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A randomised controlled trial to assess whether prehabilitation improves fitness in patients undergoing neoadjuvant treatment prior to oesophago-gastric cancer surgery: Protocol

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A randomised controlled trial to assess whether prehabilitation improves fitness in patients undergoing neoadjuvant treatment prior to oesophago-gastric cancer surgery: Protocol

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Abstract

Introduction

Neoadjuvant therapy prior to oesophago-gastric resection is the gold standard of care for patients with T2 and/or nodal disease. Despite this, studies have taught us that chemotherapy decreases patients' functional capacity as assessed by cardiopulmonary exercise (CPX) testing. We aim to show that a multimodal prehabilitation programme comprising of supervised exercise, psychological coaching

and nutritional support, will physically, psychologically and metabolically optimise these patients prior to oesophago-gastric cancer surgery so they may better withstand the immense physical and metabolic stress placed upon them by radical curative major surgery.

Methods and Analysis

This will be a prospective, randomised, controlled, parallel, single-centre superiority trial comparing a multimodal 'prehabilitation' intervention with 'standard care' in patients with oesophago-gastric malignancy who are treated with neoadjuvant therapy prior to surgical resection. The primary aim is to demonstrate an improvement in baseline cardiopulmonary function as assessed by anaerobic threshold during CPX testing in an interventional (Prehab) group following a 15-week preoperative exercise programme, throughout and following neoadjuvant treatment, when compared with those that undergo standard care (Control group). Secondary objectives include changes in Peak VO_2 and Work Rate (total watts achieved) at CPX testing, insulin resistance, quality of life, chemotherapy related toxicity and completions, nutritional assessment, postoperative complication rate, length of stay, and overall mortality.

Ethics and dissemination

This study has been approved by the London-Bromley Research Ethics Committee and registered on ClinicalTrials.gov. The results will be disseminated in a peer-reviewed journal. Trial registration number: NCT02950324.

'Article summary' Strengths of limitations

Strengths:

- To our knowledge, no studies assessing the feasibility of a supervised exercise programme during chemotherapy before surgery for oesophago-gastric cancer have been published.
- This is a prospective, parallel, randomised-controlled trial with patients randomised in a 1:1 manner and subjects analysed on an intention-to-treat basis.
- The exercise component of the prehabilitation programme is supervised by a Clinical Exercise Scientist who will construct a rigorous, tailored, individual, exercise programme for each patient based on their baseline functional capacity as assessed by cardiopulmonary exercise testing.
- CPX is established, noninvasive and safe and may be considered the 'gold standard' method of assessing patients' cardiopulmonary reserve prior to surgery. CPX outcome measures will be objectively measured by an experienced consultant anaesthetist, external to the trial study group.

Limitations:

- The unblinded, single-centre trial has a relatively small sample size is powered for AT and not clinical outcomes.

Introduction

As a result of the MAGIC [1] and OEO2 [2] trials, neoadjuvant therapy followed by surgery gives the best chance of cure for patients diagnosed with locally advanced oesophago-gastric cancer. It aims to increase the chance of curative resection by

eliminating micrometastases, downsizing the tumour and increasing the R0 resection rate [1, 3, 4]. The ongoing open label, phase III Neo-AEGIS trial [5], compares pre and postoperative chemotherapy and neoadjuvant chemoradiotherapy as per the MAGIC and CROSS [6] protocols respectively.

Adequate cardiopulmonary function is of great importance to patients undergoing oesophago-gastric cancer surgery (OGCS) such as Ivor Lewis oesophagectomy, as this major two stage, two field elective operation is associated with a large metabolic stress response and significant morbidity [7]. Reported side effects of chemotherapy are a reduction in functional capacity, which can be objectively measured using cardiopulmonary exercise testing (CPX). CPX is an established, noninvasive and safe method of assessing patients' cardiopulmonary reserve prior to surgery. Both anaerobic threshold (AT) and peak oxygen uptake (Peak VO_2) have consistently been associated with morbidity and functional outcomes in patients undergoing major elective surgery [8-11], with a reported average decrease in AT of 2 ml/kg/min in patients undergoing neoadjuvant chemotherapy (NAC) prior to oesophagectomy. Furthermore, this decrease in fitness has been associated with diminished one year survival in these patients [12].

The emerging concept of 'prehabilitation' is the process of enhancing an individual's functional capacity to enable them to withstand a stressful event such as major elective surgery. A key component of prehabilitation, physical exercise training, has led to improvements in AT [13, 14]. When initiated in the neoadjuvant setting, prehabilitation may have important implications as exercise training can stimulate skeletal muscle adaptations such as increased mitochondrial content and improve

oxygen uptake capacity [15]. Both West et al. [16] and Heldens et al. [17] have demonstrated than an exercise programme during neoadjuvant therapy for cancer is feasible, with minimal patient drop-out.

Another key component of prehabilitation is a psychological intervention which aims to reduce the pre and perioperative anxiety associated with neoadjuvant treatment and major surgery, as well as maintain adherence to a preoperative exercise prehabilitation programme [18].

In addition to cardiopulmonary function and anxiety, the physiological stress of surgery is associated with various metabolic derangements, central to which is the development of insulin resistance (IR). The degree of insulin resistance appears to be related to the magnitude of the 'surgical stress'. IR may be one of the key mechanisms triggering major inflammatory complications following surgery [19, 20].

Sarcopenia, the involuntary loss of muscle mass, is readily induced as a result of chemotherapy. Oesophago-gastric cancer patients with signs of sarcopenia have been shown to have high rates of treatment drop-out, higher postoperative complication rates, and reduced overall survival [21, 22].

To our knowledge there are no published studies assessing the feasibility of a supervised exercise programme during chemotherapy before surgery for oesophago-gastric cancer. The primary aim is to demonstrate an improvement in baseline cardiopulmonary function as assessed by anaerobic threshold during CPX testing in an interventional (Prehab) group following a 15 week preoperative exercise

programme, throughout and following neoadjuvant treatment, when compared with those that undergo standard care (Control group).

Methods and Analysis

Study setting

This study is a prospective, randomised, controlled, parallel, open single-centre superiority trial which will compare 'prehabilitation' with 'standard care' in patients with oesophago-gastric cancer who are treated with neoadjuvant chemotherapy or chemoradiotherapy (as part of the Neo-AEGIS trial) prior to surgical resection. The trial and treatment will be conducted at the Royal Surrey County Hospital (UK), a tertiary referral centre for oesophago-gastric malignancy.

Study objectives

In the intervention (Prehab) group, the primary objective is to demonstrate an improvement in baseline AT following a 15-week preoperative exercise programme which will take place throughout NAC and during the 6-week period of recovery prior to surgical resection. AT will be compared with those that undergo standard care (the control group).

Secondary objectives will include assessment of the protocol feasibility (as determined by subject drop-out, and both attendance, and adherence, to Prehab exercise sessions). Alternative measures of functional reserve will be evaluated, in particular change in Peak VO_2 and Work Rate (total watts achieved) during CPX testing. The effect of a Prehab programme on insulin resistance will be assessed by the HOMA2

calculation. Further secondary objectives include the effect of the Prehab programme on chemotherapy related toxicities, tolerance and completion rates, the impact of preoperative psychological coaching on validated quality of life scores (EORTC QLQ-C30, EORTC QLQ –OG25, Beck Anxiety Inventory (BAI)), and Beck Depression Inventory (BDI II)), and the effect of prehabilitation on nutritional status as assessed using hand grip strength and sarcopenia. Postoperative complications will be assessed using the Clavien-Dindo classification and as agreed per the Esophagectomy Complications Consensus Group [23]. Length of intensive care and hospital stay, 30 day, 90 day, 1 year and 5 year mortality will also be analysed.

Inclusion and exclusion criteria

Patients with T2 and / or N1 resectable oesophago-gastric carcinoma being considered for neoadjuvant therapy prior to oesophago-gastrectomy or extended total gastrectomy will be included. Patients will be excluded if they fulfill one or more of the following criteria: <18 years of age, a known contraindication to CPX testing (e.g. unstable cardiac disease), a physical inability to perform CPX testing or undertake a prehabilitation exercise programme (e.g. lower limb dysfunction), pregnancy (or those planning to become pregnant), or a lack of capacity to give informed consent.

Guidelines to cessation of participation in the study will include withdrawal of patient consent, serious adverse event, and non-compliance. Decision for patient-withdrawal will be made by the Chief Investigator in conjunction with the trial Sponsor. In the case of withdrawal, the patient will continue standard treatment within the dedicated oesophago-gastric and oncological departments.

Interventions

Following a dedicated oesophago-gastric staging pathway, including Anaesthetic and Cancer Multi-disciplinary Team (MDT) discussions, all patients whose proposed treatment includes neoadjuvant therapy and surgery will undergo a baseline CPX test as part of standard care. Here, eligibility will be assessed. At the next consultation (surgical or oncological outpatient clinic appointment), eligible patients will be approached by the chief investigator (CI) or clinical supervisor (CS) in order to confirm inclusion and exclusion criteria. Patients will at this stage be invited to participate in the study (Appendix 1. Patient information leaflet). If interested, one of the above research team members will explain the study to the patient and give them a copy of the patient information sheet to review. The patient will be given the opportunity to ask any questions they may have about the study and will be given at least 24 hours to consider participation. The research team will emphasise that non-participation will not adversely affect any aspects of their care. The patient will attend for pre-chemotherapy blood tests as part of their standard care pathway. At this time, the patient will be invited to give written consent to the trial. Patients will be informed that they are free to withdraw at any time without giving a reason and again that this will not adversely affect any aspects of their care. If the patient is willing to provide informed consent they will be asked to sign the patient consent form. Consent will be obtained by a suitably qualified person in accordance with international Good Clinical Practice (GCP) guidelines. The patient will be randomised to the intervention (Prehab) or Control group by the consenting clinician (see 'Methodology and Study Design' below).

