperative complications from 50% to 20%, measured using the Clavien-Dindo classification. In their sample size calculation, the authors state that current postoperative morbidity post colorectal surgery is 33% but then anticipate a complication rate of 50% in the control group. Looking at the publication by Dunne et al., (Reference 28 - conference abstract), Dunne et al report preoperative improvements in cardiorespiratory fitness but do not mention postoperative complication rates. This section needs to be rechecked. Furthermore, the reported sample size appears small in comparison with other published work. For example the ongoing PREPARE-ABC trial (SupPoRtive Exercise Programs for Accelerating REcovery after major ABdominal Cancer surgery) estimate that they will require 1146 patients to detect a 25% reduction in post-operative complications from 55% with exercise prehabilitation. The authors should double-check the basis for the sample size calculation and justify more clearly in the methods section.

The first objective aims to assess changes in preoperative fitness occur with the intervention. It should be noted that preoperative fitness will be measured once in the control arm and twice in the intervention arm pre-operatively and therefore analysis of the data pertaining to this objective
will be limited to a single-arm study design. The authors should justify why they do not repeat a pre-operative CPET in the control group pre-surgery in order to test by RCT if the intervention leads to an increase in pre-op fitness.

Objective 3 states that patients with a VAT >11 mL/kg/min will not be randomised but will continue to be observed postoperatively. The analysis of this question should be further explained in the methods. For example, do the authors plan to use baseline or post-intervention CPET data for the intervention group (as the intervention aims to increase fitness)?

Objective 4 aims to investigate the value of a limited geriatric assessment to perform preoperative risk stratification. In the methods the authors outline a number of tools that will be used to evaluate geriatric assessment. From the methods it appears that all of this tools will be completed at baseline only. Do the authors have concerns that examining baseline data as predictors of outcome may be confounded by the effects of the intervention? For example, would functional status as measured by the IADL be influenced by increased aerobic fitness and muscular strength?

Objective 5 states that a cost analysis will be completed. The authors describe use of the EQ-5D tool to examine health status which is often used in the evaluation of cost effectiveness however do not describe other aspects of the cost analysis. This is an important aspect of the study, particularly in consideration that we hope for exercise prehabilitation studies to form part of standard of care for patients. The authors should include a discussion around the clinical feasibility of the proposed protocol in the context of existing clinical pathways.

The exercise intervention described appears reasonable and should elicit therapeutic response. The authors propose a novel approach with high intensity interval aerobic exercise training, resistance exercise training and self-directed home exercise.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

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None

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