PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A randomised controlled trial to assess whether prehabilitation improves fitness in patients undergoing neoadjuvant treatment prior to oesophago-gastric cancer surgery: Protocol
AUTHORS	Allen, Sophie; Brown, Vanessa; Prabhu, Pradeep; Scott, Michael; Rockall, Timothy; Preston, Shaun; Sultan, Javed

VERSION 1 – REVIEW

REVIEWER	Krishna Moorthy Imperial College, London
REVIEW RETURNED	25-Apr-2018

GENERAL COMMENTS	An important research in this rapidly emerging topic in peri-operative medicine. This trial will contribute to the growing body of evidence. My only criticism is that the focus is not on post-operative outcomes. There is already abundant evidence that a programme such as this will give rise to an improvement in functional capacity but what we really need now is evidence that such labour and capital intensive hospital based programmes actually improve outcomes My other observations are 1. Recruitment into a trial that involves 36 visits to a hospital or centre over 15 weeks is going to be challenging is a complex cohort of patients who are on chemotherapy 2. Adherence/ compliance to the intervention is an important measure that needs to be included. If there are no measurable improvements in the intervention group, this could be because they were not completely adherent to the intervention- Type 3 error in implementation science. 3. Quality of Life measurements are undertaken too frequently and may lead to 'questionnaire fatigue' and thus result in spurious results. 4. Exercise time is 5 hours per week. This is much higher than what has been recommended for clinical exercise programmes (150 mins per week). 5. The authors say that their intervention will be tailored but fail to give any details of how this will be done. Their exercise protocol is quite prescriptive and seems identical for all patients. 6. It would be useful to have details of the psychological component of the intervention and any references to the fact that this component is likely to show a benefit in this cohort of patients. 7. PPI (patient public involvement) would be very important for a trial such as this and could have been more robust.

REVIEWER	Francesco Carli

	McGill University, Canada
REVIEW RETURNED	27-Apr-2018

GENERAL COMMENTS	I enjoyed reading this manuscript. The authors wish t address an important issue and we need to have more data on the topic. I have some points to be considered. While there is an effort to describe well the exercise prescription, there is a brief comment on nutrition. This aspect is of great importance in this population and needs to be addressed otherwise patients will not be able to perform intensive exercise.

REVIEWER	Professor AG Heriot Peter MacCallum Cancer Centre, Melbourne, Australia
REVIEW RETURNED	01-May-2018

GENERAL COMMENTS	The authors present a protocol for a prospective randomised controlled trial assessing the impact of multimodal prehabilitation in patients undergoing neoadjuvant therapy prior to oesophagogastric resection. The primary endpoint of the study is an improvement in anaerobic threshold (AT) measured by CPX following a 15 week prehabilitation program. Secondary endpoints are further assessment of functional reserve, insulin resistance, post-operative complications and mortility. The study requires 58 patients to be recruited and so far 43 patients have been recruited. The study address an important question with respect to the role of multimodal prehabilitation in patients undergoing neoadjuvant therapy. AT has been demonstrated to be predictive of postoperative outcome in colorectal cancer patients. Prehabilitation has been shown to improve AT in prior studies of colorectal cancer patients but these two points have not been explored in oesophagogastric cancer patients and hence the study is very timely. As prior studies have considered an AT of 11 to be an inflexion point with respect to morbidity in prior studies, was there consideration in patients who had an AT of less than 11 on the initial CPX not to randomise and to go directly into the prehabilitation arm?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Krishna Moorthy
Institution and Country: Imperial College, London
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

An important research in this rapidly emerging topic in peri-operative medicine. This trial will contribute to the growing body of evidence. My only criticism is that the focus is not on post-operative outcomes. There is already abundant evidence that a programme such as this will give rise to an

improvement in functional capacity but what we really need now is evidence that such labour and capital intensive hospital based programmes actually improve outcomes

Thank you for this comment. We certainly agree that improving outcomes is key. Unfortunately, the numbers required to see the effect on post-operative outcome, for example length of stay, would require a very large sample size. We estimate that 250 patients per arm would be required to produce a reduction in length of stay by 1 day (Jack S et al. WesFit Trial, Southampton). We will however review the effect of prehabilitation on chemotherapy toxicity and chemotherapy completion rates which would be likely to influence survival outcomes (pages 14-15 Study Outcomes).