Study group

1) **Prehab group**

Exercise intervention: Over a 15 week period, patients will attend the Human Performance Institute at Surrey Sports Park for twice weekly one hour exercise sessions (30 sessions in total) supervised directly by a Clinical Exercise Scientist with expertise in Cancer Care. A tailored exercise programme will be constructed based on the patients' baseline CPX test and calculated heart rate reserve. Supervised exercise will include a balance of aerobic and resistance training consisting of 20 minutes of cycling at an incremental increase from 40% heart rate reserve (HRR) to 60% HRR over the duration of the course, with 2x10 repetitions of 6 variable resistance exercises using a resistance band. Resistance exercises will be scored on a rating of perceived exertion scale, when the score drops below 12 for a given exercise, the intensity of resistance will be increased. Patients will also undergo a Home Exercise Plan (HEP) for one hour, three times a week. The HEP will focus on resistance and core stability exercises and will be monitored via a patient-maintained diary. Throughout the duration of the prehabilitation programme, all patients will be asked to wear a Fitbit Flex2® physical activity monitor on their non-dominant wrist as an objective measure of background activity. The Clinical Exercise Scientist will record weekly steps at their supervised exercise sessions. They will also monitor attendance to and exercise programme adherence at these sessions.

Psychological (Medical Coaching) intervention: In conjunction with The Fountain Centre (St Luke's Cancer Centre, Guildford, UK), patients will undergo 6 medical coaching sessions during their neoadjuvant treatment. The team consists of professional medical coaches with over 200 hours experience in coaching individuals with medical conditions. They are accredited with the international and UK coaching

bodies, International Coaching Federation (ICF) and National Council of Psychotherapists (NCP). Sessions will take the following form: Discussion of medical and health status; strengths recognition; resilience profiling and development; social and support systems; emotional management; and goal setting.

Nutritional support will be as per the standard pathway with regular telephone call and specialist oesophago-gastric dietetic consultations.

2) Control group

The control group will not receive a prehabilitation intervention but will be treated according to the standard OG care pathway. As part of usual care, all patients will be fully informed to improve fitness levels and to maintain a healthy lifestyle prior to surgery in order to obtain the best outcomes from high risk surgery. Patients will continue to be offered standard dietetic and CNS led psychological support as per the hospital's current cancer pathway and standard of care. Patients will be asked to wear a Fitbit Flex2® physical activity monitor throughout their preoperative treatment. As an objective measure of background activity, weekly steps will be recorded by a member of the study's delegation log.

Study outcomes

The primary outcome (change in AT) will be measured by an incremental symptom-limited CPX test performed by an experienced consultant anaesethetist. All patients will undergo CPX testing at baseline (before the start of neoadjuvant therapy), 2 weeks following completion of NAC, and one week prior to surgery.

Feasibility will be assessed by monitoring patient attendance at exercise and medical coaching sessions and adherence to the supervised exercise programme, as well as patient drop-out. Adherence to home exercise sessions will be monitored by a patient-reported diary and weekly steps recorded via a Fitbit Flex2® physical activity monitor.

Insulin resistance will be measured using the HOMA2 calculation. All patients will undergo fasting paired insulin and glucose tests at six stages along the protocol pathway: 1) Before NAC; 2) After cycle 1 of NAC; 3) After cycle 2 of NAC (or if having chemoradiotherapy, midway through chemoradiotherapy); 4) Following completion of cycle 3 (or at the end of chemoradiotherapy); 5) At re-staging laparoscopy; and 6) on the morning of surgical resection. In addition, HbA1c will be measured at baseline and on the day of oesophagectomy/total gastrectomy.

Completion of neoadjuvant therapy will be recorded in conjunction with the patient's consultant oncologist who will be a member of the trial Delegation Log. Toxicity will be monitored between cycles and after completion of chemotherapy and will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0: Mild (Grade 1), moderate (Grade 2), severe (Grade 3), or life-threatening (Grade 4), with specific parameters according to the organ system involved.

Quality of life (QoL) will be assessed at specific time points preoperatively (at the same time fasting blood tests, see above), and postoperatively at 2 weeks, 6 weeks and 6 months following hospital discharge. Validated questionnaires will include EORTC QLQ-C30, EORTC QLQ –OG25, Beck Anxiety Inventory (BAI)), and Beck Depression Inventory (BDI II).

Nutritional assessment will take the form of hand grip strength (HGS), mid-arm muscle circumference (MAMC), triceps skin-fold thickness (TSFT), and sarcopenia. HGS, MAMC and TSFT will be measured at the same time points that preoperative blood tests are taken, HGS will be measure twice daily on postoperative days 1-3 and once daily on days 4-7. HGS, MAMC and TSFT will be measured postoperatively at 2 weeks, 6 weeks and 6 months following hospital discharge. As part of standard care, patients undergo staging CT imaging at baseline and following neoadjuvant therapy. Sarcopenia will be measured using SliceOmatic^{TM} software at these two time points. At the L3 level, total skeletal muscle (SM), subcutaneous fat and visceral fat will be measured. Skeletal muscle index (SMI) will be calculated as follows: SM/height(m)^2. Measurements will be recorded by two individuals, one of whom will be external to the Trial Group.

Surgery will be performed in a standard manner by three experienced oesophago-gastric consultants. All patients will spend a period of time on intensive care post-operatively and will follow a dedicated oesophago-gastric Enhanced Recovery After Surgery (ERAS) pathway. Length of intensive care and hospital stay will be recorded as will postoperative complications will be measured using the Clavien-Dindo classification and as per the Esophagectomy Complications Consensus Group [23]. Mortality will be assessed at 30 days, 90 days and 1 year postoperatively. Figures 1 and 2 demonstrate the flow of patients (Figure 1. Consort diagram) and study schedule (Figure 2. Study diagram).

Figure 1. Consort diagram

Figure 2. Study diagram

Methodology and study design

This trial will be conducted in a single tertiary referral centre for oesophago-gastric cancer, with all patients treated and followed up at the Royal Surrey County Hospital, Guildford UK, in conjunction with St Lukes' Cancer Centre. Full disease staging, a dedicated oesophago-gastric cancer multi-disciplinary team meeting, and assessment of eligibility will take place prior to patients being approached by the CI or CS. Patients will be informed of the trial protocol via face to face discussion and a written Patient Information Leaflet. On inclusion and formal consent to the trial, patients will be randomised to receive the intervention (Prehab) or standard care Control). Randomisation will be carried out by a designated member of staff who is not directly involved in the study. In order to yield 1 : 1 groups, he or she will use computer generated variable block randomisation, with the group name ('prehab' or 'control') placed in sequentially numbered brown opaque envelopes. The envelopes will be kept in a locked drawer. On consent of a patient to the trial, the next envelope in sequence will be handed to the CI who will open the envelope in front of the patient. Due to the nature of the intervention, the research team and trial participants will not be blinded to the assigned arm of the trial. Outcome measures are described in detail above.

Statistical considerations

Estimation of sample size

It has been shown that AT improves following neoadjuvant chemotherapy as a result of a prehabilitation programme compared with standard care, with an AT difference of

2.12ml/kg/min between Prehab and Control groups [16].

To achieve a power of 80% and a significance level of 5% and to allow for confounding factors in a post-chemotherapy population, we calculate that 48 patients (24 per group) need to be studied in order to detect an AT difference of 2ml/kg/min between Prehab and Control group subjects. To allow for a 20% patient drop-out rate (due to non-compliance or side effects from chemotherapy), 29 patients will be required for each treatment group resulting in a total accrual of 58.

Statistical analysis

Data will be analysed on an intention to treat basis using SPSS software (v24). With the exception of interim analysis, a *p* value of <0.05 will be considered significant. Normality of data will be determined by using the Shapiro-Wilk test. Baseline characteristics for the two groups will be compared and demonstrated using mean [+/- standard deviation] or the median (with interquartile range) for continuous data. A mixed-measure analysis of variance (ANOVA) will be employed for the primary outcome of AT as this will be recorded at three times points (baseline, 2 weeks following neoadjuvant therapy, and 1 week prior to surgery). An unpaired Student's *t* test will compare AT and peak VO_2 peak between the intervention (prehab) and control groups. Secondary outcomes including length of hospital stay, grip strength, quality of life, Fitbit® data etc., will also be analysed using a Student's *t* test or Mann-Whitney U test. Survival data will be determined using the Kaplan-Meier curve. Interim analysis will be performed once primary outcome data is available for 26 subjects.

Patient and Public Involvement

The CI attended the Oesophageal Patient Association Support Group to engage and empower patients to help decide upon the programme from previous experiences. All members were fully engaged, enthusiastic. Patient experience helped shape the study design, in particular regarding the frequency of researcher and patient interaction, and number of scheduled exercise sessions.

At the time of consent, all patients will be asked whether they would like to receive a copy of the trial results. If they initial this box, they will be emailed or posted (as per the patient's preference) a copy of the completed manuscript.

Once the patient has completed the programme, the burden of the intervention will be assessed by patients themselves through the use of a questionnaire.

Discussion

Neoadjuvant therapy prior to oesophago-gastric resection is the gold standard of care for patients with T2 and/or nodal disease. Despite this, studies have taught us that chemotherapy decreases a patients' functional capacity. We aim to show that a multimodal prehabilitation programme will physically and psychologically optimise these patients, during and after neoadjuvant therapy, prior to major elective OG cancer surgery so they may better withstand the immense physical and metabolic stress placed upon them by radical surgery.

Ethics and Dissemination

Approval

In accordance with the Declaration of Helsinki, the trial was presented to an independent Research Ethics Committee, the London-Bromley Research Ethics Committee. Authorisation was obtained from the NHS Health Research Authority on 16th November 2016. Any substantial amendment to the protocol or consent form will be presented to the local Research and Development team and independent Research Ethics Committee. Likewise, all serious adverse events (AE) will be reported to the local Research and Development team as well as the independent Research Ethics Committee. The study is registered on the Clinical Trials website, ClinicalTrials.gov, under the number NCT02950324. The study is sponsored by The Royal Surrey County Hospital NHS Foundation Trust and funded by Macmillan Cancer Support. The sponsorship from Macmillan Cancer Support will fund the following: Exercise sessions at Surrey Sports Park, psychological support in the form of Medical Coaching, fasting blood tests, and the Fitbit Flex2® physical activity monitors.

Patient informed consent

As per international principles, written informed consent (Appendix 2. Consent form) will be obtained from patients prior to their participation in the trial once they voluntarily confirm their understanding and willingness to participate in the trial at least 24 hours after verbal and written information has been provided and questions answered. Consent will be obtained by a suitably qualified person in accordance with international Good Clinical Practice (GCP) guidelines. Patients will be informed that they are free to withdraw from the trial at any time without giving a reason and they will be informed that this will not adversely affect any aspects of their care.

Data collection and quality management

All data will be collected, handled and stored securely in the Trial Site File only by experienced persons who have been suitably trained in Good Clinical Practice and who are a member of the trial Delegation Log. At the time of patient contact, data will be acquired using a paper case report form (CRF). All study data will be anonymised by using a using a unique study number assigned to each subject sequentially. CRFs will be stored in a locked cabinet within a locked drawer of the secure (card-access only) Research Department. Collated data will be maintained on a pre-defined confidentially stored and password protected electronic spreadsheet with access granted only to the CI, CS and Sponsor. Data will be kept for five years following recruitment of the final patient. The trial does not warrant a Data Monitoring Committee due to its short interventional duration and minimal associated risks, however trial data will be regularly monitored and audited at regular intervals by the Sponsor and local R&D department in accordance with the University of Surrey Research Department, and Good Clinical Practice policies.

Access to data and dissemination of results

The Chief Investigator and Clinical Supervisor will have full access to the completed data set, as will the trial's Sponsor. Final data will be summarised on ClinicalTrials.gov, published in a peer-reviewed journal, and presented at international conferences.

Trial status

The trial protocol (v1.2 14/10/2016) was presented to an independent Research Ethics Committee, the London-Bromley Research Ethics Committee. Authorisation was

obtained from the NHS Health Research Authority on 16th November 2016. Recruitment started on 15/12/16. To date, 43 patients have been recruited. Six patients have been lost to follow-up. Interim analysis will be performed once primary outcome data (change anaerobic threshold) is available for 26 subjects (13 per group). Recruitment will be completed by 1/6/18.

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Authors statement

Sophie Allen, Vanessa Brown, Michael Scott, Pradeep Prabhu, Timothy Rockall, Shaun Preston and Javed Sultan have all: Made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; Have been involved in drafting the manuscript or revising it critically for important intellectual content; Have given final approval of the version to be published and has participated sufficiently in the work to take public responsibility for appropriate portions of the content and have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The trial management committee (SA and JS) will be responsible for the following: Organisation of steering committee meetings; the trial site file; randomisation (performed by a person external to the trial); budget administration and liasing with the funding source and Sponsor; reporting of adverse events; completion of CRFs; identification and recruitment of patients; adherence to the study protocol; and publication of study results. The steering committee (SA/VB/PP/SP/TR/JS) were in agreement of the final protocol and will review the progress of the study, liasing with the CI to ensure the study runs smoothly.

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The funding body are responsible for funding participant participation at Surrey Sports Park, all Medical Coaching sessions, the use of Fitbit® physical activity monitors, the cost of fasting glucose and insulin blood tests, and the CPX test. This funding source had no role in the design of this study and will not be involved in analysis of the results, interpretation of data, or decision to submit results.

BMJ Group declaration of interests statement

I have read and understood the BMJ Group Policy on declaration of interests and declare the following interests: None

Name: Sophie K Allen Date: 2/3/18

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List of figures

Appendix

List of abbreviations

AE – Adverse event

AT – Anaerobic threshold

CI – Chief investigator

CNS – Clinical nurse specialist

CS – Clinical Supervisor

CPX test – Cardiopulmonary Exercise Test

CRF – Case report form

GCP – Good Clinical Practice

HEP – Home exercise plan

HOMA2 – Homeostasis model assessment

HRR – Heart rate reserve

ICF - International Coaching Federation

IR – Insulin Resistance

MDT - Multi-disciplinary Team

NAC – Neo-adjuvant chemotherapy

NCP - National Council of Psychotherapists

OGCS – Oesophago-gastric cancer surgery

POMS – Post-operative morbidity score

Prehab – Prehabilitation

RSCH – Royal Surrey County Hospital

VO_2 peak – Peak oxygen uptake

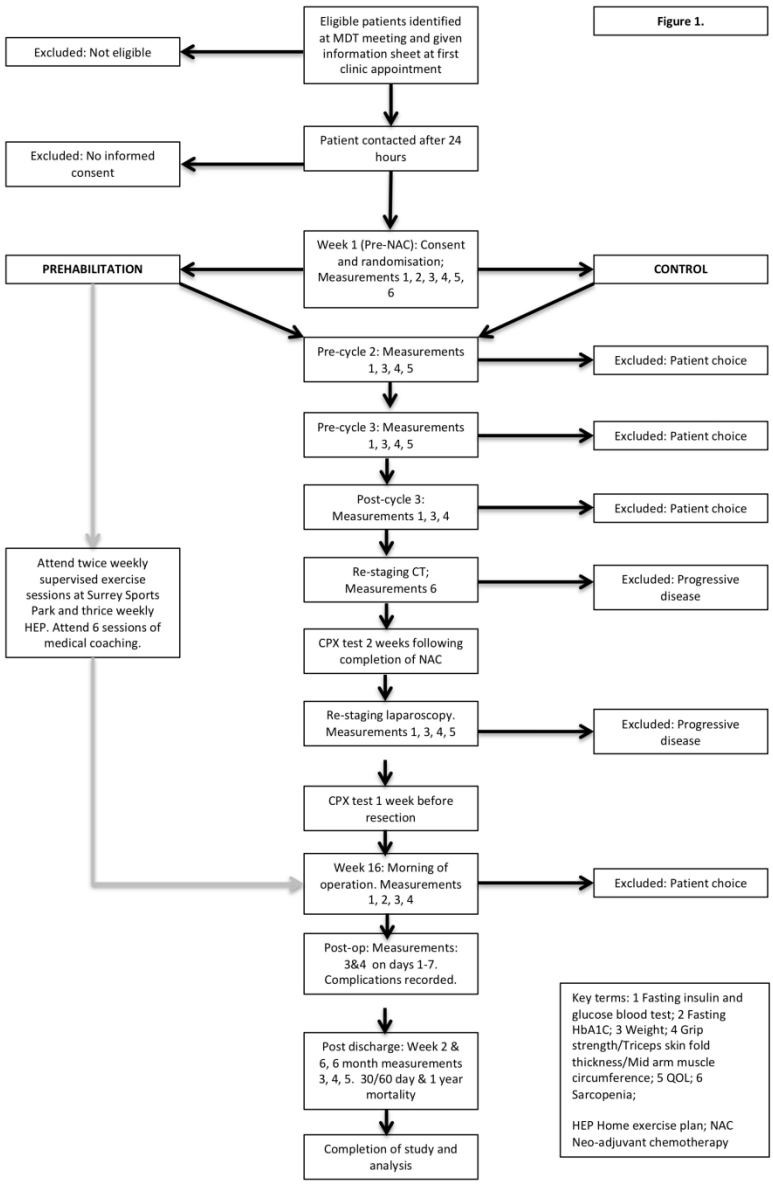

Figure 1. Consort diagram

190x254mm (300 x 300 DPI)

Timepoint	Enrolment and Allocation							Surgery	Follow up						
	Week 1	Week 4	Week 7	Week 10	Week 12	Week 13	Week 15	Week 16	Days 1-7 post-op	2 weeks post discharge	6 weeks post discharge	6 months post discharge	1 year post discharge	Close-out (1 year post discharge)
Enrolment:														
Eligibility screen	X													
Informed consent	X													
Randomisation and allocation	X													
Interventions:														
Prehab	X	X	X	X	X	X	X							
Control	X	X	X	X	X	X	X							
Assessments:														
CPX (AT and peak VO2)	X				X		X							
Sarcopenia assessment	X			X		X								
Weight	X	X	X			X		X	X	X	X	X		
Fasting HbA1c	X							X						
Fasting insulin and glucose	X	X	X	X		X		X						
Grip strength	X	X	X	X		X		X	X	X	X	X		
TSFT	X	X	X	X		X		X	X	X	X	X		
MAMC	X	X	X	X		X		X	X	X	X	X		
QOL	X	X	X			X		X	X	X	X	X	X	
Complications									X	X	X	X	X	
Mortality														X
Analysis														

Figure 2. Study diagram

- TSFT: Triceps skin fold thickness; MAMC: Mid arm muscle circumference

Figure 2. Study diagram

209x296mm (300 x 300 DPI)

(Chemotherapy)

Royal Surrey County Hospital NHS
NHS Foundation Trust

Patient information leaflet

Does prehabilitation improve cardiopulmonary exercise performance and reduce insulin resistance in patients undergoing neoadjuvant treatment and surgery for oesophagogastric cancer

Mr Javed Sultan, Consultant Surgeon
Professor Timothy Rockall, Professor of Surgery
Dr Julie Hunt, Lecturer in Sport and Exercise Sciences
Professor Mike Scott, Consultant Anaesthetist
Miss Sophie Allen, Research Fellow, Principal Investigator

"Does exercise improve exercise test results and recovery after surgery in people with oesophagogastric cancer?"

Invitation to participate

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. This information sheet is designed to help you decide whether you would like to participate in this study. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

What is the purpose of the study?

Recent studies have shown that regular supervised exercise (prehabilitation) can improve patients' fitness prior to surgery, improve the way their body handles sugar and improve their recovery after surgery. Cardiopulmonary exercise (CPX) testing measures the function of your heart and lungs in response to exercise (see separate information leaflet 'Your Cardio Pulmonary Exercise test'). Studies have shown that the better your CPX result, the less likely you are to have complications after a big operation.

The aim of this study is to see if regular supervised exercise (prehabilitation) improves performance in CPX and recovery after surgery. The study will last up to approximately 22 weeks in total.

(Chemotherapy)

Why have I been chosen?
You have been invited to take part in the study because you have a diagnosis of oesophago-gastric cancer, are having chemotherapy prior to surgery, and fit the required criteria. Approximately 50 people will be observed and tested in this study.

Do I have to take part?
It is up to you to decide whether or not to take part. If you do decide to take part you will be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?
The study will last up to approximately 22 weeks. You will be given this information sheet to read and take away today. When you attend for your blood tests before your oncology appointment we will answer any questions you have and ask you if you would like to take part in the study.