Indeed, there is evidence in many surgical fields that a prehabilitation programme will improve functional capacity. We feel that this manuscript will add to the limited amount of available literature investigating the effect of prehabilitation in oesophagogastric cancer patients receiving chemotherapy.

My other observations are

1. Recruitment into a trial that involves 36 visits to a hospital or centre over 15 weeks is going to be challenging is a complex cohort of patients who are on chemotherapy

Certainly this may prove a challenge to patients receiving chemotherapy. In order to ensure the patient's experience is as positive as possible, we will ensure that all travel and parking costs covered by the trial funding. In order to minimise the number of extra appointments, prehabilitation sessions will (where possible) be scheduled for the same day that they are due to attend a hospital appointment. Medical Coaching sessions will also be linked to the timing of the exercise sessions, or may be performed via Skype (or similar) where the patient finds this preferable.

(Methods and Analysis / Study groups (page 13))

2. Adherence/ compliance to the intervention is an important measure that needs to be included. If there are no measurable improvements in the intervention group, this could be because they were not completely adherent to the intervention- Type 3 error in implementation science.

Thank you for this comment. We agree that adherence/compliance to the intervention is a very important measure and as such will amend the protocol accordingly. Patients will be deemed 'compliant' if they complete >75% of scheduled prehabilitation sessions.

(Methods and Analysis / Study outcomes (page 14))

3. Quality of Life measurements are undertaken too frequently and may lead to 'questionnaire fatigue' and thus result in spurious results.

We agree that quality of life assessment may be too frequent. We will reduce this is in the protocol to the following: 1) Baseline (pre-chemotherapy), 2) Mid-chemotherapy, 3) Post-chemotherapy, 4) 2 weeks post hospital discharge, 5) 6 weeks post hospital discharge, and 6) 6 months post discharge.

(Methods and Analysis / Study outcomes (page 15))

4. Exercise time is 5 hours per week. This is much higher than what has been recommended for clinical exercise programmes (150 mins per week).

Indeed, exercise sessions are frequent in our protocol. It has been shown that supervised exercise yields a higher compliance rate than home exercise, however, home exercise is included to reduce

the number of visits required by the patient. Although the two supervised exercise sessions (two hours per week total) comprises aerobic and resistance training, the home exercise plan is of a lower intensity, with patients completing further resistance (with a resistance band e.g. Theraband) and flexibility exercises.

5. The authors say that their intervention will be tailored but fail to give any details of how this will be done. Their exercise protocol is quite prescriptive and seems identical for all patients.

Thank you, we will amend the manuscript to include further information regarding the exercise protocol. The study seeks to implement an exercise training program that will be flexible and adaptable depending on the wellbeing of the patient. In accordance with the American College of Sports Medicine guidelines, the exercise program will consist of cardiorespiratory, resistance and flexibility training (Nelson et al., 2007).

Please see amended Methods and Analysis section, under 'Study groups' for more detail regarding the exercise intervention (pages 10 and 11).

6. It would be useful to have details of the psychological component of the intervention and any references to the fact that this component is likely to show a benefit in this cohort of patients.

Thank you. More detail will be added to the background of the protocol to describe the reasoning behind a psychological component (Introduction (page 6), and Methods and Analysis / Study Group / Psychological (Medical Coaching) intervention (page 12).

Anxiety and depression is commonplace in patients receiving treatment for cancer. Studies have shown that the presence of depression is associated with higher levels of treatment non-compliance (DiMatteo MR et al 2000, Arch Intern Med). There is growing evidence that the psychological aspect of the intervention (Medical Coaching) can reduce anxiety and depression (Garssen B et al 2013 Psychooncology; Parker PA et al 2009, J Clin Oncol) and counteract the impairment of quality of life following chemotherapy and oesophagectomy (Scarpa et al 2017, BJS). Mayo et al have suggested that improvement in exercise capacity during the preoperative period was a result of the belief of patients that fitness levels aid recovery (Mayo NE et al 2011, Surgery).