If you agree to take part in the study we will check your weight, height, grip strength, arm circumference and skin thickness. You will be issued with a Fitbit physical activity monitor. This small device is worn on your wrist and records your physical activity. We will demonstrate how to use the device and provide written instructions. After this visit we will ask you to wear the Fitbit on your wrist continuously during chemotherapy and in the lead up to your operation.

All patients will be referred to a dietician for dietary advice.

What happens next?
The study involves being randomly entered into one of two study groups. The groups will be randomly selected by computer (a bit like tossing a coin), so you cannot choose which group you are in. You will not know which group you are in before consenting to take part in the study.

You will have a one in two chance of being randomised into either the standard care group or intervention.

(Chemotherapy)

All participants in the trial will be asked to complete the following assessments in addition to their usual treatment pathway-

- Week 1 (When you have blood tests before your oncology appointment)
  - Alongside your usual blood tests, we will perform 3 additional blood tests using an extra 10mls of blood. We will ask you to fast (not eat any food after midnight the night before but you may drink water).
  - You will be issued with a Fitbit physical activity monitor.
  - We will measure your weight, height, grip strength, arm circumference and skin thickness.
  - We will ask you to fill out a short questionnaire about your wellbeing.

- Week 5 (At the end of your first cycle of chemotherapy)
  - Please fast before your usual blood tests. Alongside your usual blood tests, we will perform 2 additional blood tests using an extra 10mls of blood.

- Week 8 (At the end of your second cycle of chemotherapy)
  - Please fast before your usual blood tests. Alongside your usual blood tests, we will perform 2 additional blood tests using an extra 10mls of blood.
  - We will check your weight, grip strength, arm circumference and skin thickness.
  - We will ask you to fill out a short questionnaire about your wellbeing.

- Week 11 (At the end of your third cycle of chemotherapy)
  - Please fast before your usual blood tests. Alongside your usual blood tests, we will perform 2 additional blood tests using an extra 10mls of blood.
  - We will ask you to perform a routine standard second CPX test. You may eat before this, once you have had your blood test.
  - We will check your weight, grip strength, arm circumference and skin thickness.
  - We will ask you to fill out a short questionnaire about your wellbeing.

- Approximately Week 13 (at the time of your repeat staging laparoscopy)
  - Please fast before your usual blood tests. Alongside your usual blood tests, we will perform 2 additional blood tests using an extra 10mls of blood.
  - We will check your weight, grip strength, arm circumference and skin thickness.
  - We will ask you to fill out a short questionnaire about your wellbeing.
  - **We will ask you to perform a third extra CPX test approximately one week before your operation.** You may eat before this, once you have had your blood test.

(Chemotherapy)

- Week 18 (The morning of your operation)
    - We will perform 3 extra blood tests using an extra 10mls of blood.
    - We will check your weight, grip strength, arm circumference and skin thickness.
    - At the time of the operation we may take a sample of the tumour which will be saved for later analysis.

After the surgery your skin fold thickness and arm circumference will be measured days 1, 3 and 7 post-surgery. Your grip strength will be measured twice a day for the first 3 days then once a day for a further 4 days. We will monitor your routine blood tests on days 1, 3 and 7 after your operation. You will also be weighed on days 1, 3 and 7. To help assess your nutritional status, the CT scans that you will have had as part of your usual care will be used to assess your muscle density.

After you are discharged you will be asked to fill in a short questionnaire about your wellbeing at 2 weeks, 6 weeks, and 6 months after surgery. We will also test your grip strength, skin thickness, and arm circumference. Other information from your medical notes will be captured approximately 90 days and one year after your operation.

(Chemotherapy)

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Week 1

Blood tests before first oncology appointment– at your appointment we will ask you if you would like to take part in the trial. If you agree, the following will occur:

- Written consent obtained
- Please **fast (do not eat any food after midnight the night before your blood test but you may drink water)** before your usual blood tests. Alongside your usual blood tests we will perform 3 additional blood tests using an extra 10mls of blood
- We will check your height, weight, grip strength, arm circumference and skin thickness and ask you to fill out a short questionnaire about your wellbeing
- We will issue you with your FitBit physical activity monitor

Week 5

End of first cycle chemotherapy

- **Please fast before your usual blood tests**. Alongside your usual blood tests we will perform 2 additional blood tests using 10mls of extra blood

Week 8

End of second cycle chemotherapy

- **Please fast before your usual blood tests**. Alongside your usual blood tests we will perform 2 additional blood tests using 10mls of extra blood
- We will check your weight, grip strength, arm circumference and skin thickness and ask you to fill out a short questionnaire about your wellbeing

Week 11

End of third cycle chemotherapy

- **We will ask you to perform a second (extra) CPX test**
- **Please fast before your usual blood tests**. Alongside your usual blood tests we will perform 2 additional blood tests using 10mls of extra blood
- We will check your weight, grip strength, arm circumference and skin thickness and ask you to fill out a short questionnaire about your wellbeing

2nd CPX

Week 13-14

At the time of your repeat laparoscopy

- We will ask you to perform a routine standard third CPX test
- **Please fast before your usual blood tests.** Alongside your usual blood tests we will
- perform 2 extra blood tests using 10mls of extra blood
- We will check your weight, grip strength, arm circumference and skin thickness.
- We will ask you to fill out a short questionnaire about your wellbeing

3rd CPX

Operation

- We will perform 3 extra blood tests using 10mls of blood
- We will check your grip strength
- At the time of the operation we may take a sample of the tumour which will be saved for later analysis

Op Date

(Chemotherapy)

Royal Surrey County Hospital NHS
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INTERVENTION ARM ONLY

Personal Trainer Week 2-17

We will invite you to the Surrey Sports Park where you will meet with a Personal Trainer

- Attend twice weekly Personal Training sessions for 15 weeks
- Home exercise plan to complete for one hour, three times a week
- Fill out a food and exercise diary

Initial assessment

Medical Coaching sessions

Six sessions in total which will be arranged to coincide with your existing appointments

- Session 2 / 3 will be during chemotherapy
- Sessions 4 / 5 will be after chemotherapy
- The final session will be a week before surgery

Initial assessment	Session 2	Session 3
Session 4	Session 5	Final session

(Chemotherapy)

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Group 1 is called the **Standard Care group.** If you are in this group we will perform one extra exercise test to monitor your fitness, monitor your physical activity via the Fitbit, and perform the extra tests mentioned above (eg blood tests, measurement of your grip strength, arm circumference, and skin thickness, and also short questionnaires about your wellbeing). This is in addition to your usual care. Psychological support at The Fountain Centre will be available.

Group 2 is the **Intervention Group.** If you are in this group we will perform one extra exercise test to monitor your fitness, monitor your physical activity via the Fitbit, and perform the above extra interventions in addition to your usual care.
We will also invite you to the Surrey Sports Park where you will meet with a Personal Trainer. They will design a 15 week fitness programme and you will be asked to attend twice weekly Personal Training sessions for 15 weeks. You will be given a home exercise plan to complete for one hour, three times a week. Some participants in this group may not be able to complete the exercise program and if this is the case, you should not feel that you have failed, and your treatment will not be affected. If you are in this group you may also find it possible to do exercise one week and not another. Your personal trainer will be aware of this and you should discuss this with them. In addition to the exercise sessions, you will be asked to fill out a food diary.

Please see page 4-5 for a detailed flow chart of what will happen to you during the study. You will be supported along the way by the research team and your specialist nurse.

You will not be expected to need to visit the GP more often during the study.

Will I be given any emotional and psychological support?
Being diagnosed with cancer can be both stressful and emotional. Emotions and needs experienced by people with cancer are diverse and individual. The Fountain Centre is a drop-in centre within St Luke's Cancer Centre at the Royal Surrey County Hospital that offers support and one-to-one counselling to patients who are under the care of a Royal Surrey County Hospital consultant. The counsellors work confidentially with patients over a short or long term period to establish a non-judgmental working relationship to support the patient and enhance their wellbeing. **All** patients participating in this study are strongly advised to seek support offered by The Fountain Centre.

The intervention group will be asked to attend medical coaching sessions at The Fountain Centre. There will be six sessions in total, which will be arranged to coincide with your existing appointments. You will have an initial assessment, two

sessions during treatment, two sessions after treatment, and a final session the week prior to surgery.

What are my responsibilities? (all patients)

- Wear the Fitbit on your wrist continuously.
- Attend for one extra exercise test (CPX).
- Fast (we will ask you to not eat any food after midnight the night before your blood test but you may drink water) before your usual blood tests. We will try to get an appointment as early in the morning as possible in order to limit the time you have to fast.
- Have an additional 10mls of blood taken when you have your usual blood tests and one extra blood test on the day of the operation.
- Fill out a short questionnaire about your wellbeing when requested.

- If you are in the **intervention group**:
    - Attend the Surrey Sports Park twice a week for 15 weeks
    - Attend medical coaching six times

You can drive and take part in sport as normal. You should continue to take your regular medication unless we specifically advise you otherwise.
You should not donate blood in the study period as this may change the results of your exercise test.

What is the drug or procedure that is being tested?
We are testing whether regular supervised exercise (prehabilitation) during chemotherapy can improve patients' fitness before surgery.

What are the side effects of any treatment received when taking part?
Regular supervised exercise can cause muscle strain but should not cause any serious problems. If you become concerned you can contact one of us via the contact details given at the end of this document. In the event of an emergency please call 999 or go to your local A+E.

What are the possible disadvantages and risks of taking part?
You will need to attend the hospital for one extra exercise test (CPX) and an extra blood test on the morning of your operation that you wouldn't usually have. Before your routine blood tests we will ask you to fast (not eat any food after midnight). You may drink water. In addition to your routine standard bloods we will take 10mls of extra blood, some of which will be frozen and stored for future research.

If you are in the intervention arm you will need to attend the Surrey Sports Park regularly for an exercise programme. This is inconvenient but may help reduce complications from surgery and potentially improve your recovery after major surgery. If we find a condition of which you were unaware this will allow us to refer you to the appropriate specialist for further treatment.

CPX - As with all medical tests there is the chance of unwanted side effects or complications. The risk of these with CPX are the same as for moderate exercise. The number of patients that develop problems during the test is low (1 in 1000). The complications that may occur during the test include abnormal blood pressure, fainting, irregular, fast or slow heart rhythms. In exceptionally rare instances there can be serious complications such as a heart attack or stroke. Please see the see separate information leaflet 'Your Cardio Pulmonary Exercise test' for more details.

What are the possible benefits of taking part?
We hope that this study will go on to produce further studies which may in time show a definite relationship between prehabilitation and faster recovery after surgery.

For the duration of the study you will be loaned a Fitbit which will track your levels of activity.

A CPX test stresses your heart and lungs in a systematic controlled fashion. If the test shows you are very unfit it will allow us to refer you to the appropriate specialist for further treatment of the medical condition, or it may allow us to offer you alternatives that you are more able to tolerate.

What if new information becomes available?
Sometimes during the course of a research project, new information becomes available about the treatment/drug that is being studied. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw, your research doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.
Also, on receiving new information your research doctor might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your care to continue.

What happens when the research study stops?
When you are admitted for surgery you will return the Fitbit. After the research stops you will be followed up in the usual manner.

(Chemotherapy)

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What if something goes wrong?
It is unlikely that you will come to any harm during this study. However, if you do come to harm there are no special compensation arrangements.
If you wish to complain or have any concerns about your treatment by members of the team or about the research itself the Patient Advice and Liaison Service (PALS) are available to provide independent help, advice and support. They can be found at the far left corner as you enter the main reception area. They can also be contacted by:

Telephone: 01483 402757
Email: rsc-tr.pals@nhs.net
In person: opening hours 9am-4pm Monday to Friday

Who has reviewed the study?
This study has been reviewed and received a favourable opinion by London-Bromley Research Ethics Committee.

Will my taking part in this study be kept confidential?
All information which is collected about you during the course of the research will be kept strictly confidential. Data will be stored in accordance with the data protection act 1998. Data will be stored on a password protected computer or encrypted USB storage device which will be securely retained in a locked office in a separate building which requires swipe card access. Data will only be accessed by members of the direct care team and will be anonymised by assigning a unique study number. Any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised from it. Data will be kept for five years once the trial has finished. Your own GP will be notified of your participation in the trial.

What will happen to the results of the research study?
The results of the research may be published in a medical journal, but you will not be identified by name in any publications. Once the study has been completed and analysed we can send you a summary of the results if you would like. Please let us know by indicating this on the consent form.

Who is organising the research?
This study is being organised and coordinated by the Royal Surrey County Hospital Guildford. Your doctors will not be paid for including you in this study.

(Chemotherapy)

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Will I get travel expenses?
Parking charges and travelling expenses incurred in addition to your routine care can be reimbursed on production of receipts at the cashier's office.

Contact for Further Information
If you have any questions concerning the study please do not hesitate to contact us:

Miss Sophie Allen, MBBCh, BSc, MRCS
Research Fellow
Department of Surgery
Royal Surrey County Hospital
Egerton Rd
Guildford
GU27XX

Telephone: 01483 571 122 extension 6374
Email: lizzie.elam@nhs.net or amcguire@nhs.net

Thank you for taking the time to read this information leaflet

When you attend for your blood tests before your oncology appointment you will be approached by the research team to ask if you wish to take part in the study. You will have the opportunity to raise any concerns or questions and if you decide to take part in the study, you will be asked to sign a written consent form.

You will be given a copy of the information sheet and a signed consent form to keep

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Study Number: REC 16/LO/1702 R+D 16SURN213028 IRAS ID: 213028 ***Patient copy***

Patient Identification Number for this trial:

CONSENT FORM

Title of Project: Does prehabilitation improve cardiopulmonary exercise performance and reduce insulin resistance in patients undergoing neoadjuvant treatment and surgery for oesophagogastric cancer?

	Please initial boxes
1. I confirm that I have read and understand the information sheet (Version 3.1 Date 13/10/2017) for the above study and have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	
3. I understand that the relevant sections of any of my medical notes and data collected may be looked at by responsible individuals or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my relevant records.	
4. I am aware of the need for psychological support whilst taking part in this study and it has been explained to me how I can obtain this support.	
5. I agree to take part in the above study and to my General Practitioner being informed of my participation I the study	
6. I agree that my biological materials (blood and tumour samples) collected, and CT scans performed during the study as part of the standard of care, but not related to study procedures etc, may be saved and used for later analysis	
7. Once the study has been completed and analysed I would like to be sent you a summary of the results.	

_____	_____	_____
Name of Patient	**Signature**	**Date**
_____	_____	_____
Name of Person taking consent (if different from researcher)	Signature	Date
_____	_____	_____
Researcher	Signature	Date

Study Number: REC16/LO/1702 R+D 16SURN213028 IRAS ID: 213028 ***Researcher copy***

Patient Identification Number for this trial:

CONSENT FORM

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_____	_____	_____
Name of Patient	**Signature**	**Date**
_____	_____	_____
Name of Person taking consent (if different from researcher)	Signature	Date
_____	_____	_____
Researcher	Signature	Date

Royal Surrey County Hospital NHS
NHS Foundation Trust

Study Number: REC 16/LO/1702 R+D 16SURN213028 IRAS ID: 213028 ***Notes copy***

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6. I agree that my biological materials (blood and tumour samples) collected, and CT scans performed during the study as part of the standard of care, but not related to study procedures etc, may be saved and used for later analysis	
7. Once the study has been completed and analysed I would like to be sent you a summary of the results	

_____	_____	_____
Name of Patient	**Signature**	**Date**
_____	_____	_____
Name of Person taking consent (if different from researcher)	Signature	Date
_____	_____	_____
Researcher	Signature	Date

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1, 2
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1, 4-13, 16-18, 22, 23
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	22, 23
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 2, 23

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	24
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	22, 23
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	22
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4, 5, 6, 7
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4, 5, 6, 7
Objectives	#7	Specific objectives or hypotheses	7, 8
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	14
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	14
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	8

		individuals who will perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10, 11, 12, 13
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	8
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	11, 12, 13
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11, 12, 13
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	13 (Figure 2)
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14, 15
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	14, 15, 16
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any	

		factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	14
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	14
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	14
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10, 11, 12, 13
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10,11
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values).	18

		Reference to where details of data management procedures can be found, if not in the protocol	
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	8, 17
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	8
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	18
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	17
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	17

Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	17
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	18
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	22, 23
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	22
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	24
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in	n/a

the current trial and for future use in ancillary studies, if applicable

BMJ Open

A randomised controlled trial to assess whether prehabilitation improves fitness in patients undergoing neoadjuvant treatment prior to oesophago-gastric cancer surgery: Protocol

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Secondary Subject Heading:	Sports and exercise medicine
Keywords:	Prehabilitation, Oesophageal, Cancer, Neoadjuvant, Cardiopulmonary Exercise Test

A randomised controlled trial to assess whether prehabilitation improves fitness in patients undergoing neoadjuvant treatment prior to oesophago-gastric cancer surgery: Protocol

Trial registration number: NCT02950324 1/11/16

V2.1 10/07/2018

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Word count 4142

Abstract

Introduction

Neoadjuvant therapy prior to oesophago-gastric resection is the gold standard of care for patients with T2 and/or nodal disease. Despite this, studies have taught us that chemotherapy decreases patients' functional capacity as assessed by cardiopulmonary exercise (CPX) testing. We aim to show that a multimodal prehabilitation programme comprising of supervised exercise, psychological coaching

and nutritional support, will physically, psychologically and metabolically optimise these patients prior to oesophago-gastric cancer surgery so they may better withstand the immense physical and metabolic stress placed upon them by radical curative major surgery.

Methods and Analysis

This will be a prospective, randomised, controlled, parallel, single-centre superiority trial comparing a multimodal 'prehabilitation' intervention with 'standard care' in patients with oesophago-gastric malignancy who are treated with neoadjuvant therapy prior to surgical resection. The primary aim is to demonstrate an improvement in baseline cardiopulmonary function as assessed by anaerobic threshold during CPX testing in an interventional (Prehab) group following a 15-week preoperative exercise programme, throughout and following neoadjuvant treatment, when compared with those that undergo standard care (Control group). Secondary objectives include changes in Peak VO_2 and Work Rate (total watts achieved) at CPX testing, insulin resistance, quality of life, chemotherapy related toxicity and completions, nutritional assessment, postoperative complication rate, length of stay, and overall mortality.

Ethics and dissemination

This study has been approved by the London-Bromley Research Ethics Committee and registered on ClinicalTrials.gov. The results will be disseminated in a peer-reviewed journal. Trial registration number: NCT02950324.

'Article summary' Strengths of limitations

Strengths:

- To our knowledge, no studies assessing the feasibility of a supervised exercise programme during chemotherapy before surgery for oesophago-gastric cancer have been published.
- This is a prospective, parallel, randomised-controlled trial with patients randomised in a 1:1 manner and subjects analysed on an intention-to-treat basis.
- The exercise component of the prehabilitation programme is supervised by a Clinical Exercise Scientist who will construct a rigorous, tailored, individual, exercise programme for each patient based on their baseline functional capacity as assessed by cardiopulmonary exercise testing.
- CPX is established, noninvasive and safe and may be considered the 'gold standard' method of assessing patients' cardiopulmonary reserve prior to surgery. CPX outcome measures will be objectively measured by an experienced consultant anaesthetist, external to the trial study group.

Limitations:

- The unblinded, single-centre trial has a relatively small sample size is powered for AT and not clinical outcomes.

Introduction

As a result of the MAGIC [1] and OEO2 [2] trials, neoadjuvant therapy followed by surgery gives the best chance of cure for patients diagnosed with locally advanced oesophago-gastric cancer. It aims to increase the chance of curative resection by

eliminating micrometastases, downsizing the tumour and increasing the R0 resection rate [1, 3, 4]. The ongoing open label, phase III Neo-AEGIS trial [5], compares pre and postoperative chemotherapy and neoadjuvant chemoradiotherapy as per the MAGIC and CROSS [6] protocols respectively.