It is hoped that the psychological element will empower patients to proactively take control of their behaviour preoperatively and therefore lead to improved engagement with the exercise aspect of the intervention.

7. PPI (patient public involvement) would be very important for a trial such as this and could have been more robust

Thank you. We concur that PPI is key in conducting a trial successfully, particularly amongst this cohort of patients. Prior to protocol finalisation, the research team attended the Oesophageal Patient Association Support Group where they were able to learn and understand about patient's previous experiences. From this, they were able to engage and empower the patient to contribute to the construction of a patient-centered trial. We will amend the manuscript accordingly.

(Methods and Analysis / Study setting (page 7))

Reviewer: 2
Reviewer Name: Francesco Carli

Institution and Country: McGill University, Canada
Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below

I enjoyed reading this manuscript. The authors wish to address an important issue and we need to have more data on the topic. I have some points to be considered.
While there is an effort to describe well the exercise prescription, there is a brief comment on nutrition. This aspect is of great importance in this population and needs to be addressed otherwise patients will not be able to perform intensive exercise.

Thank you. Indeed, we believe that nutrition is of great importance, particularly to this cohort of patients who may be cachexic at presentation. At Guildford, we are extremely fortunate to have the input of 2.4 equivalent specialist oesophagogastric dieticians per 60 cancer resections. They are highly trained in the field of oesophagogastric surgery and have great experience in the management on complex nutritional problems related to the disease. Patients do not receive a specific nutritional intervention in addition to the above, but receive individually tailored, regular, dietetic input, increasing calorie and protein intake where appropriate.

(Nutritional support (pages 12-13)).

Reviewer: 3
Reviewer Name: Professor AG Heriot
Institution and Country: Peter MacCallum Cancer Centre, Melbourne, Australia
Please state any competing interests or state 'None declared': None Declared

Please leave your comments for the authors below

The authors present a protocol for a prospective randomised controlled trial assessing the impact of multimodal prehabilitation in patients undergoing neoadjuvant therapy prior to oesophagogastric resection. The primary endpoint of the study is an improvement in anaerobic threshold (AT) measured by CPX following a 15 week prehabilitation program. Secondary endpoints are further assessment of functional reserve, insulin resistance, post-operative complications and mortality.

The study requires 58 patients to be recruited and so far 43 patients have been recruited.

The study address an important question with respect to the role of multimodal prehabilitation in patients undergoing neoadjuvant therapy. AT has been demonstrated to be predictive of postoperative outcome in colorectal cancer patients. Prehabilitation has been shown to improve AT in prior studies of colorectal cancer patients but these two points have not been explored in oesophagogastric cancer patients and hence the study is very timely.

As prior studies have considered an AT of 11 to be an inflexion point with respect to morbidity in prior studies, was there consideration in patients who had an AT of less than 11 on the initial CPX not to randomise and to go directly into the prehabilitation arm?

Thank you. Certainly, this would be beneficial. Older et al (Chest 1999) revealed an AT of 11 to define the 'low' or 'high' risk patient, however, this paper comprised a different patient demographic. We still believe however that 11 is a useful figure from which one is able to classify risk. On construction of the trial protocol, is was indeed initially our intent to sub-classify patients into low and high risk based

on their baseline AT, but to power the study adequately, would require a larger sample size for each of the 4 groups (prehab more than and less that AT 11, and control more and less than AT 11). We will however do a sub-group analysis to this effect on our cohort of patients (page 18).

VERSION 2 – REVIEW

REVIEWER	Krishna Moorthy Imperial College, London, UK
REVIEW RETURNED	14-Aug-2018

GENERAL COMMENTS	The changes made have greatly enhanced the manuscript. I still believe that the PPI could have been more structured, organised and robust. Probably something work considering when the results inform a larger trial.