Adequate cardiopulmonary function is of great importance to patients undergoing oesophago-gastric cancer surgery (OGCS) such as Ivor Lewis oesophagectomy, as this major two stage, two field elective operation is associated with a large metabolic stress response and significant morbidity [7]. Reported side effects of chemotherapy are a reduction in functional capacity, which can be objectively measured using cardiopulmonary exercise testing (CPX). CPX is an established, noninvasive and safe method of assessing patients' cardiopulmonary reserve prior to surgery. Both anaerobic threshold (AT) and peak oxygen uptake (Peak VO_2) have consistently been associated with morbidity and functional outcomes in patients undergoing major elective surgery [8-11], with a reported average decrease in AT of 2 ml/kg/min in patients undergoing neoadjuvant chemotherapy (NAC) prior to oesophagectomy. Furthermore, this decrease in fitness has been associated with diminished one year survival in these patients [12].

The emerging concept of 'prehabilitation' is the process of enhancing an individual's functional capacity to enable them to withstand a stressful event such as major elective surgery. A key component of prehabilitation, physical exercise training, has led to improvements in AT [13, 14]. When initiated in the neoadjuvant setting, prehabilitation may have important implications as exercise training can stimulate skeletal muscle adaptations such as increased mitochondrial content and improve

oxygen uptake capacity [15]. Both West et al. [16] and Heldens et al. [17] have demonstrated than an exercise programme during neoadjuvant therapy for cancer is feasible, with minimal patient drop-out.

Another key component of prehabilitation is a psychological intervention, 'Medical Coaching'. Anxiety and depression are commonplace in patients receiving cancer treatment and depression and may be associated with reduced treatment compliance [18]. Psychological support aims to reduce anxiety and depression prior to surgery [19, 20]. It has been suggested that improvement in exercise capacity during the preoperative period may a result of the belief of patients that fitness levels aid recovery [21]. Using Bandura's Social Cognitive Theory, it is proposed that psychological coaching can lead to an increase in self-belief to carry out a particular task and that it will empower patients to proactively take control of their behaviour preoperatively, leading to improved engagement with the exercise aspect of the intervention [22].

In addition to cardiopulmonary function and anxiety, the physiological stress of surgery is associated with various metabolic derangements, central to which is the development of insulin resistance (IR). The degree of insulin resistance appears to be related to the magnitude of the 'surgical stress'. IR may be one of the key mechanisms triggering major inflammatory complications following surgery [23, 24].

Sarcopenia, the involuntary loss of muscle mass, is readily induced as a result of chemotherapy. Oesophago-gastric cancer patients with signs of sarcopenia have been shown to have high rates of treatment drop-out, higher postoperative complication rates, and reduced overall survival [25, 26].

To our knowledge there are no published studies assessing the feasibility of a supervised exercise programme during chemotherapy before surgery for oesophago-gastric cancer. The primary aim is to demonstrate an improvement in baseline cardiopulmonary function as assessed by anaerobic threshold during CPX testing in an interventional (Prehab) group following a 15 week preoperative exercise programme, throughout and following neoadjuvant treatment, when compared with those that undergo standard care (Control group).

Methods and Analysis

Study setting

This study is a prospective, randomised, controlled, parallel, open single-centre superiority trial which will compare 'prehabilitation' with 'standard care' in patients with oesophago-gastric cancer who are treated with neoadjuvant chemotherapy or chemoradiotherapy (as part of the Neo-AEGIS trial) prior to surgical resection. The trial and treatment will be conducted at the Royal Surrey County Hospital (UK), a tertiary referral centre for oesophago-gastric malignancy.

The research team attended the Oesophageal Patient Association Support Group where they were able to learn and understand about patient's previous experiences of cancer treatment. Patients' experiences and views were taken into account when writing the study protocol to include the content of the prehab programme and mode of intervention delivery. The team were able to engage and empower the patient to contribute to the construction of a patient-centered trial.

Study objectives

In the intervention (Prehab) group, the primary objective is to demonstrate an improvement in baseline AT following a 15-week preoperative exercise programme which will take place throughout NAC and during the 6-week period of recovery prior to surgical resection. AT will be compared with those that undergo standard care (the control group).

Secondary objectives will include assessment of the protocol feasibility (as determined by subject drop-out, and both attendance, and adherence, to Prehab exercise sessions). Alternative measures of functional reserve will be evaluated, in particular change in Peak VO_2 and Work Rate (total watts achieved) during CPX testing. The effect of a Prehab programme on insulin resistance will be assessed by the HOMA2 calculation. Further secondary objectives include the effect of the Prehab programme on chemotherapy related toxicities, tolerance and completion rates, the impact of preoperative psychological coaching on validated quality of life scores (EORTC QLQ-C30, EORTC QLQ –OG25, Beck Anxiety Inventory (BAI)), and Beck Depression Inventory (BDI II)), and the effect of prehabilitation on nutritional status as assessed using hand grip strength and sarcopenia. Postoperative complications will be assessed using the Clavien-Dindo classification and as agreed per the Esophagectomy Complications Consensus Group [27]. Length of intensive care and hospital stay, 30 day, 90 day, 1 year and 5 year mortality will also be analysed.

Inclusion and exclusion criteria

Patients with T2 and / or N1 resectable oesophago-gastric carcinoma being considered for neoadjuvant therapy prior to oesophago-gastrectomy or extended total gastrectomy will be included. Patients will be excluded if they fulfill one or more of the following criteria: <18 years of age, a known contraindication to CPX testing (e.g. unstable cardiac disease), a physical inability to perform CPX testing or undertake a prehabilitation exercise programme (e.g. lower limb dysfunction), pregnancy (or those planning to become pregnant), or a lack of capacity to give informed consent.

Guidelines to cessation of participation in the study will include withdrawal of patient consent, serious adverse event, and non-compliance. Decision for patient-withdrawal will be made by the Chief Investigator in conjunction with the trial Sponsor. In the case of withdrawal, the patient will continue standard treatment within the dedicated oesophago-gastric and oncological departments.

Interventions

Following a dedicated oesophago-gastric staging pathway, including Anaesthetic and Cancer Multi-disciplinary Team (MDT) discussions, all patients whose proposed treatment includes neoadjuvant therapy and surgery will undergo a baseline CPX test as part of standard care. Here, eligibility will be assessed. At the next consultation (surgical or oncological outpatient clinic appointment), eligible patients will be approached by the chief investigator (CI) or clinical supervisor (CS) in order to confirm inclusion and exclusion criteria. Patients will at this stage be invited to participate in the study (Appendix 1. Patient information leaflet). If interested, one of the above research team members will explain the study to the patient and give them a copy of the patient information sheet to review. The patient will be given the opportunity to ask any

questions they may have about the study and will be given at least 24 hours to consider participation. The research team will emphasise that non-participation will not adversely affect any aspects of their care. The patient will attend for pre-chemotherapy blood tests as part of their standard care pathway. At this time, the patient will be invited to give written consent to the trial. Patients will be informed that they are free to withdraw at any time without giving a reason and again that this will not adversely affect any aspects of their care. If the patient is willing to provide informed consent they will be asked to sign the patient consent form. Consent will be obtained by a suitably qualified person in accordance with international Good Clinical Practice (GCP) guidelines. The patient will be randomised to the intervention (Prehab) or Control group by the consenting clinician (see 'Methodology and Study Design' below).

Study group

1) **Prehab group**

Exercise intervention: Over a 15 week period, patients will attend the Human Performance Institute at Surrey Sports Park for twice weekly one hour exercise sessions (30 sessions in total) supervised directly by a Clinical Exercise Scientist with expertise in Cancer Care.

The exercise program will consist of cardiorespiratory, resistance and flexibility training in accordance with the American College of Sports Medicine guidelines [28].

At the first supervised exercise session, patients will be counselled by the trainer and issued with FitBit Flex2® physical activity monitor. The trainer will construct a tailored

programme for each patients based on their baseline (pre-chemotherapy) cardiopulmonary exercise test performance and calculated heart rate reserve.

During the aerobic training component, the intensity of cardiorespiratory exercise will be monitored every 5 minutes using the BORG rating of perceived exertion scale (RPE) (Borg, 1998), with power output on the cycle ergometer (Ergoline, Lovemedical, UK) controlled within the ranges of 11 (*"Fairly light"*) and 14 (*"Somewhat hard/Hard"*) on the BORG scale. Heart rate will be recorded every 5 minutes using a Polar HR monitor (Polar FT1, Polar, UK). The trainer will aim for the patient to complete 20 minutes of cycling at an incremental increase from 40% heart rate reserve (HRR) to 60% HRR over the duration of the course.

The resistance exercises performed will provide stimulus to each of the major muscle groups. Resistance training will be of a sufficient intensity tailored to each individual patient to enhance strength, muscular endurance and maintain fat-free mass with a progressive approach to exercise training over the 15 weeks. Two sets of 12 repetitions of each exercise will be performed. Flexibility exercises will be incorporated into the overall fitness program sufficient to develop and maintain range of motion including appropriate static and/or dynamic stretches. Resistance exercises will be scored on a rating of perceived exertion scale, when the score drops below 12 for a given exercise, the intensity of resistance will be increased.

Patients will also undergo a Home Exercise Plan (HEP) for one hour, three times a week. The HEP will focus on resistance and core stability exercises and will be monitored via a patient-maintained diary.

Throughout the duration of the prehabilitation programme, all patients will be asked to wear a Fitbit Flex2® physical activity monitor on their non-dominant wrist as an objective measure of background activity. The Clinical Exercise Scientist will record weekly steps at their supervised exercise sessions. They will also monitor session compliance.

Psychological (Medical Coaching) intervention: In conjunction with The Fountain Centre (St Luke's Cancer Centre, Guildford, UK), patients will undergo 6 medical coaching sessions during their neoadjuvant treatment. The team consists of professional medical coaches with over 200 hours experience in coaching individuals with medical conditions. They are accredited with the international and UK coaching bodies, International Coaching Federation (ICF) and National Council of Psychotherapists (NCP). Sessions will take the following form: Discussion of medical and health status; strengths recognition; resilience profiling and development; social and support systems; emotional management; and goal setting. The Medical Coach will provide suggestions on how to enhance and reinforce patients' motivation to comply with the exercise aspect of the intervention.

Nutritional support: Nutrition is of great importance to this cohort of patients as they are often malnourished and cachexic at presentation. The Trust employs 2.4 equivalent specialist dieticians per 60 cancer resections who are highly trained in the field of oesophagogastric surgery and have extensive experience in the management of complex nutritional problems related to the disease. All patients will receive

frequent, tailored dietetic input, with calorie and protein intake increase where appropriate.

In order to minimize the number of appointments required to attend by the Prehab group, where possible supervised exercise sessions will be scheduled for the day of a pre-existing oncology or surgical appointment. Following a face-to-face meeting with the Medical Coach, meetings will take place according to the patient's preference, either in person (following on from their supervised exercise session), or via teleconference (eg Skype).

2) Control group

The control group will not receive a prehabilitation intervention but will be treated according to the standard OG care pathway. As part of usual care, all patients will be fully informed to improve fitness levels and to maintain a healthy lifestyle prior to surgery in order to obtain the best outcomes from high risk surgery. Patients will continue to be offered standard dietetic and CNS led psychological support as per the hospital's current cancer pathway and standard of care. Patients will be asked to wear a Fitbit Flex2® physical activity monitor throughout their preoperative treatment. As an objective measure of background activity, weekly steps will be recorded by a member of the study's delegation log. Nutritional support will be as per the standard pathway with regular telephone call and specialist oesophago-gastric dietetic consultations.

The control group will not be required to attend any extra appointments as outcome measure will be performed at the time of a pre-scheduled routine appointment (with the oncologist or surgeon).

Study outcomes

The primary outcome (change in AT) will be measured by an incremental symptom-limited CPX test performed by an experienced consultant anaesethetist. All patients will undergo CPX testing at baseline (before the start of neoadjuvant therapy), 2 weeks following completion of NAC, and one week prior to surgery. Other CPX outcomes (Peak VO_2 and Total Work Rate) will also be analysed.

Feasibility will be assessed by monitoring patient attendance at exercise and medical coaching sessions and adherence to the supervised exercise programme, as well as patient drop-out. Adherence to home exercise sessions will be monitored by a patient-reported diary. Patients will be deemed compliant to the intervention if they complete >75% of scheduled prehabilitation sessions. Weekly steps recorded via a Fitbit Flex2® physical activity monitor.

Insulin resistance will be measured using the HOMA2 calculation. All patients will undergo fasting paired insulin and glucose tests at five stages along the protocol pathway: 1) Before NAC; 2) After cycle 1 of NAC; 3) After cycle 2 of NAC (or if having chemoradiotherapy, midway through chemoradiotherapy); 4) Following completion of cycle 3 (or at the end of chemoradiotherapy); 5) At re-staging laparoscopy; and 6) on the morning of surgical resection. In addition, HbA1c will be measured at baseline and on the day of oesophagectomy/total gastrectomy.

Completion of neoadjuvant therapy will be recorded in conjunction with the patient's consultant oncologist who will be a member of the trial Delegation Log. Toxicity will be

monitored between cycles and after completion of chemotherapy and will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0: Mild (Grade 1), moderate (Grade 2), severe (Grade 3), or life-threatening (Grade 4), with specific parameters according to the organ system involved.

Quality of life (QoL) will be assessed at specific time points: 1) Before commencement of NAC (baseline); 2) Midway through NAC; 3) Following NAC completion; 4) 2 weeks post hospital discharge; 5) 6 weeks post discharge; and 6) 6 months following discharge. Validated questionnaires will include EORTC QLQ-C30, EORTC QLQ – OG25, Beck Anxiety Inventory (BAI)), and Beck Depression Inventory (BDI II).

Nutritional assessment will take the form of hand grip strength (HGS), mid-arm muscle circumference (MAMC), triceps skin-fold thickness (TSFT), and sarcopenia. HGS, MAMC and TSFT will be measured at the same time points that preoperative blood tests are taken, HGS will be measure twice daily on postoperative days 1-3 and once daily on days 4-7. HGS, MAMC and TSFT will be measured postoperatively at 2 weeks, 6 weeks and 6 months following hospital discharge. As part of standard care, patients undergo staging CT imaging at baseline and following neoadjuvant therapy. Sarcopenia will be measured using SliceOmatic^{TM} software at these two time points. At the L3 level, total skeletal muscle (SM), subcutaneous fat and visceral fat will be measured. Skeletal muscle index (SMI) will be calculated as follows: SM/height(m)^2. Measurements will be recorded by two individuals, one of whom will be external to the Trial Group.

Surgery will be performed in a standard manner by three experienced oesophago-gastric consultants. All patients will spend a period of time on intensive care post-operatively and will follow a dedicated oesophago-gastric Enhanced Recovery After Surgery (ERAS) pathway. Length of intensive care and hospital stay will be recorded as will postoperative complications will be measured using the Clavien-Dindo classification and as per the Esophagectomy Complications Consensus Group [23]. Mortality will be assessed at 30 days, 90 days and 1 year postoperatively. Figures 1 and 2 demonstrate the flow of patients (Figure 1. Consort diagram) and study schedule (Figure 2. Study diagram).

Figure 1. Consort diagram

Figure 2. Study diagram

Methodology and study design

This trial will be conducted in a single tertiary referral centre for oesophago-gastric cancer, with all patients treated and followed up at the Royal Surrey County Hospital, Guildford UK, in conjunction with St Lukes' Cancer Centre. Full disease staging, a dedicated oesophago-gastric cancer multi-disciplinary team meeting, and assessment of eligibility will take place prior to patients being approached by the CI or CS. Patients will be informed of the trial protocol via face to face discussion and a written Patient Information Leaflet. On inclusion and formal consent to the trial, patients will be randomised to receive the intervention (Prehab) or standard care Control). Randomisation will be carried out by a designated member of staff who is not directly involved in the study. In order to yield 1 : 1 groups, he or she will use computer generated variable block randomisation, with the group name ('prehab' or 'control')

placed in sequentially numbered brown opaque envelopes. The envelopes will be kept in a locked drawer. On consent of a patient to the trial, the next envelope in sequence will be handed to the CI who will open the envelope in front of the patient. Due to the nature of the intervention, the research team and trial participants will not be blinded to the assigned arm of the trial. Outcome measures are described in detail above.

Statistical considerations

Estimation of sample size

It has been shown that AT improves following neoadjuvant chemotherapy as a result of a prehabilitation programme compared with standard care, with an AT difference of 2.12ml/kg/min between Prehab and Control groups [16].

To achieve a power of 80% and a significance level of 5% and to allow for confounding factors in a post-chemotherapy population, we calculate that 48 patients (24 per group) need to be studied in order to detect an AT difference of 2ml/kg/min between Prehab and Control group subjects. To allow for a 20% patient drop-out rate (due to non-compliance or side effects from chemotherapy), 24 patients will be required for each treatment group resulting in a total accrual of 58.

Statistical analysis

Data will be analysed on an intention to treat basis using SPSS software (v24). With the exception of interim analysis, a *p* value of <0.05 will be considered significant. Normality of data will be determined by using the Shapiro-Wilk test. Baseline characteristics for the two groups will be compared and demonstrated using mean [+/-

standard deviation] or the median (with interquartile range) for continuous data. A mixed-measure analysis of variance (ANOVA) will be employed for the primary outcome of AT as this will be recorded at three times points (baseline, 2 weeks following neoadjuvant therapy, and 1 week prior to surgery). An unpaired Student's *t* test will compare AT and peak VO_2 between the intervention (prehab) and control groups. A sub-group analysis will be performed, categorising patients into 'low risk' (AT>11 ml/kg/min, peak VO_2 >800 ml/min/m^2) and 'high risk' (AT<11 ml/kg/min; peak VO_2 <800 ml/min/m^2) [29, 30]. Secondary outcomes including length of hospital stay, grip strength, quality of life, Fitbit® data etc., will also be analysed using a Student's *t* test or Mann-Whitney U test. Survival data will be determined using the Kaplan-Meier curve. Interim analysis will be performed once primary outcome data is available for 26 subjects.

Patient and Public Involvement

The CI attended the Oesophageal Patient Association Support Group to engage and empower patients to help decide upon the programme from previous experiences. All members were fully engaged, enthusiastic. Patient experience helped shape the study design, in particular regarding the frequency of researcher and patient interaction, and number of scheduled exercise sessions.

At the time of consent, all patients will be asked whether they would like to receive a copy of the trial results. If they initial this box, they will be emailed or posted (as per the patient's preference) a copy of the completed manuscript.

Once the patient has completed the programme, the burden of the intervention will be assessed by patients themselves through the use of a questionnaire.

Discussion

Neoadjuvant therapy prior to oesophago-gastric resection is the gold standard of care for patients with T2 and/or nodal disease. Despite this, studies have taught us that chemotherapy decreases a patients' functional capacity. We aim to show that a multimodal prehabilitation programme will physically and psychologically optimise these patients, during and after neoadjuvant therapy, prior to major elective OG cancer surgery so they may better withstand the immense physical and metabolic stress placed upon them by radical surgery.

Ethics and Dissemination

Approval

In accordance with the Declaration of Helsinki, the trial was presented to an independent Research Ethics Committee, the London-Bromley Research Ethics Committee. Authorisation was obtained from the NHS Health Research Authority on 16th November 2016. Any substantial amendment to the protocol or consent form will be presented to the local Research and Development team and independent Research Ethics Committee. Likewise, all serious adverse events (AE) will be reported to the local Research and Development team as well as the independent Research Ethics Committee. The study is registered on the Clinical Trials website, ClinicalTrials.gov, under the number NCT02950324. The study is sponsored by The

Royal Surrey County Hospital NHS Foundation Trust and funded by Macmillan Cancer Support. The sponsorship from Macmillan Cancer Support will fund the following: Exercise sessions at Surrey Sports Park, psychological support in the form of Medical Coaching, fasting blood tests, and the Fitbit Flex2® physical activity monitors.

Patient informed consent

As per international principles, written informed consent (Appendix 2. Consent form) will be obtained from patients prior to their participation in the trial once they voluntarily confirm their understanding and willingness to participate in the trial at least 24 hours after verbal and written information has been provided and questions answered. Consent will be obtained by a suitably qualified person in accordance with international Good Clinical Practice (GCP) guidelines. Patients will be informed that they are free to withdraw from the trial at any time without giving a reason and they will be informed that this will not adversely affect any aspects of their care.

Data collection and quality management

All data will be collected, handled and stored securely in the Trial Site File only by experienced persons who have been suitably trained in Good Clinical Practice and who are a member of the trial Delegation Log. At the time of patient contact, data will be acquired using a paper case report form (CRF). All study data will be anonymised by using a using a unique study number assigned to each subject sequentially. CRFs will be stored in a locked cabinet within a locked drawer of the secure (card-access only) Research Department. Collated data will be maintained on a pre-defined confidentially stored and password protected electronic spreadsheet with access granted only to the CI, CS and Sponsor. Data will be kept for five years following

recruitment of the final patient. The trial does not warrant a Data Monitoring Committee due to its short interventional duration and minimal associated risks, however trial data will be regularly monitored and audited at regular intervals by the Sponsor and local R&D department in accordance with the University of Surrey Research Department, and Good Clinical Practice policies.

Access to data and dissemination of results

The Chief Investigator and Clinical Supervisor will have full access to the completed data set, as will the trial's Sponsor. Final data will be summarised on ClinicalTrials.gov, published in a peer-reviewed journal, and presented at international conferences.

Trial status

The trial protocol (v1.2 14/10/2016) was presented to an independent Research Ethics Committee, the London-Bromley Research Ethics Committee. Authorisation was obtained from the NHS Health Research Authority on 16th November 2016. Recruitment started on 15/12/16. To date, 43 patients have been recruited. Six patients have been lost to follow-up. Interim analysis will be performed once primary outcome data (change anaerobic threshold) is available for 26 subjects (13 per group). Recruitment will be completed by 1/6/18.

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Authors statement

Sophie Allen, Vanessa Brown, Michael Scott, Pradeep Prabhu, Timothy Rockall, Shaun Preston and Javed Sultan have all: Made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; Have been involved in drafting the manuscript or revising it critically for important intellectual content; Have given final approval of the version to be published and has participated sufficiently in the work to take public responsibility for appropriate portions of the content and have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The trial management committee (SA and JS) will be responsible for the following: Organisation of steering committee meetings; the trial site file; randomisation (performed by a person external to the trial); budget administration and liasing with the

funding source and Sponsor; reporting of adverse events; completion of CRFs; identification and recruitment of patients; adherence to the study protocol; and publication of study results. The steering committee (SA/VB/PP/SP/TR/JS) were in agreement of the final protocol and will review the progress of the study, liasing with the CI to ensure the study runs smoothly.

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BMJ Group declaration of interests statement

I have read and understood the BMJ Group Policy on declaration of interests and declare the following interests: None

Name: Sophie K Allen Date: 2/3/18

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List of figures

Figure 1. Consort diagram

Figure 2. Study diagram

Appendix

Appendix 1. Patient information leaflet

Appendix 2. Consent form

List of abbreviations

AE – Adverse event

AT – Anaerobic threshold

CI – Chief investigator

CNS – Clinical nurse specialist

CS – Clinical Supervisor

CPX test – Cardiopulmonary Exercise Test

CRF – Case report form

GCP – Good Clinical Practice

HEP – Home exercise plan

HOMA2 – Homeostasis model assessment

HRR – Heart rate reserve

ICF - International Coaching Federation

IR – Insulin Resistance

MDT - Multi-disciplinary Team

NAC – Neo-adjuvant chemotherapy

NCP - National Council of Psychotherapists

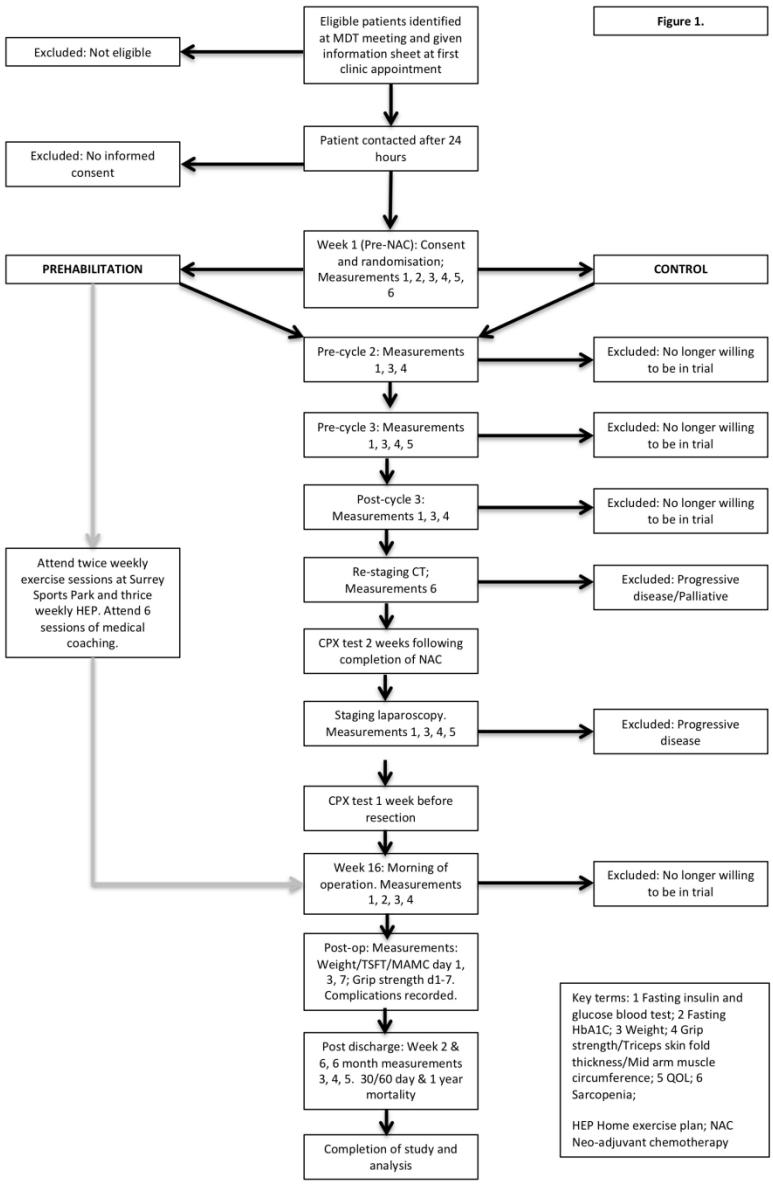
OGCS – Oesophago-gastric cancer surgery

POMS – Post-operative morbidity score

Prehab – Prehabilitation

RSCH – Royal Surrey County Hospital

VO_2 peak – Peak oxygen uptake



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	Enrolment and Allocation							Surgery	Follow up					
Timepoint	Week 1	Week 4	Week 7	Week 10	Week 12	Week 13	Week 15	Week 16	Days 1-7 post-op	2 weeks post discharge	6 weeks post discharge	6 months post discharge	1 year post discharge	Close-out (1 year post discharge)
Enrolment:														
Eligibility screen	X													
Informed consent	X													
Allocation	X													
Interventions:														
Prehab	X	X	X	X	X	X	X							
Control	X	X	X	X	X	X	X							
Assessments:														
CPX (AT and peak VO2)	X				X		X							
Sarcopenia assessment	X			X										
Weight	X	X	X			X		X	X	X	X	X		
Fasting HbA1c	X							X						
Fasting insulin and glucose	X	X	X	X		X		X						
Grip strength	X	X	X	X		X		X	X	X	X	X		
TSFT	X	X	X	X		X		X	X	X	X	X		
MAMC	X	X	X	X		X		X	X	X	X	X		
QOL	X		X			X				X	X	X		
Complications									X	X				
Mortality										X	X		X	
Analysis														X

Figure 2. Study diagram

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(Chemotherapy)

Royal Surrey County Hospital NHS
NHS Foundation Trust

Patient information leaflet

Does prehabilitation improve cardiopulmonary exercise performance in patients undergoing neoadjuvant treatment and surgery for oesophagogastric cancer

Mr Javed Sultan, Consultant Surgeon
Professor Timothy Rockall, Professor of Surgery
Dr Julie Hunt, Lecturer in Sport and Exercise Sciences
Professor Mike Scott, Consultant Anaesthetist
Miss Sophie Allen, Research Fellow, Principal Investigator

"Does exercise improve exercise test results and recovery after surgery in people with oesophagogastric cancer?"

Invitation to participate

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. This information sheet is designed to help you decide whether you would like to participate in this study. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

What is the purpose of the study?

Recent studies have shown that regular supervised exercise (prehabilitation) can improve patients' fitness prior to surgery, improve the way their body handles sugar and improve their recovery after surgery. Cardiopulmonary exercise (CPX) testing measures the function of your heart and lungs in response to exercise (see separate information leaflet 'Your Cardio Pulmonary Exercise test'). Studies have shown that the better your CPX result, the less likely you are to have complications after a big operation.

The aim of this study is to see if regular supervised exercise (prehabilitation) improves performance in CPX and recovery after surgery. The study will last up to approximately 22 weeks in total.

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Royal Surrey County Hospital NHS
NHS Foundation Trust

Study Number: REC 16/LO/1702 R+D 16SURN213028 IRAS ID: 213028 ***Patient copy***
Patient Identification Number for this trial:

CONSENT FORM

Title of Project: Does prehabilitation improve cardiopulmonary exercise performance in patients undergoing neoadjuvant treatment and surgery for oesophagogastric cancer?

	Please initial boxes
1. I confirm that I have read and understand the information sheet (Version 3.1 Date 13/10/2017) for the above study and have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	
3. I understand that the relevant sections of any of my medical notes and data collected may be looked at by responsible individuals or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my relevant records.	
4. I am aware of the need for psychological support whilst taking part in this study and it has been explained to me how I can obtain this support.	
5. I agree to take part in the above study and to my General Practitioner being informed of my participation I the study	
6. I agree that my biological materials (blood and tumour samples) collected, and CT scans performed during the study as part of the standard of care, but not related to study procedures etc, may be saved and used for later analysis	
7. Once the study has been completed and analysed I would like to be sent you a summary of the results.	

Name of Patient	**Signature**	**Date**
Name of Person taking consent (if different from researcher)	Signature	Date
Researcher	Signature	Date

209x296mm (300 x 300 DPI)

		individuals who will perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10, 11, 12, 13
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	8
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	11, 12, 13
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11, 12, 13
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	13 (Figure 2)
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14, 15
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	14, 15, 16
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any	

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